Neuronal activity representing visuospatial mnemonic processes associated with target selection in the monkey dorsolateral prefrontal cortex

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Abstract

To investigate how visuospatial mnemonic and target selection processes are represented in the dorsolateral prefrontal cortex (PFC), we studied neuronal attributes of the dorsolateral PFC while monkeys were performing oculomotor delayed visual search (ODVS) and oculomotor delayed-response (ODR) tasks. In the ODVS task, the subject made a memory-guided saccade to a remembered target location that had been presented along with distractors before a delay period; in the ODR task, the target was presented without any distractors. A total of 252 neurons in the dorsolateral PFC showed directional delay-period activity and were divided into two groups; neurons that showed directional delay-period activity predominantly in the ODVS task (n/C30/C112), and those that showed such activity similarly in both the ODVS and ODR tasks (n/C140). These neuronal groups shared similar temporal properties (i.e. onset latency, peak time of delay-period activity) and spatial tuning. Our findings suggest that the dorsolateral PFC contains a particular visuospatial memory system for information selected by target selection (selective attention), and this attention-memory system (or 'memory system for special use') appears to be represented in the dorsolateral PFC, in parallel with a more 'general' memory system that is not specifically associated with target selection.

Keywords: Prefrontal cortex; Selective attention; Working memory; Attention-memory system; Visual search; Macaque monkey

1. Introduction

We often search for a relevant target among several distractors (a function referred to as 'target selection' or 'selective attention'), and memorize it for a while ('short-term memory'). Since the short-term memory system in the brain has a limited capacity (Luck and Vogel, 1997; Rainer et al., 1998; Miller, 1999) and the brain has a working memory system that is considered to involve both attention and mnemonic processes (Baddeley, 1986, 1992), it is reasonable to assume that there is a short-term memory system that is associated with target selection processes (Rainer et al., 1998). One possible substrate of such a system, particularly for visuospatial information, is a neuronal population in the dorsolateral prefrontal cortex (PFC), since this area plays a major role in visuospatial working memory for guiding goal-directed behaviors (Kubota and Niki, 1971; Funahashi et al., 1989; Chafee and Goldman-Rakic, 1998; Hasegawa et al., 1998, 1999; Sawaguchi, 1998; Sawaguchi and Yamane, 1999; for reviews, see Funahashi and Kubota, 1994; Goldman-Rakic, 1995), although previous studies at the cellular level have not adequately addressed the mnemonic processes associated with target selection. Further, we recently demonstrated that local inactivation with muscimol in the dorsolateral PFC of monkeys induced a specific deficit in visuospatial target selection (Iba et al., 1998; Iba and Sawaguchi, 1998) using a visual search paradigm that has been used to assess target selection processes in human psychological studies (for reviews, see Kinchla, 1992; Treisman, 1988) and neuron-recording studies in monkeys (Schall and Hanes, 1993; Schall et al., 1995; for a review, see Schall and Thompson, 1999). In addition, Hasegawa et al. (2000) demonstrated that neurons in the dorsolateral PFC are
involved in target selection, using a visual search paradigm. Further, the dorsolateral PFC is strongly connected with the posterior parietal cortex (Petrides and Pandya, 1984) and frontal eye field (FEF) (Arikuni et al., 1988; Watanabe-Sawaguchi et al., 1991), which have been demonstrated to play a major role in visuospatial target selection/attention (Bushnell et al., 1981; Corbetta et al., 1991, 1993; Schall and Hanes, 1993; Schall et al., 1995; for reviews, see Colby and Goldberg, 1999; Schall and Thompson, 1999; Donner et al., 2000). Based on these findings, we hypothesized that the dorsolateral PFC might contain a neuronal population that is involved in a mnemonic process associated with target selection for visuospatial information.

To address this hypothesis, we examined attributes of neurons in the dorsolateral PFC while macaque monkeys were performing an oculomotor delayed visual search (ODVS) task and an oculomotor delayed-response (ODR) task. The ODR paradigm is sensitive to visuospatial mnemonic processes and has been frequently used to investigate neuronal processes of visuospatial memory in the dorsolateral PFC (Funahashi et al., 1989; Chafee and Goldman-Rakic, 1998; Sawaguchi, 1998, 2001). In the ODVS task, the subject has to select a target stimulus among distractors during the cue period and maintain the selected information during the delay period; hence, the ODVS task is suitable for examining both target selection and the memorization of visuospatial information. We report here that a subset of PFC neurons show directional delay-period activity predominantly in the ODVS task, and this appears to represent visuospatial mnemonic processes associated with target selection. Preliminary reports of these findings have appeared in abstract form (Iba and Sawaguchi, 1999a,b).

