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Prefrontal Activity During Serial Probe Reproduction Task: Encoding, Mnemonic, and Retrieval Processes

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Inoue, Masato and Akichika Mikami. Prefrontal activity during serial probe reproduction task: Encoding, mnemonic, and retrieval processes. *J Neurophysiol* 95: 1008–1041, 2006. First published October 5, 2005; doi:10.1152/jn.00552.2005. To study the prefrontal neuronal mechanism for the encoding and mnemonic processing of multiple objects, the order of object presentation, and the retrieval of an object among objects in the working memory, we recorded neuronal activity from the lateral prefrontal cortex while two monkeys performed the serial probe reproduction task. In the task, two objects (C1 and C2) were presented sequentially interleaved with a delay (D1) period, and after the second delay (D2) period, a color cue was presented. Monkeys were trained to select one target object on the basis of the color stimulus. During the C1 and C2 periods, we found responses that depended on the order of presentation (order-selective response). During the D1 and/or D2 periods, two-thirds of the neurons with object-selective delay-period activity showed order-selective activity coding either C1 or C2. Neurons with larger response magnitudes during the C2 period showed order-selective delay-period activity during the D2 period. These order-selective responses during the C2 period could also contribute to order-selective delay-period activity, and order-selective delay-period activity during the D1 and D2 periods could play an essential role in storing information on both the object and the temporal order of presentation. During the color cue period, two-thirds of the neurons with responses showed target object selectivity (CT and T responses), although the target object was not presented during this period. The CT and T responses could play a critical role in the retrieval of an item among various items in the working memory.

INTRODUCTION

Previous studies provided evidence that the lateral prefrontal cortex is involved in memory for temporal order. Patients with lesions involving the mid-dorsolateral prefrontal cortex perform more poorly than control subjects or patients with other cortical lesions in a task requiring judgment on which of two items was presented more recently (Kesner et al. 1994; McAndrew and Milner 1991; Milner 1971; Milner et al. 1991; Shimamura et al. 1990). Animal lesion studies also strongly implicated the prefrontal cortex in temporal order memory. Petrides (1991) found that monkeys with lesions involving the mid-dorsolateral prefrontal cortex were impaired in judging the order of object stimuli that had been presented in the middle of a list of objects. Similarly, rats with medial prefrontal lesions performed poorly on tests of temporal order memory for spatial locations (Chiba et al. 1994; Kesner and Holdbrook 1987). These studies of humans and animals with focal brain damage support the idea that the prefrontal cortex plays an important role in memory for temporal order.

On the other hand, many electrophysiological studies have provided evidence that the lateral prefrontal cortex participates in the process of temporary storage of spatial or object information (Chafee and Goldman-Rakic 1998; Constantinidis et al. 2001; di Pellegrino and Wise 1991, 1993; Funahashi et al. 1989, 1993b; Fuster 1973; Fuster et al. 1982; Kubota and Niki 1971; Kubota et al. 1974; Miller et al. 1996; Niki 1974; Niki and Watanabe 1976; Rainer et al. 1998a; Rao et al. 1997; Sawaguchi and Yamane 1999; Takeda and Funahashi 2002; Watanabe 1981; Wilson et al. 1993). Tonic delay-period activity with directional selectivity or object selectivity has been considered to be a neuronal correlate of temporal storage mechanism for spatial or object information in the prefrontal cortex.

A few studies showed prefrontal neuronal activities when monkeys retain information on multiple items simultaneously. Barone and Joseph (1989) recorded prefrontal neuronal activities while a monkey performed a delayed-response task in which a monkey was required to memorize three target positions and the temporal order of presentation and to respond by performing sequential saccades and hand-reaching movements toward the targets in the same temporal order. They found that one class of prefrontal neurons exhibit tonic activity with spatial and temporal selectivity, such that tonic activity was observed only when the first visual cue was presented at one particular position out of three. Funahashi et al. (1997) recorded prefrontal neuronal activities while a monkey performed a delayed sequential reaching task, in which the monkey is required to memorize two of three target positions and the temporal order of presentation and to respond by performing hand-reaching movements toward the targets in the same temporal order. They found two types of delay-period activity: position-dependent and pair-dependent activities. Position-dependent delay-period activity is a selective response to one of three positions. Most of the position-dependent activities arise when a cue is presented at a particular position in a particular temporal order. Pair-dependent delay-period activity is a selective response to a particular combination of two of three positions. Most of the pair-dependent activities arise when two cues are presented in a particular temporal order. Ninokura et al. (2003) found that 43% of delay-period activity is selective for the sequence in which visual objects are presented during the cue period. They further found that 31% of this activity was selective for only one of six sequences, and the remaining activity was selective for multiple sequences. These findings suggest that prefrontal neurons can retain information on mul-

tiple items (spatial positions or objects) and the temporal order of cue presentation. However, Ninokura et al. (2003) found the delay-period activity that was selective for multiple sequences, but they did not clarify what information was coded in this delay-period activity. In addition, Funahashi et al. (1997) and Ninokura et al. (2003) used tasks in which monkeys had to memorize spatial locations or objects and to respond by performing sequential movements toward memorized locations or objects, and analyzed neuronal activity during only delay period preceding the sequential movements. Thus these prefrontal neuronal activities could reflect the preparation for the first or second movement or sequential movements. Indeed, there were delay-period activities that coded the direction of movements rather than the location of the cue (Funahashi et al. 1993b; Niki and Watanabe 1976; Takeda and Funahashi 2002). To clarify the neuronal mechanism for the retention of information on multiple items simultaneously, it is necessary to dissociate memorized items and preparation for movements.

In this study, we introduced a serial probe reproduction (SPR) task, in which a monkey had to memorize two objects and their order of presentation, and one target object was selected from two memorized objects on the basis of a color stimulus. In this task, because the target object was determined on the basis of the color cue during the color cue period, monkeys could not determine the target object until the color cue period. Thus the memory during the first and second delay periods must be nothing else but the two objects and their order of presentation.

Previous studies indicated that neurons with cue-period and delay-period activities exhibited a similar spatial or object preference between the cue and delay periods, suggesting that the visual input to the prefrontal cortex plays an important role in contrasting delay-period activity (Funahashi and Inoue 2000; Funahashi et al. 1990; O'Scalaidhe et al. 1999). Recently, Ninokura et al. (2004) have found visual responses in the lateral prefrontal cortex that depend on both the object and the order of object presentation. However, because Ninokura et al. (2004) did not analyze the relationship between visual response and delay-period activity, the functional role of these responses in the process of encoding object information and temporal order information has not been clarified. To examine this issue, we analyzed prefrontal neuronal activities during the first and second cue periods of the SPR task and compared the visual response and delay-period activity.

In addition, the lateral prefrontal cortex (LPFC) plays a crucial role in response selection, which is the ultimate goal of purposeful behavior. Many studies showed that the responses of the prefrontal cortex to visual stimuli are related to the selection of an object from an array of objects (Hasegawa et al. 2000; Iba and Sawaguchi 2002) and the selection of forthcoming movements based on external stimuli (Hasegawa et al. 1998; Hoshi and Tanji 2004; Hoshi et al. 2000; Kim and Shadlen 1999; Sakagami and Niki 1994a,b; Sakagami and Tsutsui 1999; Sakagami et al. 2001; Watanabe 1986). These results suggest that the LPFC contributes to the retrieval of one object from the working memory. Although a few human neuroimaging studies showed that the LPFC is also involved in the retrieval of one item from the working memory (Rowe and Passingham 2001; Rowe et al. 2000), the neuronal mechanism for the retrieval of one item from the working memory in the LPFC has not been clarified. To investigate the neuronal

mechanism in the LPFC for this process, we analyzed neuronal activity during the color cue period of the SPR task. In this period, a monkey retrieves one object from two memorized objects. These data were reported elsewhere in abstract form (Inoue and Mikami 2001, 2002a,b, 2003).
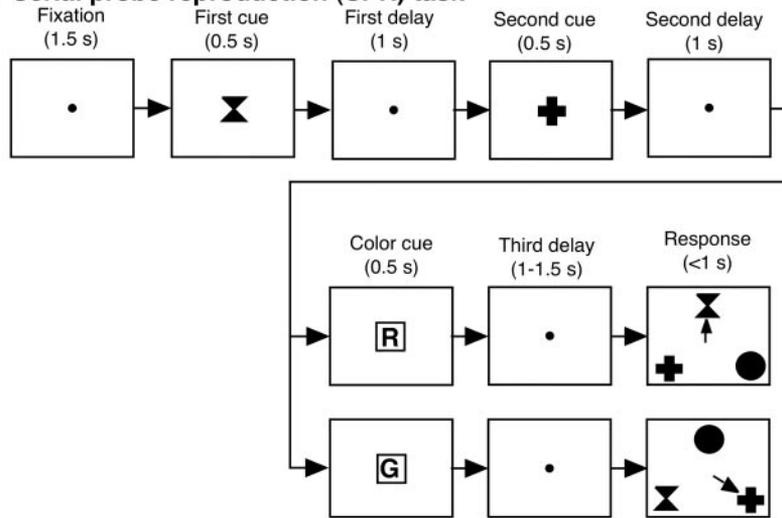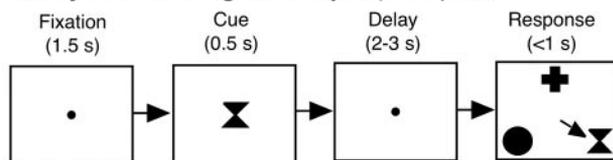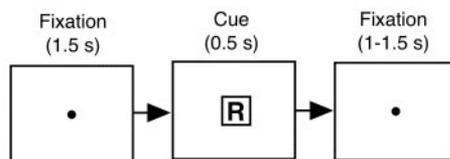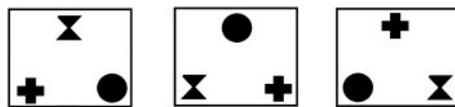
METHODS

Animals and apparatus

We used one male and one female rhesus monkey (*Macaca mulatta*; monkey G, 9 kg; monkey H, 5 kg). Experiments were conducted according to the Guide for the Care and Use of Laboratory Animals by the National Institute of Health and the Guide for the Care and Use of Laboratory Primates by the Primate Research Institute, Kyoto University.

The monkey was seated on a primate chair in a dark room, and a head-restraining device was fixed its head. It was trained to look at a 17-in CRT monitor (FlexScan T565, Nanao), which was placed 40 cm from its face. A computer (PC-9821Xa200, NEC) presented a fixation spot and a stimulus on the CRT monitor. The monkey's horizontal and vertical eye positions were sampled at 250 Hz with a monitoring system using an infrared camera (R-21C-AC, RMS Hirosaki). Sampled eye positions were fed into a computer (PC-9801BX, NEC) through an A/D converter to determine whether the monkey maintained its fixation and performed a correct saccade.

Behavioral task

The monkeys were trained to perform an SPR task (Fig. 1*A*). In this task, after a 1-s intertrial interval, a fixation spot (a white circle; 0.1° diam) was presented at the center of the monitor. After the monkey maintained its fixation for 1.5 s, the first object cue (C1), which was one of three objects (a double cone, a cross, and a circle, 3° × 3° in size), was presented at the center of the monitor for 0.5 s. After 1 s of the first delay (D1) period, the second object cue (C2), which was one of the two remaining objects, was presented at the center of the monitor for 0.5 s. After 1 s of the second delay (D2) period, a color cue (a red or a green rectangle, 3° × 3°) was presented at the center of the monitor for 0.5 s. The presentation of a color cue was followed by the third delay (D3) period of 1–1.5 s. Then the three objects were presented in the upper, lower left, and lower right positions at 9° of eccentricity from the center of the monitor. The fixation spot was extinguished simultaneously. When the color cue was red, the monkey had to perform a saccade to the object presented as the first cue (C1), and when the color cue was green, the monkey had to perform a saccade to the object presented as the second cue (C2). We prepared three patterns of arrangement of target objects (Fig. 1*D*), and one of the patterns was randomly selected during the response period. Therefore the monkeys could not determine the spatial location to which a saccade should be performed until the appearance of objects during the response period.

The monkeys also performed a delayed-matching-to-sample (DMS) task (Fig. 1*B*). In this task, after a 1-s intertrial interval, a fixation spot (a white circle; 0.1° diam) was presented at the center of the monitor. After the monkey maintained its fixation for 1.5 s, the object cue, which was one of three objects (a double cone, a cross, and a circle, 3° × 3° in size), was presented at the center of the monitor for 0.5 s. After 2–3 s of the delay period, the three objects were presented in the upper, lower left, and lower right positions from the center of the monitor at 9° of eccentricity. The fixation spot was extinguished simultaneously. The monkey had to perform a saccade to the object presented as the object cue. We prepared three patterns of arrangement of target objects (Fig. 1*D*), and one of the patterns was randomly selected during the response period. Therefore the monkeys could not determine the spatial location to which a saccade should be performed until the appearance of objects during the response period.

FIG. 1.   Sequence of trial events of serial probe reproduction (SPR) task (*A*), delayed-matching-to-sample (DMS) task (*B*), and fixation task (*C*). R and G indicate the red and green stimuli, respectively. *D*: arrangement of target objects during response period.

The monkeys also performed a fixation task (Fig. 1C), which allows the examination of neuronal activity when selection was not required. While the monkey maintained its fixation, we presented a color stimulus, which was the same as that used in the SPR task.

Surgical procedure

To fix the head during training, a head-restraining device was attached to the skull. Surgery was performed under aseptic conditions. The monkeys were first administered ketamine (10 mg/kg body weight) intramuscularly, and then an intravenous injection of pentobarbital sodium (20 mg/kg body weight). After partially exposing the skull, polycarbonate screws (3 mm in diameter and 5 mm in length) were used to attach firmly the head-restraining device to the skull. These screws and the head-restraining device were fixed with dental acrylic resin. The monkeys were administered systemic antibiotics for 1 wk after surgery and were allowed free access to water and chow for at least 1 wk after surgery.