2. Materials and methods

2.1. Subjects and behavioral tasks

Two male macaque monkeys (Macaca mulatta, 10 kg; Macaca fuscata, 9 kg) were used in this study. Throughout the experiment, the subjects were treated in accordance with the Guidelines for the Care and Use of Laboratory Animals (National Institutes of Health) and the Guide for the Care and Use of Laboratory Animals of our institute.

Before training, preliminary surgery was performed under pentobarbital anesthesia (25 mg/kg, iv) and aseptic conditions. Two head-holding devices (hollow rods, 8-mm diameter) were implanted using stainless steel bolts (3-mm in diameter) with dental acrylic. To prevent infection, prophylactic antibiotics were injected intramuscularly on the day of surgery and daily for 7 days after surgery.

A few weeks after surgery, each monkey was trained to perform the ODVS and ODR tasks (Fig. 1). During the training and experimental sessions, each animal sat on a monkey chair in a dark room and faced a 21-in. CRT monitor (PC-TV471, NEC) 32 cm in front of them. The monkey’s head was rigidly fixed by two stainless steel bars (8-mm diameter) to a stereotaxic frame located at the top of the monkey chair. Eye positions and movements were monitored and sampled by an infrared eye-camera system (R-21C-A, RMS, Hirosaki, Japan) with a 4-ms sampling rate. In the ODVS task, while the monkey fixated on a central spot (white square, 0.5 × 0.5) for 2 s, a stimulus array appeared for 1 s (cue period), followed by a delay period of 3 s. The monkey had to maintain fixation within a window (3° diameter); if the monkey broke fixation, the trial was aborted. The stimulus array consisted of a target (red cross, 2 × 2°) with five distractors. In the ‘ODVS-S’ condition, the distractors differed from the target with regard to shape (red bar, 2 × 2°) (Fig. 1(A)). We usually used this ODVS-S condition, and the data in Section 3 generally reflect the findings in the ODVS-S task. However, in some sessions, we introduced the ‘ODVS-C’ condition, where the distractors differed from the target with regard to color (green cross, 2 × 2°) (Fig. 1(A)). The target stimulus was presented randomly at one of six possible target locations (right, 0°; upper-right, 60°; upper-left, 120°; left, 180°; lower-left, 240°; lower-right, 300°) with an eccentricity of 13°, and distractors were presented at the remaining five locations (Fig. 1(B)). After the delay period, the fixation spot turned off (‘go’ signal), instructing the subject to make a memory-guided saccade to the remembered target location within a window of 4° around the target location. A correct response was rewarded with a drop of water 0.2 s after the end of the correct saccade. The ODR task was exactly the same as the ODVS task except that only the target (red cross, 2 × 2°) was presented (Fig. 1(A)). These two tasks were randomly intermixed so that the monkeys could not anticipate which task was in progress until the cue period. The subjects performed about 800–1200 trials during daily training or recording sessions.

To examine whether the target selection process actually occurred during the cue period, we also introduced oculomotor visual search (OVS) and oculomotor detection (OD) tasks in some sessions without neuronal data recording. The OVS and OD tasks were exactly the same as the ODVS and ODR tasks, respectively, except that neither task included a delay and the monkeys were required to make saccadic eye movement to the target immediately after cue appearance.
2.2. Neuronal recordings and data analysis

After training was complete, a stainless steel cylinder (20 × 40 mm) was implanted under pentobarbital sodium anesthesia (25 mg/kg, iv) and aseptic conditions. An oval opening (about 20 × 40 mm) was made in the skull with a trephine to expose the dura covering the frontal cortex, and the stainless steel cylinder was positioned over the dorsolateral PFC with dental acrylic. Prophylactic antibiotics were injected intramuscularly on the day of surgery and daily for 7 days after surgery.