After the training was completed, surgery for attaching a recording chamber was performed under aseptic conditions. We performed MRI before surgery, and on the basis of this MRI, we determined the stereotaxic position of the principal sulcus. The position of the recording chamber (anterior-posterior = 32 mm and lateral = 18 mm) was determined by this sterotaxic coordination.

Training procedure

The monkeys were first trained to perform the DMS task. When the monkeys showed an 80% correct performance or higher for 2 wk, the monkeys were trained to perform the SPR task. The SPR task training was divided into three stages. In stage 1, the monkeys were trained to perform the red cue trials, in which the monkeys had to select the C1 object. During the early period of training, the duration of C2 presentation was 100 ms. When the monkeys showed a 70% correct performance or higher for 2 wk, the duration of C2 presentation was progressively extended to 500 ms. In stage 2, monkeys were trained to perform the green cue trials, in which the monkeys had to select the C2 object. During the early period of training, the duration of C1 presentation was 100 ms. When the monkeys showed a 70% correct performance or higher for 2 wk, the duration of C1 presentation was progressively extended to 500 ms. In stage 3, we intermingled the red cue trials and green cue trials. The training was considered completed

when the monkeys showed a 70% correct performance or higher for 2 wk. The training process was completed in ~18 (monkey G) and 24 (monkey H) mo.

Recording procedure and data analysis

Neuronal activity was recorded using glass-coated Elgiloy microelectrodes (1–2 MΩ). Single-neuronal activity was isolated and converted to pulses by a window discriminator (DIS-1, BAK), and stored with task events as a data file on a hard disk. Recording sites were determined by MRI. The dorsolateral prefrontal cortex (DLPFC) was defined as the region dorsal to the principal sulcus, and the ventrolateral prefrontal cortex (VLPFC) was defined as the region ventral to the principal sulcus (Fig. 2). To determine whether the recording site was in the frontal eye field, we applied intracortical microstimulation (ICMS) through the tips of inserted electrodes (22 pulses of 0.25-ms duration at 333 Hz; current intensity, 100 μA). In this study, there were no recording sites where ICMS evoked saccades.

In this study, we analyzed neuronal activity during the C1 and C2 periods, D1 and D2 periods, color cue period, and D3 period. When we analyzed neuronal activity during the C1 and C2 periods, six perievent time histograms triggered by the onset of the C1 and C2

Monkey G

Monkey H

○ DLPF
● VLPF

FIG. 2. Surface location of recording sites of neurons. Surface images were obtained by MRI performed before training. ○, recording sites in the dorsolateral prefrontal cortex (DLPFC); ●, recording sites in the ventrolateral prefrontal cortex (VLPFC). AS, arcuate sulcus; PS, principal sulcus.

were constructed for each stimulus: a double cone, a cross, and a circle (bin width, 10 ms). From these histograms, when a neuron exhibited an excitatory response during the C1 and/or C2 period, the histogram with the highest peak value for the C1 and C2 periods was chosen for determining the response window. In this histogram, the starting point of response (the time at which the 1st 3 consecutive bins differed from the discharge rates for 1 s before the cue presentation by >2 SD or <2 SD) and the endpoint of response (the time of the last bin) were determined. The time from the onset of the cue to the starting point of the response was taken as onset latency. When the discharge rate during the response window of the cue period differed significantly (Mann-Whitney U test) from that of the fixation period (for 1 s before the 1st cue period), we concluded that the neuron exhibited a response. When the starting and the endpoints of response could not be determined, we calculated mean discharge rate from 100 ms after cue onset to the end of the cue period. We performed two-way ANOVA of responses during the C1 and C2 periods, in terms of the order (C1 or C2 period) and object (a double cone, a cross, or a circle) factors. When the difference in response in terms of the object factor was significant and the difference in response in terms of the order factor was not significant, we classified the response as object-selective and order-nonselective. When the difference in response in terms of the object factor was not significant and the difference in response in terms of the order factor was significant, we classified the response as object-nonselective and order-selective. When the difference in responses in terms of both the object factor and order factor were significant or the difference of interaction was significant, we classified the response as object-selective and order-selective. When the differences in responses in terms of both the object factor and order factor were not significant, we classified the response as object-nonselective and order-nonselective.

When we analyzed neuronal activity during the D1 and D2 periods, we constructed six histograms and rasters for each combination of C1 and C2 objects aligned at the start of the D1 and D2 periods. We calculated mean discharge rate during the last 1-s interval of the fixation period (control period) and the D1 and D2 periods. First, we analyzed neuronal activity during the D1 period when the mean discharge rate during the D1 period was significantly different from that during the control period (Mann-Whitney U test; $P < 0.05$); we considered that the neuron had a significant delay-period activity. We considered that delay-period activity was object-selective when the difference was significant as determined by ANOVA ($P < 0.05$).

A significant response during the D2 period was determined similarly (Mann-Whitney U test; $P < 0.05$). To determine whether delay-period activity during the D2 period depends on the C1 object, C2 object, or one sequence, we compared delay-period activities during the D2 period under six trial conditions by ANOVA. When the difference in delay-period activity under the six trial conditions was significant ($P < 0.05$), we compared the highest delay-period activity with other delay-period activities by a post hoc test (Fisher's PLSD) and determined whether delay-period activity was selective in only one sequence. Results showed that there were no neurons activated during the D2 period in only one of six sequences, and the delay-period activity depended on either the C1 object or the C2 object. We calculated selectivity index for the C1 object (SI_{C1}) and that for the C2 object (SI_{C2}). SI is defined as

$$SI_{C1} = 1 - |R_{C1pref, C2pref} - R_{C1pref, C2nonpref}| / (R_{C1pref, C2pref} + R_{C1pref, C2nonpref})$$

$$SI_{C2} = 1 - |R_{C1pref, C2pref} - R_{C1nonpref, C2pref}| / (R_{C1pref, C2pref} + R_{C1nonpref, C2pref})$$

where $R_{C1pref, C2pref}$ = firing rate of the highest delay-period activity during the D2 period, $R_{C1pref, C2nonpref}$ = firing rate in response to the same C1 object and a different C2 object during the D2 period, and $R_{C1nonpref, C2pref}$ = firing rate in response to a different C1 object and the same C2 object during the D2 period. If the delay-period activity depended on the C1 object, SI_{C1} is 1, and if the delay-period activity depended on the C2 object, SI_{C2} is 1. When SI_{C1} was greater than
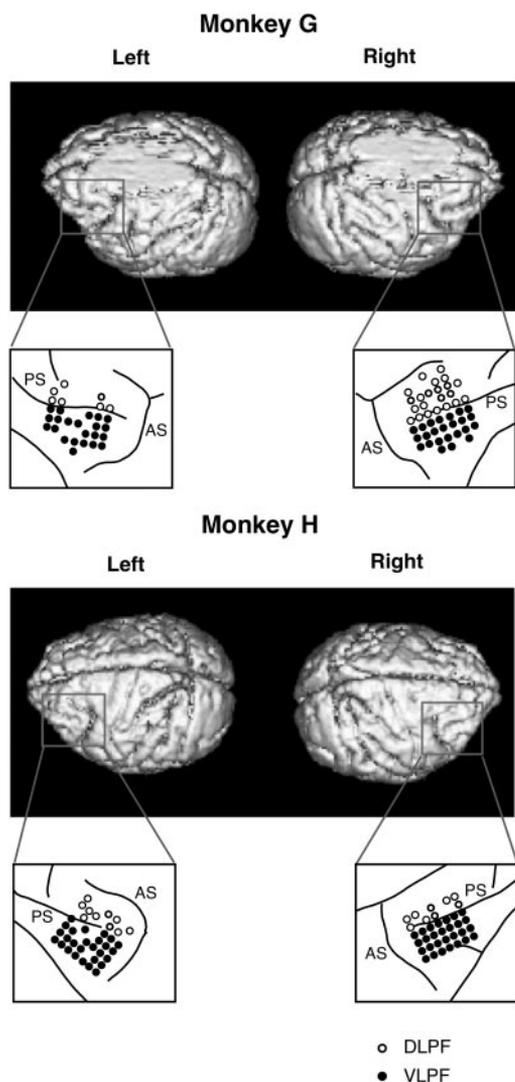
SI_{C2}, we defined that this delay-period activity depended on the C1 object, and when SI_{C2} was greater than SI_{C1}, we defined that this delay-period activity depended on the C2 object.

We classified object-selective delay-period activities into three types: order-nonselective activity, C1-coding activity, and C2-coding activity. In a neuron with order nonselective activity, delay-period activity during the D1 period depended on the C1 object, delay-period activity during the D2 period depended on the C2 object, and the preferred objects during the D1 and D2 periods were identical. In a neuron with C1-coding activity, delay-period activity during the D1 and/or D2 period depended on the C1 object. In a neuron with C2-coding activity, delay-period activity during the D1 period was not detected or object-nonselective, but delay-period activity during the D2 period depended on the C2 object.

When we analyzed neuronal activity during the color cue period, six averaged perievent time histograms (2 colors and 3 objects to which a saccade should be performed) triggered by the onset of the color cue were constructed (bin width, 10 ms). From these histograms, when a neuron exhibited an excitatory response, the histogram with the highest peak value was chosen for determining the response window, and when a neuron exhibited an inhibitory response, the histogram with the lowest peak value was chosen. In this histogram, the starting point of response (the time at which the 1st 3 consecutive bins differed from discharge rates for 1 s before the color cue presentation by >2 SD or <2 SD) and the endpoint of response (the time of the last bin) were determined. The time from the onset of the color cue to the starting point of the response window was taken as onset latency. When the discharge rate of a neuron during the response window of the color cue period differed significantly (Mann-Whitney U test) from that during the fixation period (for 1 s before the 1st cue period), we concluded that the neuron exhibited a response. We performed two-way ANOVA of the response magnitude during the color cue period in terms of the color (red or green) and target (object to which a saccade should be performed; a double cone, a cross, or a circle) factors. When the difference in response magnitude in terms of the color factor was significant and the difference in terms of the target factor was not significant, we considered the neuron as having a C response. When the difference in response magnitude in terms of the color factor was not significant and the difference in response magnitude in terms of the target factor was significant, we considered the neuron as having a T response. When the difference in response magnitude in terms of both the color factor and target factor were significant or the difference of interaction was significant, we considered the neuron as having a CT response.

When we analyzed neuronal activity during the D3 period, six averaged perievent time histograms (2 colors and 3 objects to which a saccade should be performed) triggered by the offset of the color cue were constructed (bin width, 50 ms). When the discharge rate of a neuron during the first 1 s of the D3 period differed significantly (Mann-Whitney U test) from that during the fixation period (for 1 s before the 1st cue period), we concluded that the neuron exhibited delay-period activity during the D3 period. We performed two-way ANOVA of delay-period activity during the D3 period in terms of the color (red or green) and the target (object to which a saccade should be performed; a double cone, a cross, or a circle) factors. When the difference in response magnitude in terms of the color factor was significant and the difference in response magnitude in terms of the target factor was not significant, we considered the neuron as having a C delay-period activity. When the difference in response magnitude in terms of the color factor was not significant and the difference in response magnitude in terms of the target factor was significant, we considered the neuron as having a T delay-period activity. When the difference in response magnitude in terms of both the color factor and target factor were significant or the difference of interaction was significant, we considered the neuron as having a CT delay-period activity.

RESULTS

Behavioral performance

Two monkeys performed the SPR task well but not perfectly. The chance level of this task is 33%, and the monkeys performed much higher than the chance level. We examined performance accuracy during trials for all recording sessions. The mean correct percent during recording trials was $75 \pm 5\%$ (SD) for monkey G and $70 \pm 3\%$ for monkey H. There was no tendency for direction preference, but there was tendency for object preference. Both monkeys performed better when the target object was a circle ($84 \pm 10\%$ for monkey G, $88 \pm 9\%$ for monkey H) than when the target object was a double cone ($70 \pm 6\%$ for monkey G, $62 \pm 6\%$ for monkey H) or a cross ($72 \pm 8\%$ for monkey G, $66 \pm 7\%$ for monkey G). Monkey G performed better in the trials in which the C2 object was the target ($86 \pm 7\%$) than in the trials in which the C1 object was the target ($66 \pm 6\%$). In contrast, for monkey H, there was no difference in performance between the trials in which the C1 object was the target ($69 \pm 5\%$) and the trials in which the C2 object was the target ($71 \pm 5\%$). The mean latencies for saccades from the onset of target object presentation were 284 ± 105 ms for monkey G and 260 ± 89 ms for monkey H.

Neuronal database

While two monkeys performed the SPR task, we recorded the activity of 611 single neurons from the DLPFC ($n = 173$) and the VLPFC ($n = 438$). Of these neurons, 483 responded during at least one epoch of the SPR task. Of these, 119 neurons showed a response during the C1 and/or C2 period, 183 neurons exhibited delay-period activity during the D1 and/or D2 period, 139 neurons showed a response during the color cue period, 260 neurons showed delay-period activity during the D3 period, and 361 neurons exhibited a response during the response period. In this paper, we focused on neuronal activity in the C1, D1, C2, D2, color cue, and D3 periods, and we will deal with the response period in a separate report.

Object-selective response during C1 and C2 periods

During the C1 and/or C2 periods, 119 neurons exhibited responses. Of these, 81 neurons showed the object-selective response during the C1 or C2 period. Of these, 22 neurons showed response magnitudes that were not significantly different between the C1 and C2 periods (order-nonselective). On the other hand, the magnitudes of responses of 59 neurons during the C1 and C2 periods were significantly different (order-selective). Of these neurons, 33 showed larger response magnitudes during the C1 period than during the C2 period (C1-dominant), and 26 showed larger response magnitudes during the C2 period than during the C1 period (C2-dominant).

Figure 3*A* shows the histograms of the C1-dominant response of a neuron. During the C1 period, the neuron exhibited a large response magnitude (36.92 spikes/s) to the circle, a small response magnitude (20.22 spikes/s) to the cross, and no response to the double cone. Although the activity slightly increased in all trial conditions toward the end of the D1 period, discharge rates during the D1 period were not significantly different from those during the control period. During
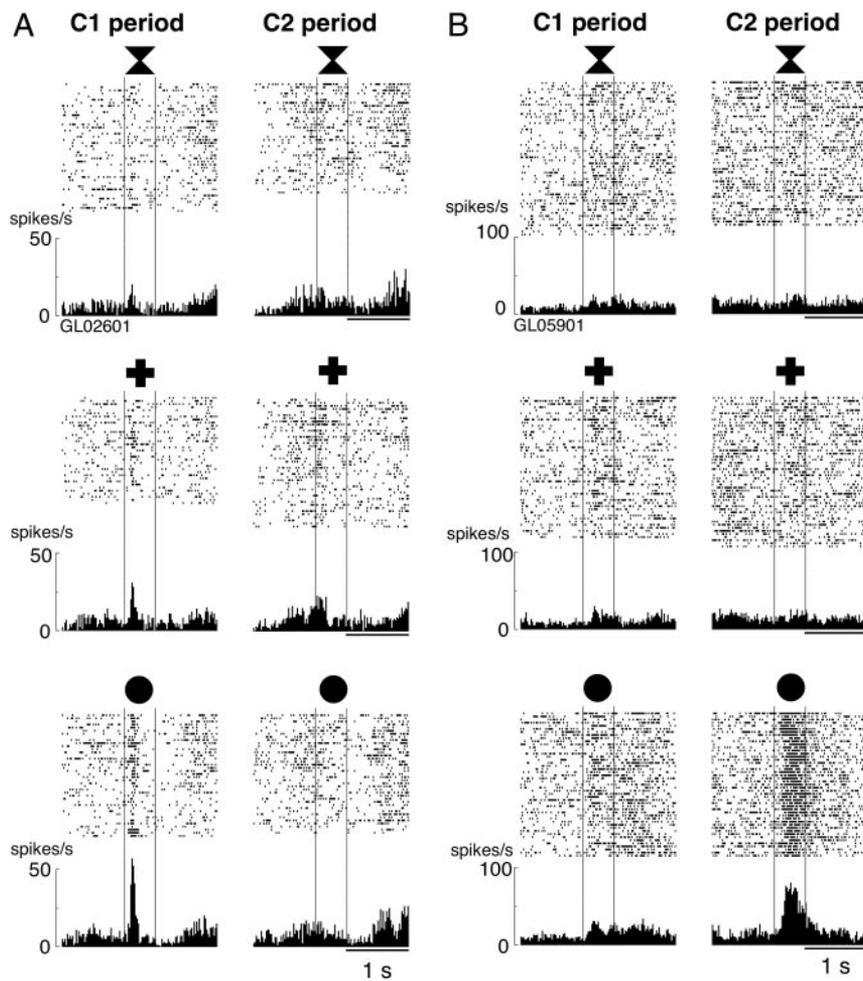
FIG. 3. Histograms of object-selective and order-selective responses. *A*: histograms of C1-dominant response of a neuron. The neuron exhibited response when the circle was presented during the C1 period but did not show response during C2 period. *B*: histograms of C2-dominant response of a neuron. The neuron exhibited a small response magnitude when the circle was presented during C1 period but showed a large response magnitude when the circle was presented during C2 period. Bin width is 20 ms.

the C2 period, this neuron did not respond to any of the three visual stimuli. The difference in response magnitude was significant in terms of both the object [$F(2,228) = 8.62$, $P < 0.0005$] and order factors [$F(1,228) = 29.72$, $P < 0.0001$]. Therefore this neuron was considered as having the C1-dominant response, and we defined the circle as the preferred object of this neuron.

Figure 3*B* shows an example of the C2-dominant response. During the C1 period, the neuron showed a small response magnitude when the circle was presented (27.03 spikes/s). During the C2 period, the neuron exhibited a large response magnitude when the circle was presented (60.44 spikes/s). During the D1 and D2 periods, this neuron also exhibited delay-period activity after the presentation of the circle. The difference in response magnitude between the C1 and C2 periods was significant in terms of both the object [$F(2,280) = 87.72$, $P < 0.0001$] and order factors [$F(1,280) = 38.44$, $P < 0.0001$]. Therefore this neuron was considered as having the C2-dominant response, and we defined the circle as the preferred object of this neuron.

To compare the temporal profiles of the order-nonselective, C1-dominant, and C2-dominant responses, we constructed population histograms of these responses (Fig. 4*A*). Neurons with the order-nonselective response showed large responses to the preferred object presented during both C1 and C2 periods (Fig. 4*A*, black lines). Neurons with the

C1-dominant and C2-dominant responses showed large responses to the preferred object presented during the C1 and C2 period, respectively. Although these differential responses depended on the object and/or the order of presentation, the temporal profiles of the order-nonselective, C1-dominant, and C2-dominant responses were similar. Figure 4*B* shows the cumulative summation curves of the latencies of the order-nonselective, C1-dominant, and C2-dominant responses. During the C1 period, the mean latencies of responses were 137 ± 44 (order-nonselective), 124 ± 34 (C1-dominant), and 127 ± 51 ms (C2-dominant). During the C2 period, the mean latencies of responses were 160 ± 45 (order-nonselective), 137 ± 70 (C1-dominant), and 141 ± 56 ms (C2-dominant). Although the difference in latency among these responses was not statistically significant [$F(2,123) = 1.48$, $P > 0.05$], the latencies of the C1-dominant and C2-dominant responses were slightly shorter than that of the order-nonselective response. The durations of these responses were also not different. During the C1 period, the mean durations of responses were 172 ± 25 (order-nonselective) and 156 ± 15 ms (C1-dominant). During the C2 period, the mean durations of responses were 154 ± 21 (order-nonselective) and 157 ± 14 ms (C2-dominant). The difference in durations among these responses was not statistically significant [$F(2,123) = 0.06$, $P > 0.05$].

A

Order-nonselective response

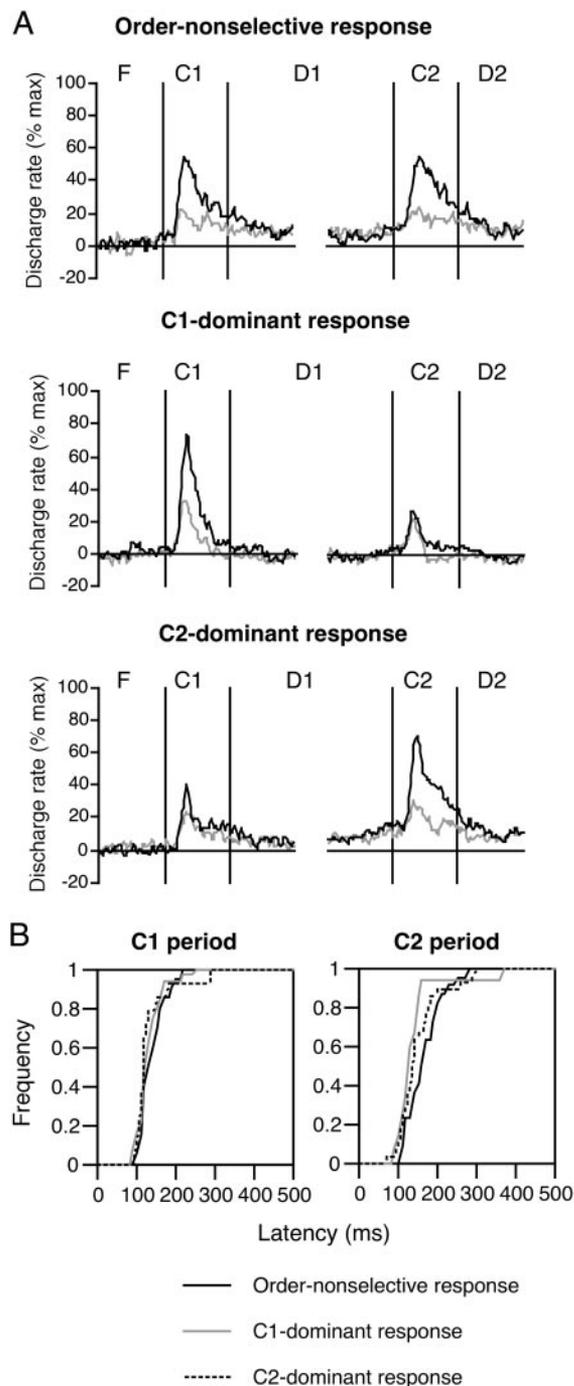### C1-dominant response

C2-dominant response

B

FIG. 4. *A*: population activities in preferred object trials (black) and non-preferred object trials (gray) of neurons with order-nonselective, C1-dominant, and C2-dominant responses. F, fixation period; C1, 1st cue period; D1, 1st delay period; C2, 2nd cue period; D2, 2nd delay period. *B*: cumulative summation curve of latencies of order-nonselective, C1-dominant, and C2-dominant responses during C1 and C2 periods.

For the order-nonselective response, the significant difference in response magnitude appeared 120 ms after the C1 onset and 140 ms after the C2 onset. For the C1-dominant response, the significant difference in response magnitude appeared 110 ms after the C1 onset, but could not be detected during the C2 period. For the C2-dominant response, the significant difference in response magnitude appeared 120 ms after the C2 onset, but could not be detected during the C1 period.

C1 objects modulated responses during C2 period

We examined whether responses during the C2 period were affected by the C1 object. Among neurons with the C1-dominant response ($n = 33$), most of these neurons ($n = 32$) did not show a significant difference in response magnitude during the C2 period depending on the C1 object presented (Mann-Whitney *U* test, $P < 0.05$). Among neurons with the C2-dominant response ($n = 26$), 35% ($n = 9$) showed a significant difference in response magnitude during the C2 period depending on the C1 object presented (Mann-Whitney *U* test, $P < 0.05$).

Figure 5 shows an example of the C2-dominant response of a neuron that varied depending on the C1 object presented. As shown in Fig. 5*A*, the neuron exhibited the response when the cross was presented, and the response magnitude during the C2 period (34.43 spikes/s) was significantly larger than that during the C1 period (16.49 spikes/s). The magnitude of response to the cross during the C2 period varied significantly with the C1 (Fig. 5*B*). When the double cone was presented during the C1 period, the magnitude of response to the cross during the C2 period was 22.31 spikes/s. When the circle was presented during the C1 period, the magnitude of response to the cross during the C2 period was 46.15 spikes/s. These response magnitudes were significantly different ($z = 4.13$; $P < 0.0001$).

Object-selective response during DMS task

Order-selective response magnitudes were significantly different between the C1 period and C2 period. This difference

A

SPR task

B

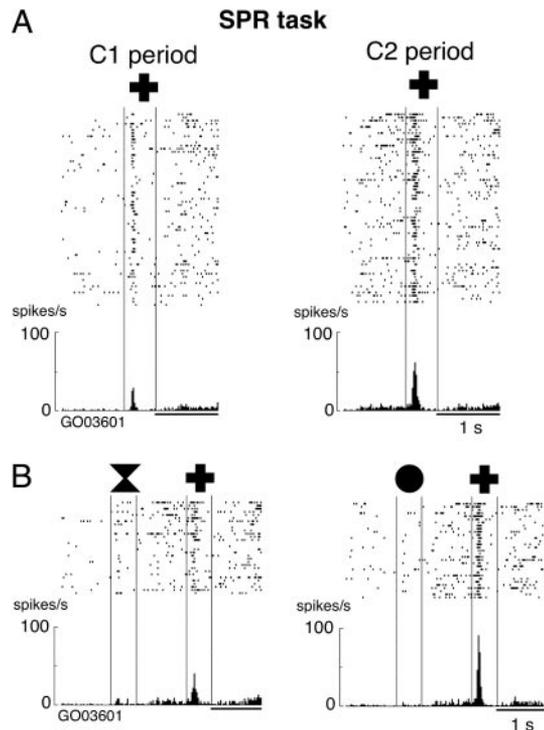FIG. 5. Histograms of C2-dominant responses of a neuron that varied with C1 object. The neuron showed response when the cross was presented, and magnitude of response during C2 period was larger than that during C1 period (*A*). Response magnitude during C2 period when the double cone was presented during C1 period was significantly different from that when the circle was presented during C1 period (*B*).