We recorded single-neuron activity extracellularly from the dorsolateral PFC with glass-coated elgiloy electrodes (impedance, 0.2–1.0 MΩ). 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-μm steps to enable monitoring of the extracellular activity of single neurons while the monkey was performing the ODVS and ODR tasks. Data for neuronal activity were digitized by a window discriminator (DDIS-1, BAK Electronics) for analysis on a personal computer. To detect significant changes in activity during the task events, we compared, trial-by-trial, the discharge rate (spikes/s) during each task event to that during a ‘control’ pre-cue (1 s) period, using the Mann–Whitney U-test (P < 0.05). Since we were interested in target selection and mnemonic processes in the present study, we focused on cue-related and delay-period activities. When the discharge rate of a neuron during the cue period was significantly greater than that during the control period for at least one target direction, it was considered to show ‘cue-related activity’. When the discharge rate of a neuron during the delay period was significantly greater than that during the control period for at least one target direction, it was considered to show ‘delay-period activity’. Further, when delay-period activity of a neuron differed significantly with the target direction for at least one task condition (ANOVA, P < 0.05), it was considered to show ‘directional delay-period activity’. We also applied two-way ANOVA (task condition and direction as factors, P < 0.05) for directional delay-period activity.

Fig. 1. The behavioral paradigm and target locations. (A) The ODVS and the ODR tasks. In the ODVS task, after the monkey fixated on the central spot for 2 s, a stimulus array (a red cross and five distractors) was presented for 1 s. After a 3-s delay period, the fixation spot extinguished (‘go’ signal), instructing the monkey to make a memory-guided saccade (arrow) to the target location that had been indicated by the cue prior to the delay. A correct response was rewarded by a drop of water 0.2 s after the saccade. Trials were separated by an inter-trial interval (ITI) of 2 s. There were two conditions in the ODVS task: ‘ODVS-S’ and ‘ODVS-C’. In the ODVS-S task, the distractors differed from the target with regard to shape (red bar), and in the ODVS-C task they differed from the target with regard to color (green cross). The ODR task was exactly the same as the ODVS task except that only a target stimulus (red cross) appeared during the cue period. (B) The six target locations and fixation spot. Eccentricity was 13°.
to examine the effect of the task condition. To quantitatively examine the spatial tuning of the cue-related and delay-period activities, we calculated tuning curves with a Gaussian function, as follows:

\[
f(d) = B + \sum_{i=1}^{3} \frac{A}{\sqrt{2\pi T_d^2}} \exp \left[ -\frac{(d - D + (i - 2)T_d)^2}{2T_d^2} \right]
\]

where \(f(d)\) is discharge frequency, \(d\) is cue direction, and the remaining terms are constants: \(B\) is the baseline discharge rate in the task period, \(D\) is the best direction, \(T\) is 360°, \(A\) indicates the activity response strength (calculated as the summed area minus baseline), and \(T_d\) indicates tuning with respect to cue direction. In neurons with directional delay-period activity, the time from the onset of the stimulus array to the onset of such activity was calculated in the averaged histogram (10 ms/bin) for the ‘preferred direction’, 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 (cf. Hasegawa et al., 1998; Sawaguchi and Yamane, 1999). The delay-period activity was generally maintained until the end of the delay period (see the population histogram in Fig. 9). The peak time (i.e. time at the maximal rate of discharge) of delay-period activity, from the onset of the cue, for each neuron was also calculated in the averaged histogram (10 ms/bin) for the preferred direction (see Sawaguchi, 1987).

At the end of each recording session, to examine whether the recorded site was located within the FEF, we applied intracortical microstimulation (ICMS, a train of 22 cathodal pulses of 0.3-ms duration at 333 Hz, \(\leq 100\) μA) in each recording session. When eye movement was induced by ICMS of \(<50\) μA, the site was considered to be in the FEF (Bruce and Goldberg, 1985; Bruce et al., 1985). Data from the FEF were excluded from this analysis.

2.3. Histology

After the experiments were complete, the monkeys were deeply anesthetized with an overdose of sodium pentobarbital and perfused with physiological saline followed by 10% formalin. The removed brains were photographed and the penetration sites were reconstructed on the cortical surface. The recorded neurons were located in the dorsolateral PFC (areas 8 and 46) rostral to the FEF where eye movements were induced by ICMS \(<50\) μA.

3. Results

3.1. Behavioral data

The performance level during the recording sessions was \(>95\%\) correct, and there were no significant differences in the performance level between the ODVS and ODR tasks for each monkey. During a typical recording session, the mean onset latencies for saccadic eye movement from the onset of the ‘go’ signal were 262.8 ± 87.0 (SD) ms (\(n = 76\)) in the ODVS task and 245.4 ± 64.5 ms (\(n = 74\)) in the ODR task for Monkey S, and 223.5 ± 25.4 ms (\(n = 55\)) in the ODVS task and 238.1 ± 91.1 ms (\(n = 57\)) in the ODR task for Monkey T. There were no significant differences in onset latency between the ODVS and ODR tasks for either monkey (Mann–Whitney U-test, \(P > 0.05\)). Thus, each monkey performed the ODVS and ODR tasks with a similar performance level and saccade responses.

To obtain evidence that target selection occurred in the ODVS task, we measured the onset latency of saccadic eye movements during performance of the OD and OVS tasks, which required the subject to make a response immediately after cue appearance. The onset latencies of saccades for a typical experimental session are summarized in Table 1. As shown, for each target location, the onset latency in the OVS task was significantly longer than that in the OD task, suggesting that target selection actually occurred during the OVS task, and probably also during the cue period of the ODVS task, to select the target from among distractors.

3.2. Neuronal data

We recorded the activities of a total of 728 PFC neurons (588 in Monkey S and 140 in Monkey T). Of these, 522 neurons (416 in Monkey S and 106 in Monkey T) showed significant changes in activity during at least one of the task phases (Mann–Whitney U-test, \(P < 0.05\)). Of these, 97 neurons (69 in Monkey S and 28 in Monkey T) showed cue-related activity, 411 (337 in Monkey S and 74 in Monkey T) showed delay-period activity and 13 (nine in Monkey S and four in Monkey T) showed saccade-related activity. All of the neurons that showed cue-related activity were directional, in that the magnitude of the activity varied significantly with the cue direction (one-way ANOVA, \(P < 0.05\)). Of the 411 neurons that showed delay-period activity, 252 showed a significant difference in activity with cue direction (one-way ANOVA, \(P < 0.05\)); i.e. directional delay-period activity. The remaining 159 neurons showed omni-directional delay-period activity (\(n = 110\)) or complex activity that was difficult to analyze (\(n = 49\)). Since we were interested in target selection during the cue period and subsequent mnemonic processes during
the delay period, we focused here on directional cue-related and delay-period activities.

### 3.3. Cue-related activity

Since target selection is considered to occur during the cue period, we first examined cue-related activity. Consistent with the findings of Hasegawa et al. (2000), most of the neurons with cue-related activity showed a phasic response to the target stimulus when it was presented in the receptive field. An example is shown in Fig. 2(A). This neuron showed cue-related activity when the target was presented at 300° in both the ODVS and ODR tasks, but the magnitude of this activity in the ODVS task (13.7 ± 5.7 spikes/s) was greater than that in the ODR task (10.7 ± 9.3 spikes/s). When the target was presented in the opposite location (unpreferred direction, 120°), there was no phasic activity in either the ODVS (8.0 ± 4.8 spikes/s) or the ODR task (5.2 ± 2.4 spikes/s). The greater cue-related activity in the ODVS task was also evident using the tuning curve examined with the Gaussian function, as shown in Fig. 2(B). Whereas the best direction, as examined with the tuning curve, was similar in the ODVS and ODR tasks (289° for ODVS; 281° for ODR), the peak amplitude in the ODVS task (16.5 spikes/s) was much larger than that in the ODR task (9.5 spikes/s).

To examine the overall pattern and time-course of cue-related activity at the population level, we made population histograms of neurons with cue-related activity (n = 97) for the preferred direction, as illustrated in Fig. 2(C). As shown, the neuronal population showed phasic activation following cue appearance in both the ODVS and ODR tasks, but its magnitude in the ODVS task was greater than that in the ODR task, and this greater activation persisted during the cue period. These results are consistent with those reported by Hasegawa et al. (2000), suggesting that target selection occurred during the cue period in the present behavioral paradigm.