could be caused by the enhancement or suppression of responses during the C1 or C2 period. To test this hypothesis, we compared responses during the SPR task with those during the DMS task. Figure 6*A* shows the C1-dominant response of a neuron during the SPR task and that during the DMS task. The neuron responded when the double cone was presented during

the C1 period (34.92 spikes/s), but did not respond when the same double cone was presented during the C2 period. During the DMS task, the magnitude of response to the double cone (35.61 spikes/s) was similar to that during the C1 period of the SPR task. The response magnitude during the cue period of the DMS task was not significantly different (Mann-Whitney *U*
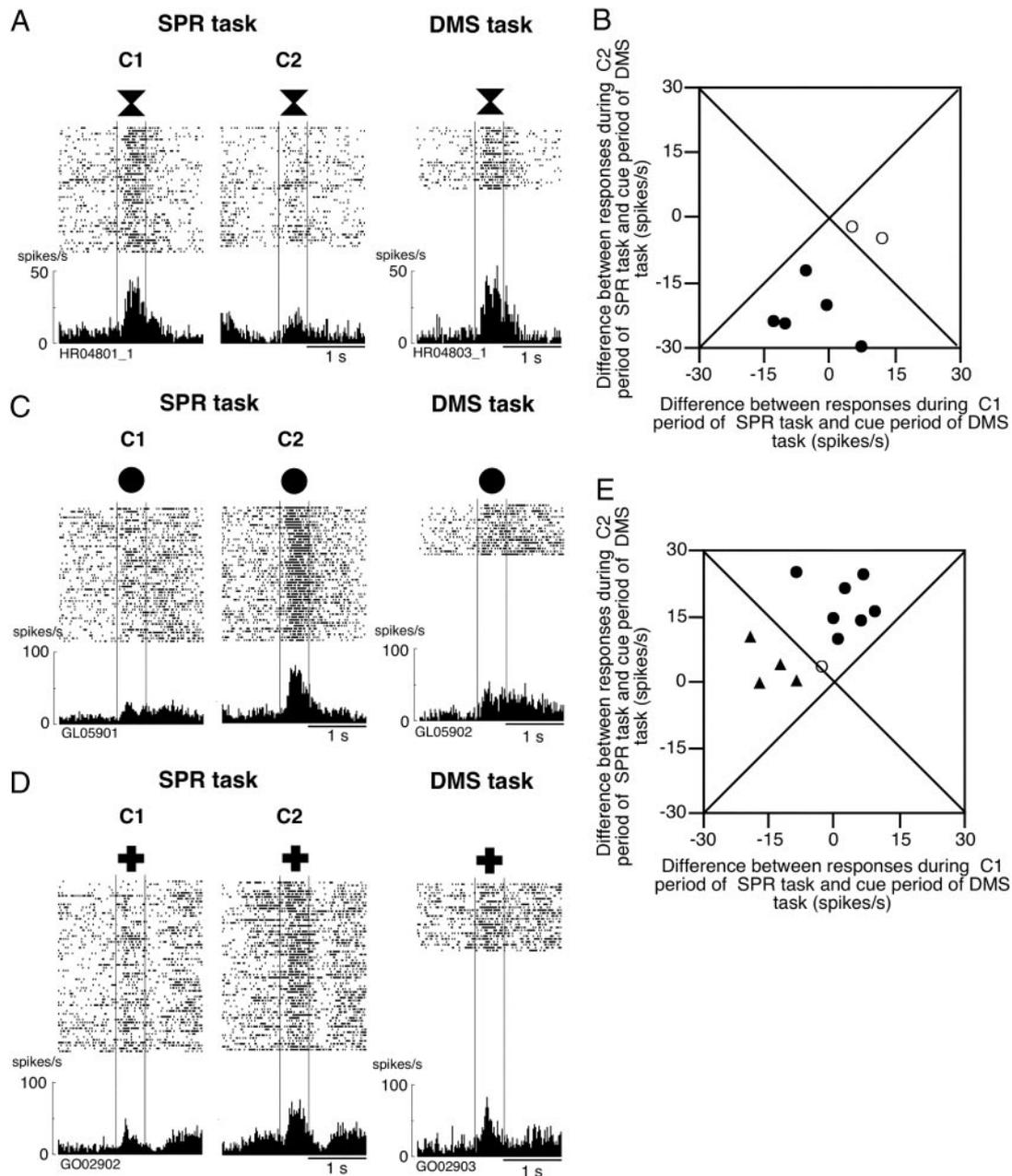

FIG. 6. *A*: histograms of C1-dominant response during SPR task and response during DMS task. Response magnitude during the DMS task was similar to that during C1 period of the SPR task. *B*: relationship between C1 and C2 periods of SPR task and DMS task. A closed circle shows that response magnitude during the DMS task was not significantly different ($P > 0.05$) from that during the C1 period of the SPR task and was significantly larger ($P < 0.05$) than that during C2 period of the SPR task. An open circle shows that response magnitude during the DMS task was not significantly different ($P > 0.05$) from that during C1 and C2 periods of the SPR task. *C*: histograms of C2-dominant response during SPR task and response during DMS task. Response magnitude during the DMS task was similar to that during C1 period of the SPR task. *D*: another example of C2-dominant response during the SPR task and response during the DMS task. Response magnitude during the DMS task was similar to that during C2 period. *E*: relationship among responses during C1 and C2 periods of SPR task and during DMS task. A closed circle shows that response magnitude during the DMS task was not significantly different ($P > 0.05$) from that during C1 period of the SPR task and was significantly smaller ($P < 0.05$) than that during C2 period of the SPR task. A closed triangle shows that response magnitude during the DMS task was not significantly different ($P > 0.05$) from that during C2 period of the SPR task and was significantly larger ($P < 0.05$) than that during C1 period of the SPR task. An open circle shows that response magnitude during the DMS task was not significantly different ($P > 0.05$) from that during C1 and C2 periods of the SPR task.

test, $z = 0.03$, $P > 0.05$) from that during the C1 period of the SPR task, and was significantly larger ($z = 4.18$; $P < 0.0001$) than that during the C2 period of the SPR task. Among seven tested neurons with the C1-dominant response, five showed a similar response magnitude during the DMS task to that during the C1 period of the SPR task (Fig. 6B).

Figure 6C shows an example of the C2-dominant response of a neuron during the SPR task and that during the DMS task. The neuron exhibited a small response magnitude (27.03 spikes/s) during the C1 period and a large response magnitude (60.44 spikes/s) during the C2 period when the visual cue was a circle. During the DMS task, this neuron exhibited a small response magnitude (35.12 spikes/s) similar to that during the C1 period in the SPR task. The response magnitude of this neuron during the cue period of the DMS task was not significantly different ($z = 1.83$, $P > 0.05$) from that during the C1 period of the SPR task and was significantly smaller ($z = 4.68$, $P < 0.0001$) than that during the C2 period of the SPR task. Figure 6D shows another example of the C2-dominant response during the SPR task and that during the DMS task. This neuron exhibited a small response magnitude (31.44 spikes/s) during the C1 period and a large response magnitude (60.84 spikes/s) during the C2 period. During the DMS task, this neuron exhibited a response magnitude (50.52 spikes/s) similar to that during the C2 period in the SPR task. The response magnitude of this neuron during the cue period of the DMS task was significantly larger ($z = 2.83$, $P < 0.005$) than that during the C1 period of the SPR task and not significantly different ($z = 1.33$, $P > 0.05$) from that during the C2 period of the SPR task. Among 12 tested neurons with the C2-dominant response, 7 showed a significant increase in response magnitude during the C2 period and 4 showed a significant decrease during the C1 period (Fig. 6E).

Object-selective response during C1 and C2 periods in error trials

To evaluate the behavioral significance of neuronal activity, we examined neuronal activity when the monkeys incorrectly performed. Although we observed two types of error in the SPR task, breaking the fixation during the cue or delay period and making a saccade to an incorrect target object during the response period, we analyzed error trials in which the monkeys had to make a saccade to a preferred object but made a saccade to an incorrect object.

To evaluate the behavioral significance of the object-selective and order-selective responses during the C1 and C2 periods in encoding information regarding the object and order of presentation, we compared the response to the preferred object in the correct trials with that in the error trials. The order-nonselective response magnitudes in the correct trials were not significantly different from those in the error trials during both the C1 (Wilcoxon signed-rank test, $z = 0.43$, $P > 0.05$, mean $= 31.87$ spikes/s in correct trials, mean $= 30.76$ spikes/s in error trials) and the C2 ($z = 1.61$, $P > 0.05$, mean $= 35.26$ spikes/s in correct trials, mean $= 33.73$ spikes/s in error trials) periods (Fig. 7A). The C1-dominant response magnitudes in the correct trials were also not significantly different from those in the error trials during both the C1 ($z = 0.64$, $P > 0.05$, mean $= 47.35$ spikes/s in correct trials, mean $= 46.68$ spikes/s in error trials) and the C2 ($z = 0.27$, $P > 0.05$, mean $= 30.88$
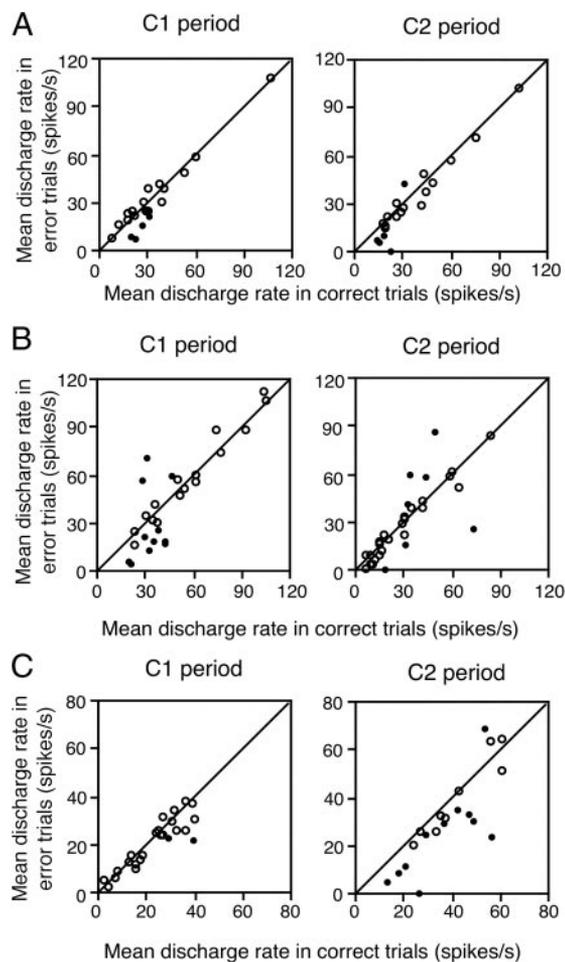

FIG. 7. Comparison of responses during correct trials and error trials. *A*: order-nonselective response during C1 and C2 periods in correct and error trials. Mean discharge rates during the C1 and C2 periods in correct and error trials were not significantly different. *B*: C1-dominant response in correct and error trials. Mean discharge rates in correct and error trials were not significantly different during C1 and C2 periods. *C*: C2-dominant response in correct and error trials. Mean discharge rates in correct and error trials were significantly different during C2 period but not significantly different during C1 period. Closed circles show discharge rate of neurons whose responses were significantly different between correct and error trials (Mann-Whitney *U* test, $P < 0.05$). Open circles show discharge rate of neurons whose responses were not significantly different between correct and error trials ($P > 0.05$).

spikes/s in correct trials, mean $= 29.63$ spikes/s in error trials) periods (Fig. 7B). C2-dominant response magnitude (Fig. 7C) was not significantly different between the correct and error trials during the C1 period ($z = 1.01$, $P > 0.05$, mean $= 22.51$ s/s in correct trials, mean $= 21.00$ spikes/s in error trials), but was significantly smaller in the error trials than in the correct trials during the C2 period ($z = 2.50$, $P < 0.05$, mean $= 38.20$ spikes/s in correct trials, mean $= 31.48$ s/s in error trials).

Object-nonselective response during C1 and C2 periods

Thirty-eight neurons showed the object-nonselective response. Of these, 17 neurons showed the order-nonselective response, and 21 neurons showed the C1-dominant response. No neurons showed the C2-dominant response.

To compare the temporal profiles between the object-selective and object-nonselective responses, we constructed the

histograms of these population activities (Fig. 8*A*). We could not find differences in latency and duration between the object-selective and object-nonselective responses in the order-nonselective response. However, in the C1-dominant response, the latency of the object-selective response was slightly shorter than that of the object-nonselective response. Figure 8*B* shows the difference in response latency. Neurons with the object-selective and order-selective responses were activated early, and the latencies of the object-nonselective and order-nonsel-lective responses were slightly longer.

Object-selective delay-period activity during D1 and D2 periods

One hundred eighty-three neurons were activated during the D1 and/or D2 period. Of these, 52 neurons exhibited object-nonselective delay-period activity during the D1 and/or D2 period. In the remaining 131 neurons, delay-period activity during the D1 and/or D2 period showed object selectivity. We classified these delay-period activities into three types: order-nonselective activity, C1-coding activity, and C2-coding activity.

Figure 9*A* shows the histograms of the order-nonselective delay-period activity of a neuron. The neuron exhibited delay-period activity during the D1 period when the C1 object was a circle (Fig. 9, *A,* trial conditions 5 and 6, and *B*). This delay-period activity during the D1 period was object-selective [$F(2,142) = 73.29$, $P < 0.0001$], and the activity returned to the baseline level after the appearance of the C2 object. During the D2 period, this neuron exhibited delay-period activity after the circle was presented as C2 (Fig. 9, *A,* trial conditions 2 and 4, and *C*). When the double cone or the cross was presented as C2, this neuron showed an increase in activity at the end of the D2 period (Fig. 9*A,* trial conditions 1, 3, 5, and 6), and discharge rates during the D2 period of these trials were not significantly different from those during the control period (Fig. 9*C*). The delay-period activity during the D2 period had selectivity [$F(5,139) = 57.41$, $P < 0.0001$]. This neuron showed the highest delay-period activity during the D2 period in trial condition 4, and this delay-period activity was significantly different ($P < 0.05$) from those in trial conditions 1, 3, 5, and 6, and not significantly different ($P > 0.05$) from that in trial condition 2. This indicates that this delay-period activity
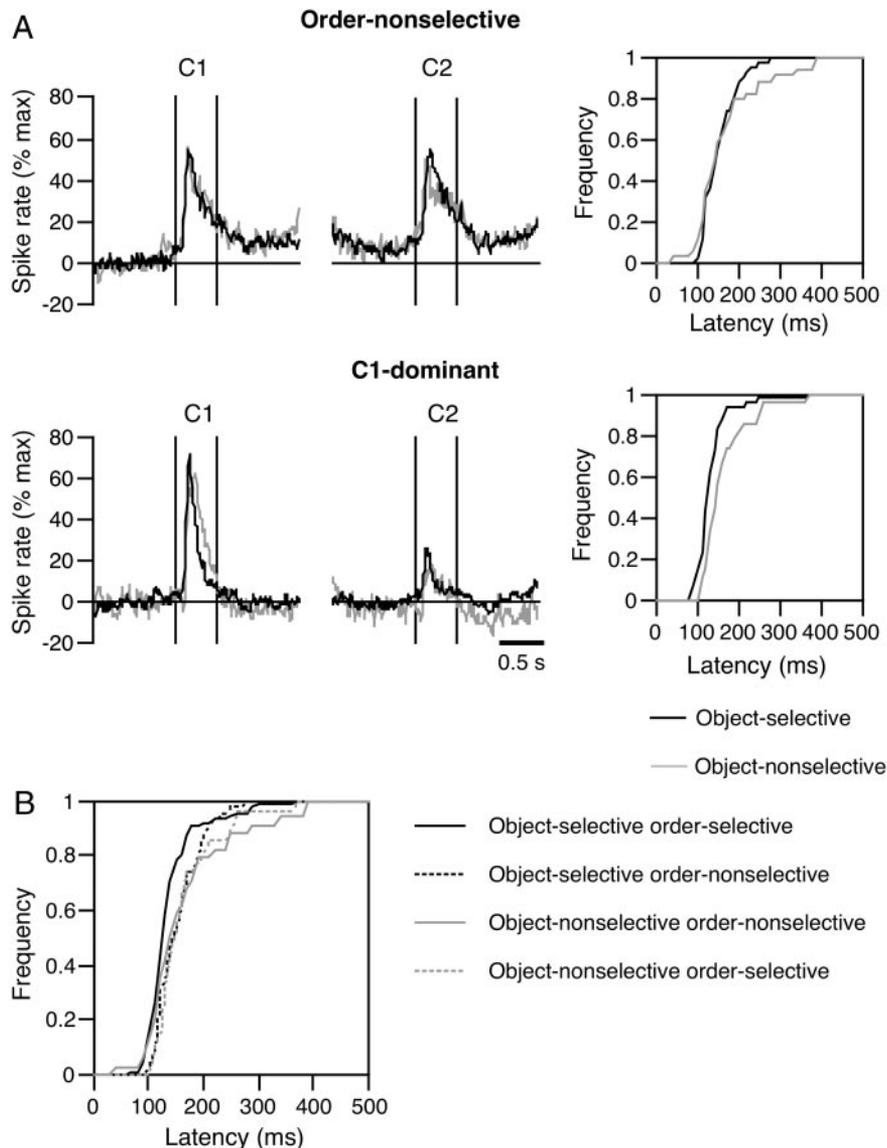