### 3.4. Delay-period activity

Of 411 neurons that showed delay-period activity, 252 (61%) showed directional delay-period activity. Of these 252 neurons, 72 showed directional delay-period activity only in the ODVS task, and these neurons were classified as ‘VS-neurons’. We applied two-way ANOVA to the remaining 180 neurons with directional delay-period activity to examine the effect of the task condition. Based on this analysis, 40 neurons showed directional delay-period activity predominantly in the ODVS task, and these neurons were also classified as ‘VS-neurons’. The remaining 140 neurons showed similar directional delay-period activity (two-way ANOVA) in both the ODVS and ODR tasks and were classified as ‘DR-neurons’. None of the neurons examined showed directional delay-period activity predominantly for the ODR task. The recording sites for VS- and DR-neurons are plotted on the cortical surface in Fig. 3(A). As shown in Fig. 3(A), both VS- and DR-neurons were distributed mainly in the caudal half of the principal sulcal area anterior to the arcuate sulcus, although VS-neurons tended to be distributed more caudally than DR-neurons (Fig. 3(B)).

Fig. 4 shows a VS-neuron, where raster displays and averaged histograms of neuronal activity are shown according to the task condition and target direction. This neuron showed directional delay-period activity in the ODVS task (Fig. 4(A)) (mean ± SD spikes/s: 0°, 4.7 ± 3.3; 60°, 7.0 ± 5.7; 120°, 12.3 ± 5.1; 180°, 8.5 ± 3.2; 240°, 6.1 ± 3.1; 300°, 5.3 ± 2.5; ANOVA, F(5, 49) = 4.7, P < 0.01). The delay-period activity was maximal for a target location of 120°, and significant delay-period activity was also seen for the 180° target direction. In contrast, this neuron did not show directional delay-period activity when the target was presented without distractors during the cue period (i.e. ODR task) (Fig. 4(B)) (0°, 3.7 ± 3.5; 60°, 5.7 ± 3.1; 120°, 6.5 ± 2.5; 180°, 5.3 ± 3.2; 240°, 5.5 ± 3.0; 300°, 4.5 ± 3.4; ANOVA, F(5, 41) = 0.84, P = 0.52, NS).

### Table 1

Onset latency of saccadic eye movements in the OD and OVS tasks without a delay

| Target location ('') | Monkey S |  | Statistics | Monkey T |  | Statistics |
|----------------------|----------|  |           |----------|  |           |
| 0                    | 170 ± 36 (24) | 199 ± 38 (27) | ** | 175 ± 20 (20) | 206 ± 26 (27) | ** |
| 60                   | 162 ± 42 (20) | 198 ± 43 (26) | *  | 149 ± 21 (21) | 192 ± 24 (33) | ** |
| 120                  | 190 ± 60 (24) | 209 ± 25 (25) |  | 148 ± 34 (20) | 194 ± 18 (31) | *  |
| 180                  | 155 ± 45 (21) | 196 ± 75 (27) | ** | 153 ± 28 (22) | 180 ± 18 (30) | ** |
| 240                  | 170 ± 60 (23) | 205 ± 42 (27) | ** | 174 ± 35 (21) | 194 ± 50 (30) | *  |
| 300                  | 170 ± 57 (20) | 202 ± 30 (28) | ** | 145 ± 12 (26) | 182 ± 20 (34) | ** |

Values are mean ± SD in ms. Number of trials is in parentheses.
* P < 0.05.
** P < 0.01.
An example of a DR-neuron is shown in Fig. 5. This neuron showed directional delay-period activity for both the ODVS (Fig. 5(A)) and ODR tasks (Fig. 5(B)), and this delay-period activity was maximal for the 180° target direction (for ODVS, 0°, 9.0 ± 11.5; 60°, 9.0 ± 5.9; 120°, 14.7 ± 8.3; 180°, 21.9 ± 8.5; 240°, 13.6 ± 7.6; 300°, 7.1 ± 3.9; ANOVA, F(5, 76) = 6.12, P < 0.001; for ODR, 0°, 5.9 ± 3.6; 60°, 9.8 ± 5.9; 120°, 18.3 ± 4.9; 180°, 22.7 ± 12.1; 240°, 13.2 ± 5.4; 300°, 7.4 ± 4.7; ANOVA, F(5, 68) = 12.4, P < 0.001). As with the VS-neuron in Fig. 4, significant delay-period activity was also seen for adjacent target directions (i.e. 120° and 240°). There were no significant differences in delay-period activity for the preferred direction between the tasks (Student’s t-test, t = 0.18, df = 21, P = 0.86, NS).

3.5. Tuning of directional delay-period activity

Both VS- and DR-neurons appeared to show spatial tuning. To examine this point quantitatively, we applied curve-fitting with a Gaussian function (see Section 2). Fig. 6(A) shows an example of a fitting curve for the neuron in Fig. 4. As shown in Fig. 6(A), this neuron showed clear directional tuning only in the ODVS task ($T_d = 46°$, best direction = 122°). Fig. 6(B) shows a fitting curve for the neuron in Fig. 5. This neuron showed directional delay-period activity in both the ODVS and ODR tasks, and, as shown in Fig. 6(B), directional tuning was similar between the ODVS and ODR tasks; i.e. the best direction, peak amplitude and $T_d$ were similar (for ODVS: best direction, 180°; peak amplitude, 21.7 spikes/s; $T_d$, 61°; for ODR: best direction, 165°; peak amplitude, 23.4 spikes/s; $T_d$, 58°).

To compare the spatial tuning in VS- and DR-neurons, we calculated the best direction and $T_d$ using the Gaussian function, and the results are shown in Fig. 7. In both VS- and DR-neurons, the best direction was significantly biased to the visual field contralateral to the recording hemisphere (for VS-neurons, ipsilateral, n = 45; contralateral, n = 67; $\chi^2$-test = 4.32, df = 1, P < 0.05; for DR-neurons, ipsilateral, n = 52; contralateral, n = 88; $\chi^2$ = 9.25, df = 1, P < 0.01 (Fig. 7(A))). There was no significant difference in the distribution of the best direction between VS- and DR-neurons (mean ±
SD, 178 ± 102 vs. 188 ± 98°, U-test, Z = 0.84, P > 0.05, NS). The values of $T_d$ were also similarly distributed in VS- and DR-neurons (mean ± SD, 73 ± 20 vs. 70 ± 20°, U-test, Z = 1.47, P > 0.05, NS) (Fig. 7(B)). Thus, VS- and DR-neurons showed similar spatial tuning during the delay period.

### 3.6. Time-course of delay-period activity

To compare the temporal properties of the activities of VS- and DR-neurons, we calculated the onset latency and peak time, from cue appearance, of the delay-period activity for the preferred direction, and the results are presented in Fig. 8. As shown, there were no significant differences in onset latency between VS- and DR-neurons (mean ± SD, 758 ± 87 vs. 636 ± 43 ms, U-test, $P > 0.05$, NS). There were also no significant differences in the peak time between VS- and DR-neurons (mean ± SD, 1648 ± 136 vs. 1656 ± 71 ms, U-test, $P > 0.05$, NS). Thus, VS- and DR-neurons showed delay-period activities with similar temporal profiles.

### 3.7. Overall patterns of VS- and DR-neurons

To further examine the overall patterns of VS- and DR-neurons, we made population histograms of VS-neurons ($n = 112$) and DR-neurons ($n = 140$) for the preferred direction. As shown in Fig. 9(A), the population of VS-neurons for performance in the ODVS task showed sustained activity during the delay period and a rapid decrease when the go signal appeared, while no obvious cue-related activity was found. As expected, the population of VS-neurons for the ODR task did not show such sustained activity during the delay period. The population of DR-neurons also showed, in both the ODVS and ODR tasks, sustained activity during the delay period and a rapid decrease when the go signal appeared. These overall changes in activity for DR-neurons were similar to those of VS-neurons in the ODVS task. However, for DR-neurons, a phasic response was observed during the cue period, and particularly for the ODR task. This is consistent with findings in previous studies with the ODR paradigm in monkeys; several PFC neurons showed delay-period activity accompanied by phasic cue-related activity during the ODR task (Chafee and Goldman-Rakic, 1998; also see review by Funahashi, 2001).