FIG. 8.   *A*: population activities of neurons with object-selective (black) and object-nonselective (gray) responses during C1 and C2 periods, and cumulative summation curve of latencies of object-selective and object-nonselective visual response. *B*: cumulative summation curve of latencies of 4 types of response.
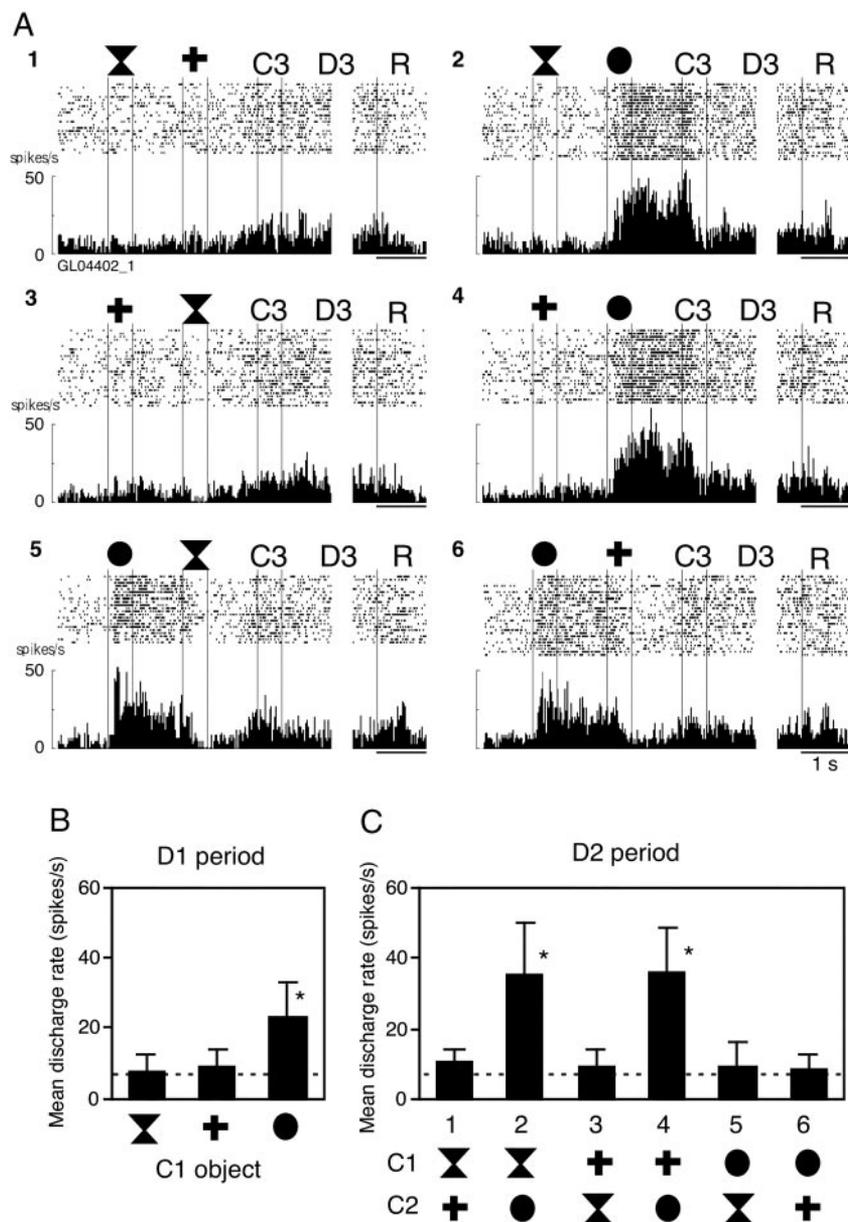
FIG. 9. *A*: histograms of order-nonselective delay-period activity of a neuron. The neuron was activated during the D1 period under trial conditions 5 and 6 and during the D2 period under trial conditions 2 and 4; this neuron was activated after presentation of a circle cue regardless of order of presentation. Bin width is 25 ms. C3, color cue period; D3, 3rd delay period; R, response period. *B*: average discharge rates during D1 period. Error bar indicates SD. Dashed line indicates mean discharge rate during control period. Asterisk indicates significant increase in activity during delay period. C: average discharge rate during D2 period for 6 trial conditions. Dashed line indicates mean discharge rate during control period. Asterisks indicate significant increase in activity during delay period.

during the D2 period was not selective in only one sequence. SI_{C1} (0.41) was lower than SI_{C2} (0.98). Therefore delay-period activity during the D2 period depended on the C2 object. Thus we classified neuronal activities depending on the degree of selectivity for both stimuli, when the delay-period activity during the D2 period was selective in terms of the C1 and C2 objects (see METHODS). In this neuron, delay-period activity was detected after the circle cue was presented as C1 or C2, and the delay-period activity during the D1 or D2 period returned to the baseline level when the C2 object or color cue was presented, respectively. Thus this delay-period activity was order-nonselective, and we defined the circle as the preferred object of this neuron. Thirty-eight neurons showed order-nonselective excitatory delay-period activity, and two neurons showed a significant decrease in activity during the delay periods.

Figure 10*A* shows the histograms of the C1-coding delay-period activity of a neuron. The neuron exhibited delay-period activity during the D1 period when the C1 object was double cone or the cross (Fig. 10, *A*, trial conditions 1–4, and *B*). This was object-selective [$F(2,122) = 15.4$, $P < 0.0001$]. During the last of the D2 period, this neuron showed activation in all trial conditions (Fig. 10*A*), but delay-period activity was not selective [$F(5,119) = 0.67$, $P > 0.05$]. Thus this neuron coded C1-object information during the D1 period and was identified as having C1-coding (D1) delay-period activity, and we defined the double cone as the preferred object of this neuron. Sixteen neurons were identified as having this type of activity.

Figure 11*A* shows other examples of the C1-coding delay-period activity of a neuron. The neuron did not show delay-period activity during the D1 period under all trial conditions (Fig. 11*B*). During the D2 period, however, this neuron exhibited a large delay-period activity when the C1 object was the circle (Fig. 11, *A,* trial conditions 5 and 6, and *C*). The delay-period activity during the D2 period had selectivity
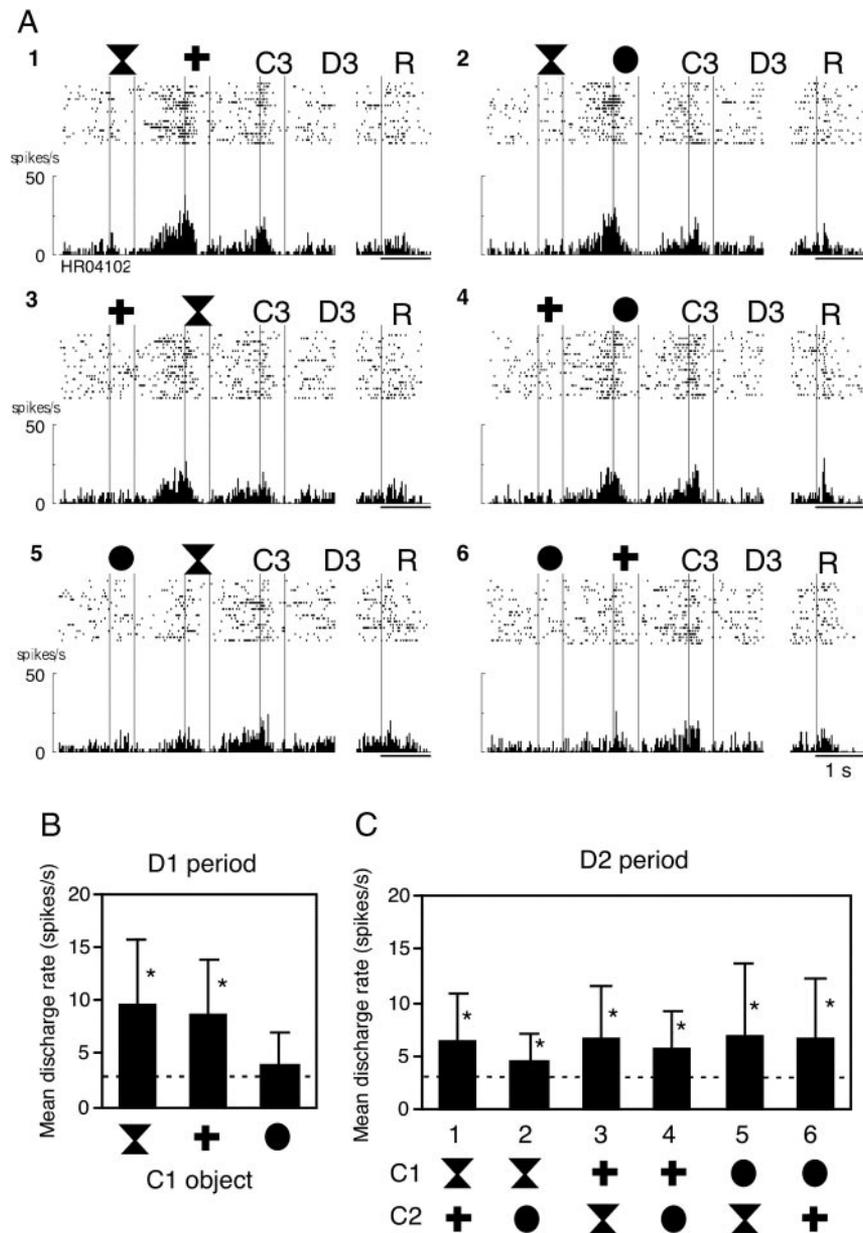
FIG. 10. *A*: histograms of C1-coding (D1) delay-period activity of a neuron. Format is the same as that in Fig. 9*A*. The neuron was activated during the D1 period under the trial conditions 1–4; this neuron was activated during D1 period when C1 object was the double cone or cross. *B*: average discharge rates during D1 period. *C*: average discharge rate during D2 period for 6 trial conditions. Format is same as that in Fig. 9, *B* and *C*.

$[F_{(5,139)} = 14.49, P < 0.0001]$. This neuron showed the highest delay-period activity during the D2 period in trial condition 6, and this delay-period activity was significantly different ($P < 0.05$) from those in trial conditions 1–4 and not significantly different ($P > 0.05$) from that in trial condition 5. SI_{C2} (0.59) was lower than SI_{C1} (0.86). Therefore this delay-period activity was classified as C1-coding (D2), and we defined the circle as the preferred object of this neuron. Thirty-four neurons were identified as having C1-coding (D2) delay-period activity, and two neurons exhibited C1-coding (D1 and D2) delay-period activity.

Figure 12*A* shows the histograms of the C2-coding delay-period activity of a neuron. The neuron did not exhibit delay-period activity during the D1 period under all trial conditions (Fig. 12*B*). During the D2 period, this neuron was significantly activated when the C2 object was the cross (Fig. 12, *A*, trial conditions 1 and 6, and *C*). The delay-period activity during the D2 period had selectivity

$[F_{(5,140)} = 15.73, P < 0.0001]$. This neuron showed the highest delay-period activity during the D2 period in trial condition 1, and this delay-period activity was significantly different ($P < 0.05$) from those in trial conditions 2–5 and not significantly different ($P > 0.05$) from that in trial condition 6. SI_{C1} (0.52) was lower than SI_{C2} (0.90). Therefore this delay-period activity was classified as C2-coding, and we defined the cross as the preferred object of this neuron. Thirty neurons exhibited C2-coding delay-period activity during the D2 period.