### 3.8. Comparison of the ODVS-S and -C tasks

To examine whether the delay-period activity of VS-neurons depended on the physical properties of the
stimulus array, such as characteristics of the distractors, we introduced the ODVS-C condition for some recording sessions. In the ODVS-C condition, the distractors differed from the target with regard to color (i.e. green cross) (Fig. 1(A)). VS-neurons showed similar delay-period activity in both the ODVS-S and -C conditions ($n = 87$). Fig. 10(A) shows typical data in the ODVS-S and -C tasks. In this case, neuronal data for the preferred direction are shown for simplicity. This neuron showed delay-period activity when the target was presented at 180°, and these responses were observed in both the ODVS-S and -C tasks (mean ± SD, $21.8 ± 22.8$ vs. $18.3 ± 9.8$ spikes/s, $U$-test, $P > 0.05$, NS), but not in the ODR task ($12.0 ± 4.5$ spikes/s). This indicates that directional delay-period activity in VS-neurons is not associated with the pattern of the stimulus array, but rather with the target selection process. Further, DR-neurons showed similar delay-period activity in the ODVS-S, -C and ODR tasks ($n = 140$), as shown in the example in Fig. 10(B). This neuron showed similar delay-period activity in each task (ODVS-S, $24.2 ± 5.5$ spikes/s; ODVS-C, $24.1 ± 8.8$ spikes/s; ODR, $21.7 ± 6.7$ spikes/s; ANOVA, df = (2, 32), $F = 0.43$, $P = 0.65$, NS).

4. Discussion

4.1. General

In the present study, we examined the delay-period activities of neurons in the dorsolateral PFC while monkeys were performing the ODVS and ODR tasks. The visual search paradigm is suitable for examining target selection processes (Schall et al., 1995), and the ODR paradigm is useful for examining visuospatial working memory (Funahashi et al., 1989; Chafee and Goldman-Rakic, 1998). The present ODVS task combined these two paradigms, and is useful for accessing neuronal processes associated with these two functions. With these tasks, we found two groups of neurons: ‘DR-neurons’ and ‘VS-neurons’. Neurons similar to the present DR-neurons have been found in the dorsolateral PFC in several studies using the ODR paradigm, and these are considered to be involved in visuospatial mnemonic processes (Funahashi et al., 1989; Chafee and Goldman-Rakic, 1998; Sawaguchi and Yamane, 1999). VS-neurons were newly found in the present study, and we will mainly discuss these neurons below.

4.2. Involvement of VS-neurons in visuospatial memory associated with target selection

VS-neurons showed directional delay-period activity predominantly in the ODVS task, and most of them showed such activity only during performance of the ODVS task. Indeed, the population of VS-neurons showed sustained delay-period activity for the ODVS but not for the ODR task. Since the onset latency of saccadic eye movements and the performance level were similar for the ODVS and ODR tasks in both monkeys and these tasks were intermixed randomly during recording sessions, it is unlikely that general arousal or task difficulty affected the delay-period activity of VS-neurons. Further, the stimulus array (i.e. target and distractors) was presented in the cue period for the ODVS but not the ODR task, and it is possible that some physical property of the stimulus array itself might affect the delay-period activity of VS-neurons. To control this problem, we introduced two different distractor conditions (i.e. ODVS-S and -C), and VS-neurons showed similar delay-period activities with both of these conditions. However, we could not control sufficiently the main aspect of the physical properties of target and distractors, since we did not introduce different kinds of targets or a different number of distractors. Nevertheless, since VS-neurons showed spatial tuning and temporal profiles similar to those of DR-neurons, it is likely that VS-neurons, like DR-neurons, code spatial information regarding the target location during the delay period. Thus, VS-neurons, like DR-neurons, may be involved in visuospatial mnemonic processes.

VS-neurons showed delay-period activity predominantly for the ODVS task, and the present ODVS task required the subject to select the target from among distractors in visual space, hence, the selection of ‘what’ (i.e. target) and ‘where’ (i.e. target position) occurred during the cue period; this process was followed by a visuospatial mnemonic process for target location during the delay period. Indeed, cue-related activity for the target was greater for the ODVS than for the ODR task, which suggests that target selection occurs during the cue period (see Hasegawa et al., 2000). This is also supported by the fact that the onset latency of the saccadic response in the OVS task was significantly longer than that in the OD task; these tasks required the subject to respond immediately after cue appearance. The subsequent delay period in the ODVS task is considered to be associated with mnemonic processes.
Fig. 4
Fig. 5. A 'DR-neuron' that showed directional delay-period activity in both the ODVS and ODR tasks. (A) Neuronal activity for the ODVS task. (B) Neuronal activity for the ODR task. This neuron showed directional delay-period activity, with maximal activity for the 180° target direction in both the ODVS and ODR tasks. The format is the same as in Fig. 4.
for visuospatial information (target location) that has been selected by the target selection process during the cue period, and the attentional/arousal level in the delay period should be similar between the ODVS and ODR tasks, as suggested by the behavioral data. Thus, VS-neurons may play a more specialized role than DR-neurons; i.e. they retain the visuospatial information (target location) identified by the target selection process during the cue period.