We were unable to detect neurons with delay-period activity coding both the C1 and C2 objects during the D2 period. We compared the highest delay-period activity with the other delay-period activities by a post hoc test (Fisher's PLSD), and determined whether delay-period activity was selective in only one sequence. Results showed that there were no neurons activated during the D2 period in only one sequence of six sequences.
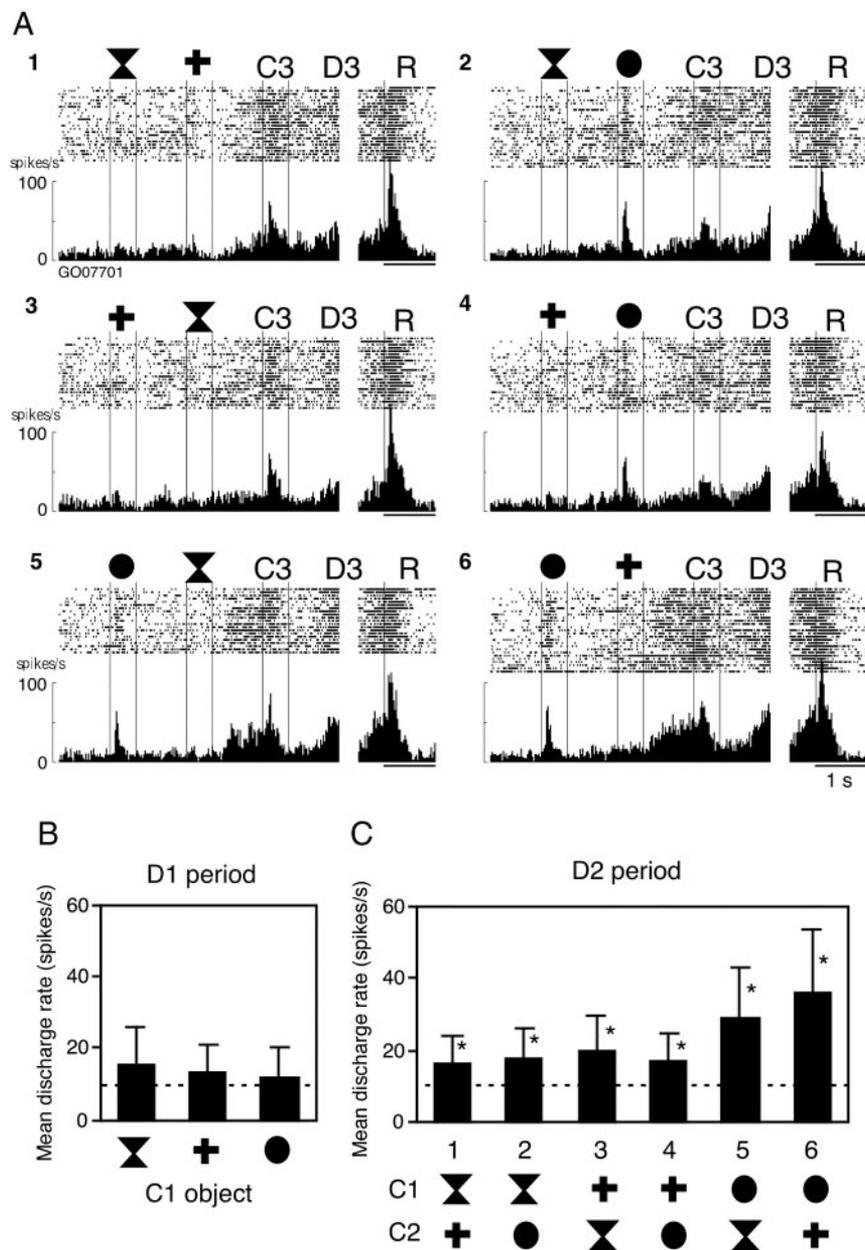
FIG. 11. *A*: histograms of C1-coding (D2) delay-period activity of a neuron. Format is the same as that in Fig. 9*A*. The neuron was activated during D2 period under trial conditions 5 and 6; this neuron was activated during D2 period when C1 object was the circle. *B*: average discharge rates during D1 period. *C*: average discharge rate during D2 period for 6 trial conditions. Format is same as that in Fig. 9, *B* and *C*.

Temporal profile of delay-period activities

To compare temporal profiles among order-nonselective, C1-coding, and C2-coding delay-period activities, we constructed the population histograms of these activities (Fig. 13, *A–D*). In these figures, red lines indicate population activities in trials in which the preferred object was presented during the C1 period, and green lines indicate population activities in trials in which the preferred object was presented during the C2 period. Blue lines indicate differences between the red and green lines. The starting point of difference in delay-period activity (the time at which the 1st 3 consecutive bins differed from the difference of activity for 1 s of the control period by >2 SD or <2 SD) and the endpoint (the time of the last bin) of the difference in delay-period activity were determined. For order-nonselective delay-period activity, when the preferred object was presented as C1, population activity was elicited at 125 ms after C1 presentation and continued during the delay

period until 100 ms after C2 presentation (Fig. 13, *A* and *E*, red line). When the preferred object was presented as C2, population activity was elicited at 175 ms after C2 presentation and continued during the delay period until 100 ms after color cue presentation (Fig. 13, *A,* green line, and *E,* red line). For the C1-coding (D1) delay-period activity, a difference in population activity was first observed 275 ms after C1 presentation and continued until 200 ms after C2 presentation (Fig. 13, *B,* blue line, and *E,* green line). Although population activity showed delay-period activity during the D2 period, a difference could not be found during the D2 period. A significant difference in C1-coding (D2) delay-period activity could not also be found during the D1 period, and it was first observed 325 ms after C2 presentation, and during the D2 period, population activity increased toward the end of the delay period until 600 ms after color cue presentation (Fig. 13, *C* and *E,* blue lines). A significant difference in C2-coding delay-
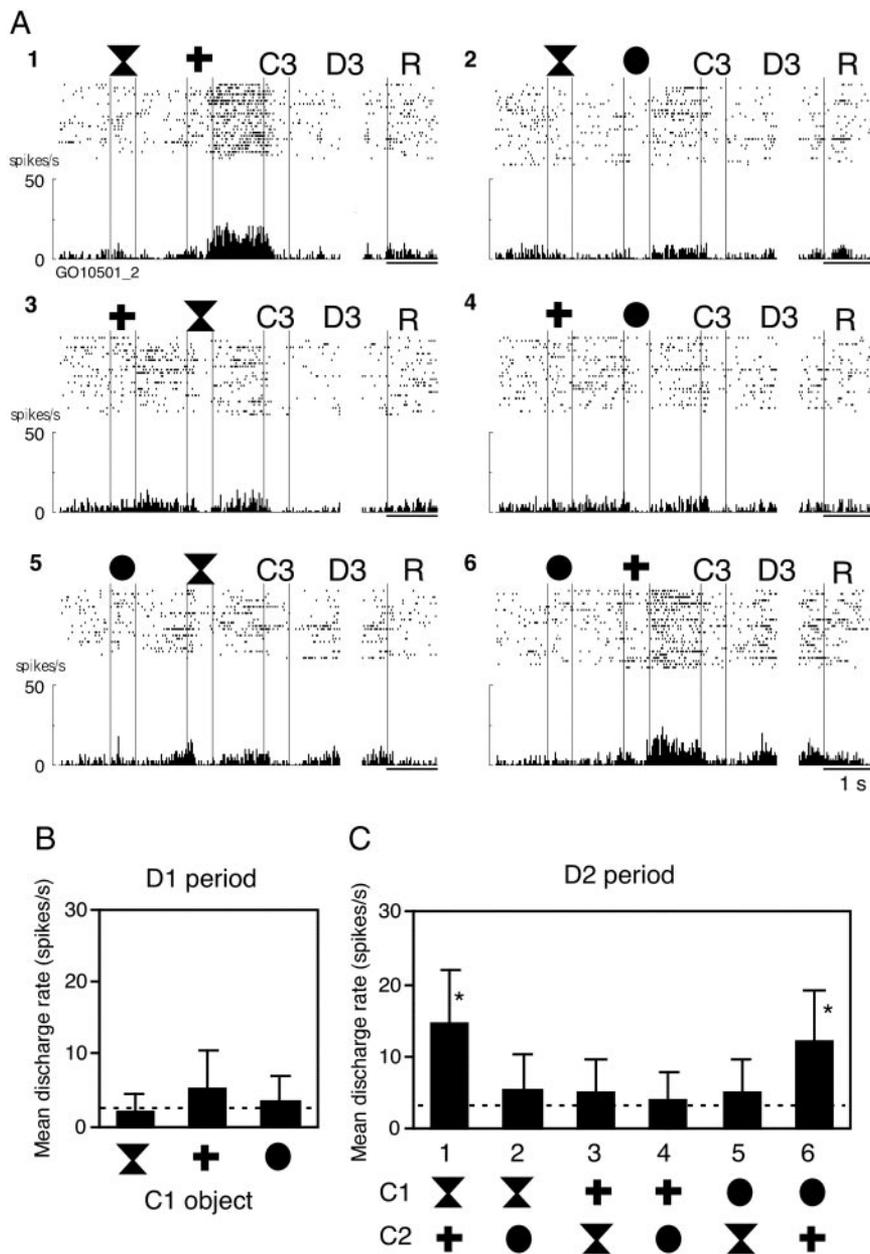
FIG. 12. *A*: histograms of C2-coding delay-period activity of a neuron. Format is the same as that in Fig. 9*A*. The neuron was activated during D2 period under trial conditions 1 and 6; this neuron was activated during D2 period when C2 object was the cross. *B*: average discharge rates during D1 period. *C*: average discharge rate during D2 period for 6 trial conditions. Format is same as that in Fig. 9, *B* and *C*.

period activity could not be found during the D1 period, and it was first observed 275 ms after C2 presentation, and population activity increased toward the end of the delay period until 175 ms after color cue presentation (Fig. 13, *D,* blue line, and *E,* light blue line).

Delay-period activities during DMS task

To evaluate the importance of order-nonselective and order-selective (C1-coding and C2-coding) delay-period activities in retaining information regarding the object cue and order of presentation, we examined neuronal activity during the DMS task, in which the monkey had to memorize only one object information during the delay period. Of 131 neurons with object-selective delay-period activity during the SPR task, 42 neurons were also tested for their activity during the DMS task.

Figure 14 shows two examples of neuronal activity during the DMS task. Figure 14*A* shows the activity during the DMS

task of a neuron, whose activity during the SPR task is shown in Fig. 9. This neuron showed order-nonselective delay-period activity during the SPR task, and the preferred object was the circle. During the DMS task, this neuron exhibited excitatory delay-period activity (early 1 s, $z = -4.51$, $P < 0.0001$; last 1 s, $z = -3.85$, $P < 0.0001$) when the object cue was the circle. This delay-period activity was object-selective during both the first 1 s [$F(2,54) = 20.83$, $P < 0.0001$] and the last 1 s [$F(2,54) = 4.39$, $P < 0.05$] of the delay period.

Figure 14*B* shows the activity during the DMS task of a neuron, whose activity during the SPR task is shown in Fig. 11. This neuron showed C1-coding delay-period activity during the SPR task. During the DMS task, the discharge rates increased during the last 1 s of the delay period under all three trial conditions. However, the delay-period activity of this neuron during the DMS task was not object-selective [$F(2,55) = 0.13$, $P > 0.05$]. This result indicates that the
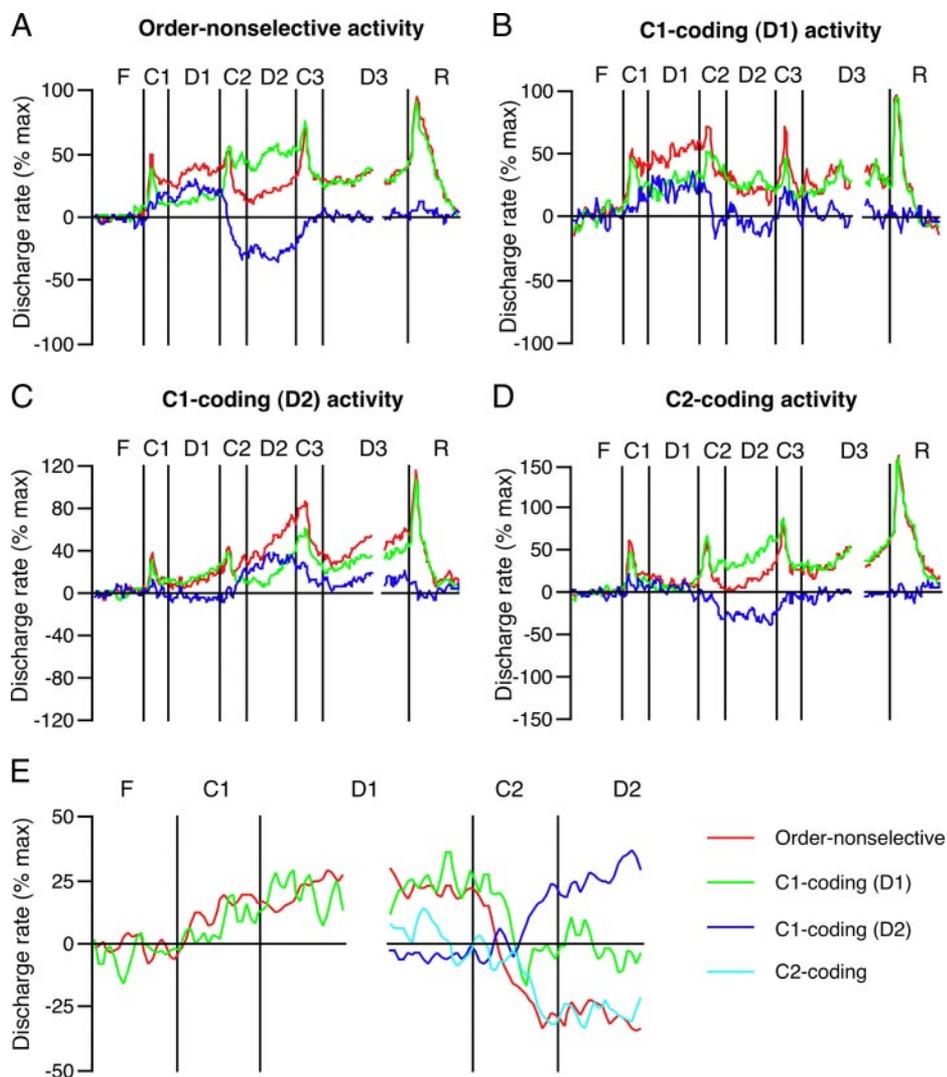
FIG. 13. Population histograms of order-non-selective delay-period activity (*A*), C1-coding (D1) delay-period activity (*B*), C1-coding (D2) delay-period activity (*C*), and C2-coding delay-period activity (*D*). Red lines indicate population histograms of trials in which preferred object was presented during C1 period, green lines indicate population histograms of trials in which preferred object was presented during C2 period, and blue lines indicate difference between red and green lines. *E*: time-course of difference in activity between trials in which preferred object was presented as C1 and C2. *F*: fixation period. C1, 1st cue period; D1, 1st delay period; C2, 2nd cue period; D2, 2nd delay period; C3, color cue period; D3, 3rd delay period; R, response period.

order-selective delay-period activities during the SPR task were not related to the preparation for the behavioral response.

Nineteen neurons with order-nonselective delay-period activity were also tested during the DMS task. Of these, 18 (95%) neurons exhibited object-selective delay-period activity during the DMS task, and 1 (5%) neuron showed object-nonselective delay-period activity (Fig. 14*C*). Fifteen neurons with C1-coding delay-period activity and five neurons with C2-coding delay-period activity were tested during the DMS task. Of these, 2 (10%) neurons exhibited object-selective delay-period activity during the DMS task, 13 (65%) neurons showed object-nonselective delay-period activity, and 5 (25%) neurons did not exhibit delay-period activity (Fig. 14*D*).

Delay-period activity in error trials

To evaluate the importance of order-nonselective and order-selective (C1-coding and C2-coding) delay-period activities in retaining information regarding the object cue and order of presentation during the D1 and D2 periods, we compared discharge rates during the delay period between the correct trials and error trials in all neurons with object-selective delay-period activity (Fig. 15, *A–D*). In the neurons with order-

nonselective delay-period activity, the delay-period activity was not significantly different between the correct and error trials during both the D1 (Fig. 15*A*; Wilcoxon signed-rank test, $z = -0.24$, $P > 0.05$, mean = 20.25 spikes/s in correct trials, mean = 20.60 spikes/s in error trials) and D2 (Fig. 15*B*; $z = -0.98$, $P > 0.05$, mean = 23.43 spikes/s in correct trials, mean = 24.23 spikes/s in error trials) periods. In contrast, neurons with C1-coding (Fig. 15*C*) and C2-coding (Fig. 15*D*) delay-period activities showed significantly weaker delay-period activities during the error trials than during the correct trials (C1-coding activity, $z = -1.96$, $P < 0.05$, mean = 23.19 spikes/s in correct trials, mean = 21.45 spikes/s in error trials; C2-coding activity, $z = -2.23$, $P < 0.05$, mean = 24.18 spikes/s in correct trials, mean = 18.04 spikes/s in error trials).

We compared discharge rates during the delay period between the correct trials and error trials in all neurons with object-selective delay-period activity during the DMS task and order-nonselective delay-period activity during the SPR task. In these neurons, the delay-period activity during the correct trials was significantly different from that during the error trials (Fig. 15*E*; Wilcoxon signed-rank test, $z = -2.12$, $P < 0.05$, mean = 17.89 spikes/s in correct trials, mean = 16.12 spikes/s in error trials).
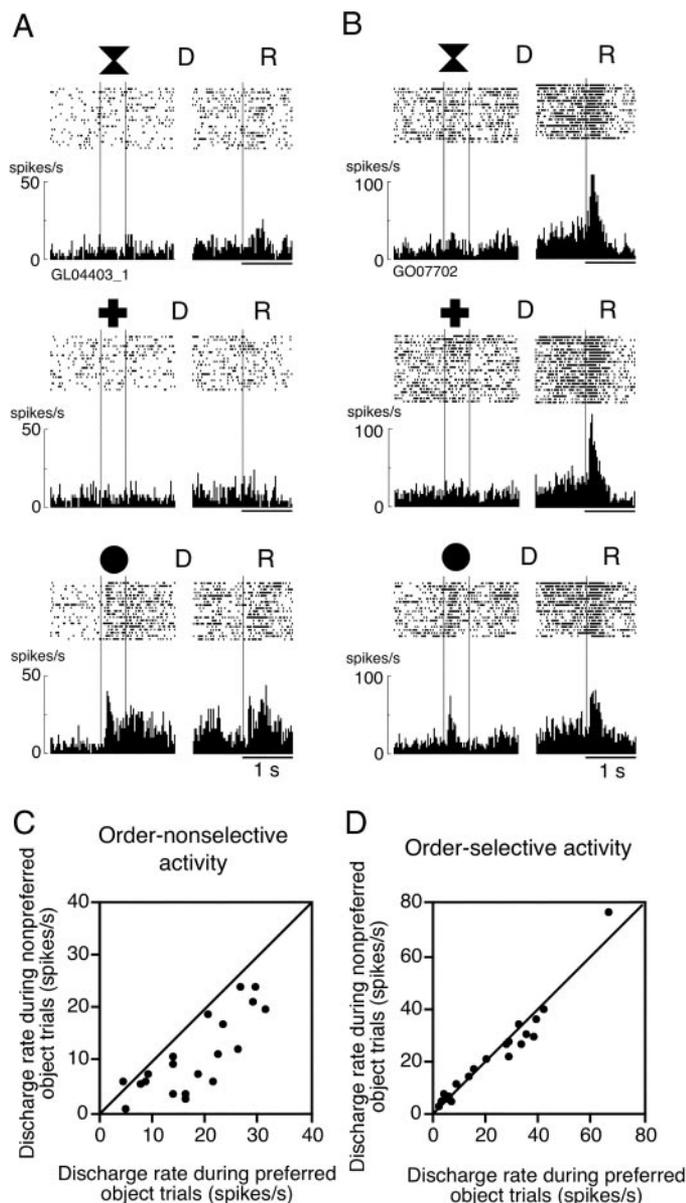
FIG. 14. Neuronal activity during DMS task. *A*: activity during DMS task of a neuron, whose activity the SPR task is shown in Fig. 9. This neuron showed order-nonselective delay-period activity during the SPR task. Because duration of delay was randomly selected to be between 2 and 3 s, rasters and histograms are aligned at onset of cue presentation and at start of response period. This neuron exhibited delay-period activity when the object cue was the circle during the DMS task. *B*: activity during DMS task of a neuron, whose activity during the SPR task is shown in Fig. 11. This neuron showed C1-coding (D2) delay-period activity during the SPR task. This neuron exhibited delay-period activity during the DMS task, but delay-period activity was not object-selective. *C*: comparison of delay-period activities between preferred object and nonpreferred object trials during DMS task for neurons with order-nonselective delay-period activity during SPR task. Preferred object trial and nonpreferred object trial were determined by result of the SPR task. *D*: comparison of delay-period activities between preferred object and nonpreferred object trials during DMS task for neurons with order-selective delay-period activity during the SPR task. Preferred object trial and nonpreferred object trial were determined by result of the SPR task. For example, the neuron shown in *B* did not show object-selective delay-period activity during the DMS task. However, this neuron showed object-selective and C1-coding delay-period activity during the SPR task (see Fig. 11), and this neuron's preferred object was the circle and nonpreferred object was the double cone.
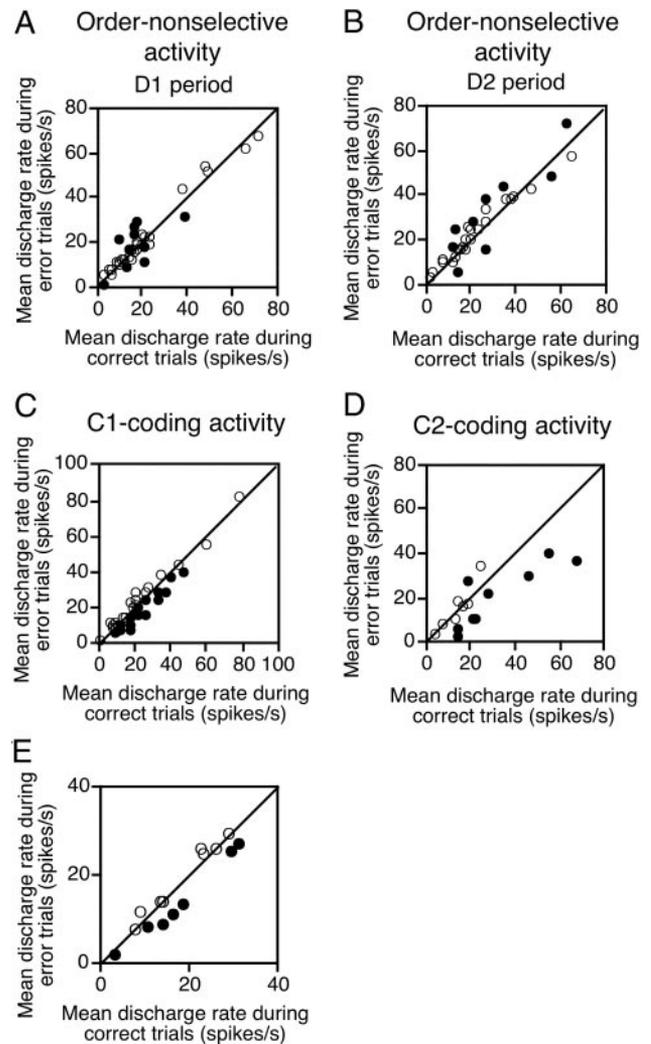

FIG. 15. Comparison between delay-period activities during correct and error trials. *A*: order-nonselective delay-period activity during D1 period in correct and error trials. Mean discharge rates during D1 period on correct and error trials were not significantly different. *B*: order-nonselective delay-period activities during D2 period in correct and error trials. Mean discharge rates during D2 period in correct and error trials were not significantly different. *C*: C1-coding delay-period activities during correct and error trials. Mean discharge rates during correct and error trials were significantly different. *D*: C2-coding delay-period activities during correct and error trials. Mean discharge rates during correct and error trials were significantly different. *E*: delay-period activities during correct and error trials in the DMS task. Mean discharge rates during correct and error trials were significantly different. Closed circles indicate discharge rate of neurons whose activities were significantly different between correct and error trials (Mann-Whitney *U* test, *P* < 0.05). Open circles indicate discharge rate of neurons whose activities were not significantly different between correct and error trials (*P* > 0.05).

Relationship between neuronal activities during C1/C2 periods and D1/D2 periods

To study the relationship between neuronal activities during the cue and delay periods, we compared the preferred object of individual neurons that had both visual and delay-period activities. During the SPR task, about one-half of the neurons with the object-selective response to the object cue also exhibited object-selective delay-period activity (Table 1). Among neurons with the order-nonselective object-selective response, eight (36%) also exhibited object-selective delay-period activity. Most of these neurons exhibited order-nonselective delay-

TABLE 1. *Number of neurons with both object-selective visual response and object-selective delay-period activity*

	D1 and D2 Period						
	Order-nonselective	C1-coding (D1)	C1-coding D2	C2-coding	Object-nonselective	No activity	Total
Object-selective							
Order-nonselective	5 (4)	2 (2)	1 (1)	0 (0)	5	9	22
C1-dominant	2 (1)	1 (0)	2 (1)	3 (3)	3	22	33
C2-dominant	6 (2)	1 (1)	3 (1)	3 (1)	5	8	26
Object-nonselective							
Order-nonselective	2	2	1	2	2	8	17
C1-dominant	1	0	2	1	3	14	21
No response	24	10	25	21	43	369	492
Total	40	16	34	30	61	430	611

Numbers in parentheses are the numbers of neurons with the same object preference during the cue period and delay period.

period activity. Figure 16*A* shows an example of the activity of a neuron with both the order-nonselective response during the C1 and C2 periods and order-nonselective delay-period activity during the D1 and D2 periods. In this histogram, black lines indicate activity in trials in which C1 was the preferred object, and gray lines indicate activity in trials in which C2 was the preferred object. This neuron showed a response when the preferred object (circle) was presented and showed delay-period activity following the presentation of the preferred object. Among neurons with the C1-dominant object-selective response, eight (24%) also exhibited object-selective delay-period activity. Figure 16*C* shows an example of the activity of a neuron with both the C1-dominant response and C2-coding delay-period activity. Among neurons with the C2-dominant object-selective response, 13 (50%) also exhibited object-selective delay-period activity. These neurons exhibited order-nonselective, C1-coding (D2), C2-coding delay-period activity. However, for the majority of these neurons, object preferences were different between the object cue period and delay period. Figure 16*E* shows an example of the activity of a
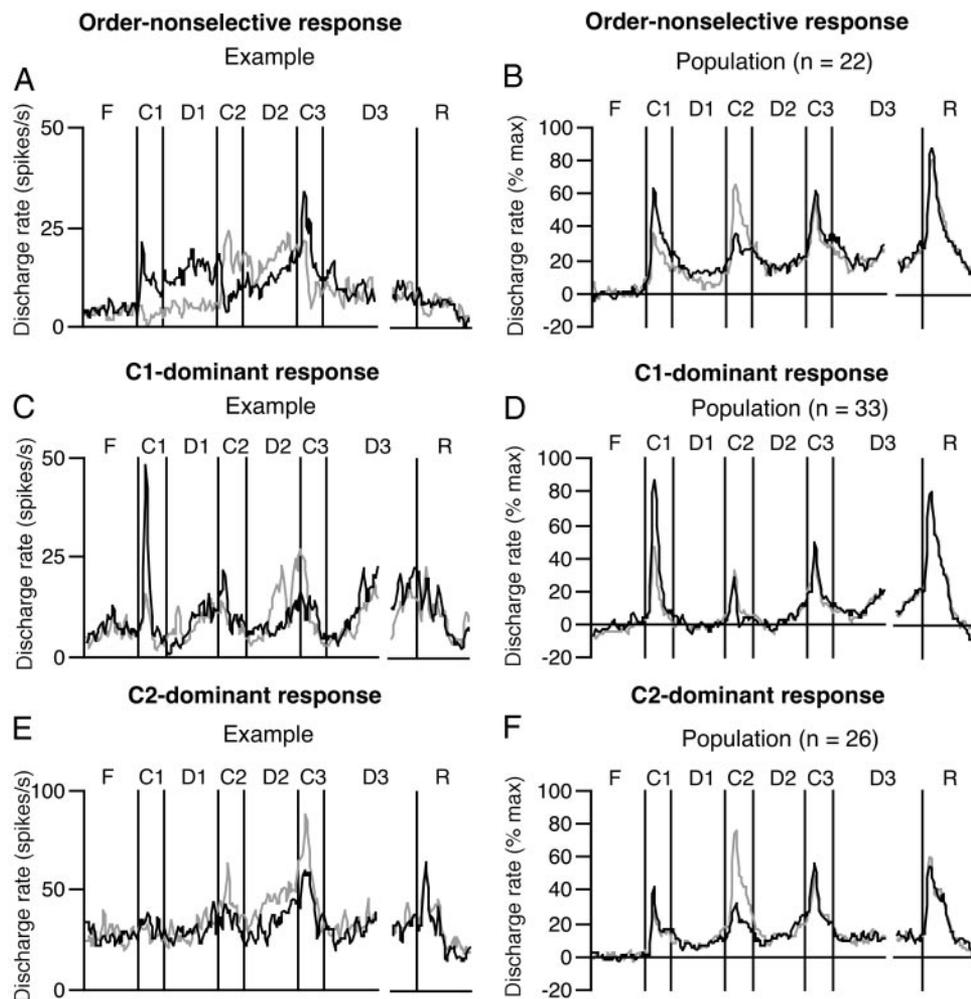
FIG. 16. Histograms of activity of neurons with order-nonselective response (*A*), C1-dominant response (*C*), and C2-dominant response (*E*), and population activity histograms of neurons with order-nonselective response (*B*), C1-dominant response (*D*), and C2-dominant response (*F*). Black lines indicate activity histograms for trials in which the preferred object of the C1 period was presented, and gray lines indicate activity histograms for trials in which the preferred object of the C2 period was presented. F, fixation period; C1, 1st cue period; D1, 1st delay period; C2, 2nd cue period; D2, 2nd delay period; C3, color cue period.