VS-neurons are in some regards similar to the neurons described by Rainer et al. (1998). They showed that neurons in the dorsolateral PFC are involved in object
target selection using a delayed matching-to-sample task. More recently, Hasegawa et al. (2000) demonstrated that neurons in the dorsolateral PFC are involved in visuospatial target selection, using an ODVS task similar to the present task. The present results are consistent with these findings that neurons in the dorsolateral PFC are involved in objective and visuospatial target selection; i.e. in the selection of ‘what’ and ‘where’ information. However, the present findings should be novel and noteworthy, since PFC neurons with directional delay-period activity were divided into DR- and VS-neurons, thus providing the first significant evidence that the dorsolateral PFC contains a particular group of neurons that is specifically involved in mnemonic processes for selected information by target selection; i.e. visuospatial mnemonic processes associated with target selection.

4.3. Attention-memory system

The visual search paradigm is thought to require visuospatial selective attention to select a target from distractors in visual space (Schall et al., 1995; Chelazzi et al., 1998; Hasegawa et al., 2000; for a review, see Desimone and Duncan, 1995). Our ODVS paradigm requires visuospatial target selection during the cue period and memorization of the selected information during the delay period. VS-neurons may be involved in this particular memory process to form an ‘attention-memory system’ or ‘visuospatial memory system for special use’; i.e. a visuospatial memory system specifically used for information identified by target selection (selective attention) processes. In addition, the temporal properties (i.e. onset latency and peak time) and spatial tuning of delay-period activity were similar in VS- and DR-neurons. Thus, it is likely that the attention-memory system is represented in the dorsolateral PFC, in parallel with a more ‘general’ visuospatial memory system (or ‘memory system for general use’) that is not specifically associated with target selection processes, as schematically illustrated in Fig. 11. This hypothesis is also supported by the fact that no neurons predominantly showed directional delay-period activity during performance of the ODR task; a system that is particularly applied in ODR task performance does not appear to be represented in the dorsolateral PFC. The attention-memory system would be specifically recruited when attention-demand is high to control interference information and to determine the target location to be memorized. Since memory is impaired by interference information and the brain must use a mechanism to
eliminate such interference (Mishkin and Delacour, 1975), this particular memory system formed by VS-neurons may help to eliminate interference information and may comprise at least part of this mechanism.

It has been demonstrated that the posterior parietal cortex plays a major role in target selection/selective attention in visual space (for a review, see Colby and Goldberg, 1999) and the FEF also participates in this function (Schall and Hanes, 1993; Schall et al., 1995). These areas are strongly connected to the dorsolateral PFC (Petrides and Pandya, 1984; Arikuni et al., 1988; Watanabe-Sawaguchi et al., 1991). Therefore, it is likely that target selection may occur in these areas and the dorsolateral PFC receives the information selected by these areas. These cortical areas should collaborate to select spatially relevant information in clusters to guide appropriate behavior. Among these areas, the dorsolateral PFC may play a particular role in retaining selected information for a while to guide goal-directed motor acts, since this area plays a major role in working memory for guiding appropriate behavior in a given situation (for reviews, see Funahashi and Kubota, 1994; Fuster, 1998). We suggest that the attention-memory system may be a critical/central system in working memory, since this cognitive function has been considered to be closely associated with attentional processes to select relevant information by controlling/eliminating various interference information (Baddeley, 1986, 1992). However, since the physical features of the target and distractors, as well as the number of distractors, were limited in the present study, further studies are required to further develop our conclusions.

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**Fig. 10.** Examples of delay-period activities of a VS- (A) and DR-neurons (B) during the ODVS-S (upper), ODVS-C (middle) and ODR (lower) tasks. For simplicity, neuronal activities for the preferred direction (180° for (A) and 300° for (B)) are shown. Conventions are the same as in Fig. 4.

**Fig. 11.** Hypothetical model of attention-memory and general memory system in the dorsolateral PFC. When visuospatial information comes with distractors (i.e. attentional demand is high), both attention- and general memory systems are recruited, whereas without distractors, only the general memory system is recruited.
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