neuron with the C2-dominant response and C1-coding (D2) delay-period activity. In this neuron, the preferred object during the cue period was the double cone and the preferred object during the delay period was the circle.

To examine the relationship between responses during the cue period and delay-period activity, we constructed the histograms of the population activities of neurons with the order-nonselective, C1-dominant, and C2-dominant responses (Fig. 16, *B*, *D,* and *F*). In these histograms, black lines indicate population activity in trials in which C1 was the preferred object, and gray lines indicate population activity in trials in which C2 was the preferred object. Figure 16*B* shows the population activities of neurons with the order-nonselective response during the cue period. Population activity coded information on the C1 object during the C1 and the D1 periods and on the C2 object during the C2 period. During the D2 period, population activity increased, but a difference in population activity between the C1-preferred and C2-preferred trials could not be found. Figure 16*D* shows the population activities of neurons with the C1-dominant response during the cue period. During the D1 period and the early phase of the D2 period, population activity did not increase in terms of discharge rate. During the last phase of the D2 period, population activity slightly increased, but a difference in population activity between the C1-preferred and C2-preferred trials could not be found. Figure 16*F* shows the population activities of neurons with the C2-dominant response during the cue period. During the first phase of the D1 period, population activity did not change, but during the last phase of the D1 period, population activity was higher in the C2-preferred trials than in the C1-preferred trials. During the D2 period, population activity was higher in the C2-preferred trials than in the C1-preferred trials.

To examine how many neurons showed anticipatory activity preceding the C2 presentation, we compared activity for 500 ms preceding the C2 presentation with activity for 500 ms preceding the C1 presentation by repeated measures ANOVA. In the neurons with the order-nonselective response, 10 (45%) neurons did not show a significant increase or decrease in activity during the pre-C2 period, 10 (45%) neurons showed a significant ($P < 0.05$) increase in activity during the pre-C2 period, and 2 (10%) neurons showed a significant ($P < 0.05$) decrease in activity during the pre-C2 period. In the neurons with the C1-dominant response, 17 (52%) neurons did not show a significant increase or decrease in activity during the pre-C2 period, 9 (27%) neurons showed a significant ($P < 0.05$) increase in activity during the pre-C2 period, and 7 (21%) neurons showed a significant ($P < 0.05$) decrease in activity during the pre-C2 period. In the neurons with the C2-dominant response, 10 (38%) neurons did not show a significant increase or decrease in activity during the pre-C2 period, 16 (62%) neurons showed a significant ($P < 0.05$) increase in activity during the pre-C2 period, and no neuron showed a significant ($P < 0.05$) decrease in activity during the pre-C2 period.

Object-nonselective delay-period activity

Sixty-one neurons exhibited object-nonselective delay-period activity during the D1 and/or D2 periods. Of these, 38 neurons (63%) exhibited this activity during both the D1 and D2 periods. Three neurons (5%) showed object-nonselective delay-period activity during the D1 period but did not show delay-period activity during the D2 period. Twenty neurons (33%) showed object-nonselective delay-period activity during the D2 period but did not show delay-period activity during the D1 period.

Target- and/or color-selective response during color cue period

During the color cue period, 139 neurons exhibited a significantly larger response magnitude than the baseline response during the fixation period. Figure 17*A* shows the histograms of the responses of a neuron that depended on both the color cue and the target object. The neuron was activated during the color cue period when the color cue was green and the target object was the circle. However, when the target object was the double cone or cross and the color cue was green, this neuron showed a small response magnitude; therefore the neuron was not simply responding on the basis of color information. When the color cue was red, this neuron did not respond during the color cue period. The response magnitudes of this neuron were significantly different in terms of both the color factor [$F(1,118) = 61.67, P < 0.0001$] and the target factor [$F(2,118) = 16.47, P < 0.0001$]. Thus this response during the color cue period depended on both the color cue and target object, and we defined green as the preferred color of this neuron and the circle as the preferred target object of this neuron. These histograms showed that movements in all directions occurred. In addition, the monkey could not determine the direction of a movement until the response period. These findings indicate that this selective neuronal activity was not caused by the movements. This type of activity was classified as the CT response. Seventy neurons were identified as having the CT response in this study.

Figure 17*B* shows the histograms of the responses of a neuron that depended on the color cue. The neuron exhibited a response when the color cue was red regardless of the target object. The response magnitudes were significantly different in terms of the color factor [$F(1,127) = 88.95, P < 0.0001$] but not significant in terms of the target factor [$F(2,127) = 1.45, P > 0.05$]. Thus this response during the color cue period depended on the color cue. This type of response was classified as the C response, and we defined red as the preferred color of this neuron. Thirty-six neurons were identified as having the C response in this study.

Figure 17*C* shows the histograms of the response of a neuron that depended on the target object. The neuron was activated when the target object was the circle and was not activated when the target object was the double cone or cross. The magnitudes of responses that depended on the color itself were not significantly different. The response magnitude was significantly different in terms of the target factor [$F(2,76) = 14.37, P < 0.0001$] but not significant in terms of the color factor [$F(1,76) = 0.05, P > 0.05$]. Thus the response of this neuron during the color cue period depended on the target object not on the color. This type of response was classified as the T response, and we defined the circle stimulus as the preferred target object of this neuron. Fifteen neurons were identified as having the T response in this study.
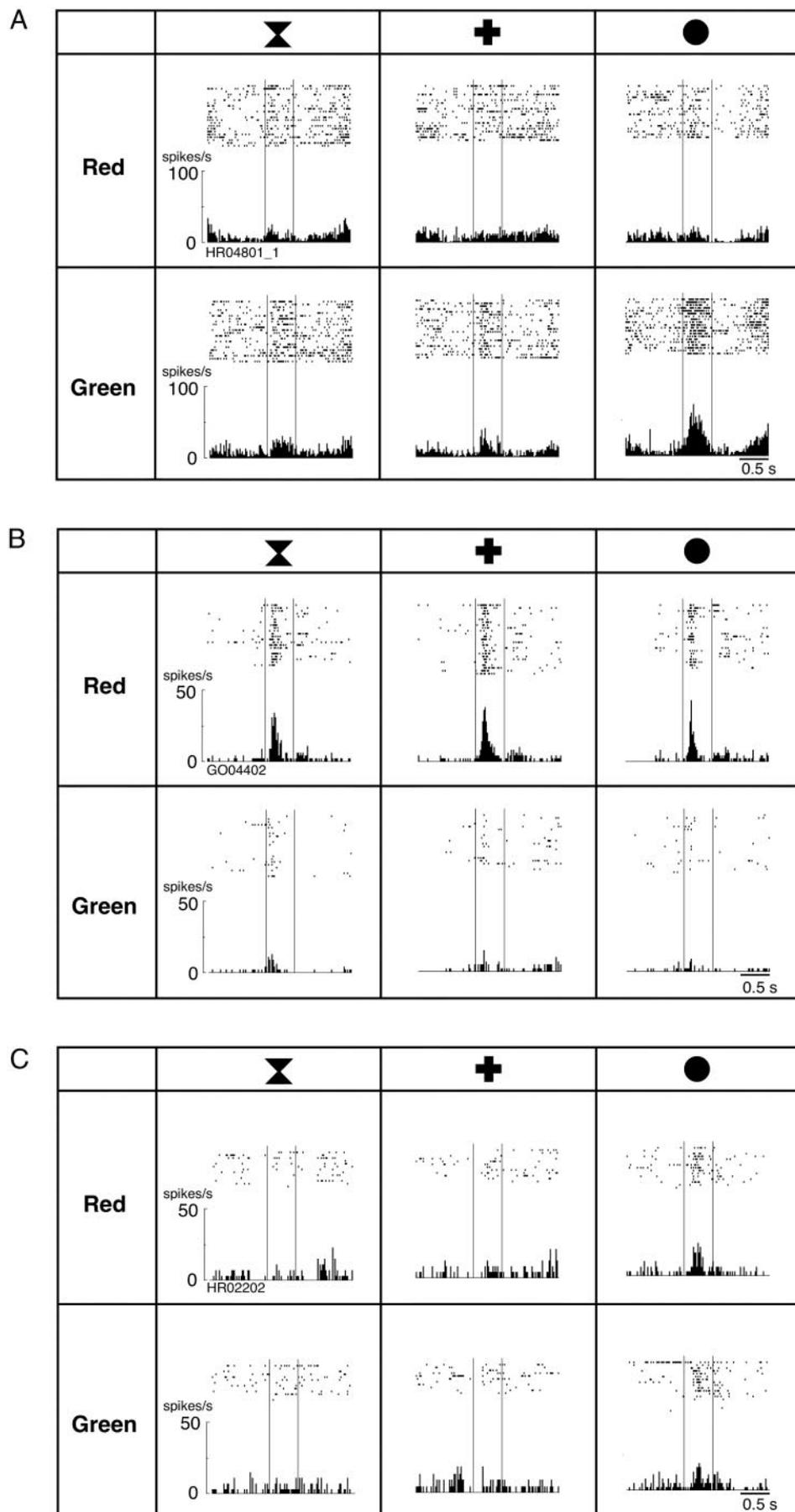
FIG. 17. *A*: histograms of CT response of a neuron. Each histogram was aligned to onset of color cue presentation. *Top* and *bottom histograms* correspond to neuronal activities when color cues were red and green, respectively. *Left, middle,* and *right histograms* correspond to neuronal activities when the monkey had to perform a saccade to the double cone, cross, and circle, respectively. Two vertical lines in each histogram indicate onset and offset of color cue presentation. This neuron was activated when color cue was green and target object was the circle. Bin width is 20 ms. *B*: histograms of C response of a neuron. This neuron was activated when color cue was red. Activities did not depend on target object. *C*: histograms of T response of a neuron. This neuron was activated when target object was the circle. These activities did not depend on color.

Response during color cue period in error trials

To evaluate the importance of the CT, T, and C responses during the color cue period in memory retrieval, we examined neuronal activity when the monkeys performed incorrectly. The magnitudes of the CT responses (Fig. 18*A*) during the error trials were significantly smaller than those during the correct preferred-color and preferred-target trials (Wilcoxon signed-rank test, $z = -4.72$, $P < 0.0001$, mean $= 42.86$ spikes/s in correct trials, mean $= 34.60$ spikes/s in error trials). Similarly, the magnitudes of the T responses (Fig. 18*B*) during the error trials were significantly smaller than those during the correct preferred-target trials ($z = -2.78$, $P < 0.01$, mean $= 39.97$ spikes/s in correct trials, mean $= 32.52$ spikes/s in error trials). In contrast, the magnitudes of the C responses (Fig. 18*C*) were not significantly different between the correct and error preferred-color trials ($z = -0.74$, $P > 0.05$, mean $= 39.33$ spikes/s in correct trials, mean $= 38.43$ spikes/s in error trials).

Latency of target- and/or color-selective response

Latencies were slightly different among the CT, C, and T responses. Figure 19 shows the cumulative summation of the latencies of the CT, C, and T responses that were <200 ms. The latencies of the T responses (mean $= 137$ ms) were slightly longer than those of the CT (mean $= 127$ ms) and C responses (mean $= 121$ ms), but these differences were not statistically significant [$F(2,78) = 0.98$, $P > 0.05$].

Comparison of response with color cue response in the fixation task

When selection is not required, do neurons with the CT response or T response also respond to color stimuli? To answer this question, we examined neuronal activity during a fixation task. While the monkey maintained its fixation, we presented the same color stimulus as that used in the SPR task. Figure 20*A* shows the histograms of the CT response during the SPR task and the fixation task. The response magnitude during the fixation task (61.00 ± 29.65 spikes/s) was similar to that during the preferred-color and preferred-target trials of the SPR task (46.82 ± 17.01 spikes/s). Differences between these response magnitudes were not significant (Mann-Whitney *U* test, $z = 1.46$, $P > 0.05$). Thus the object-selectivity in this CT response was elicited by the suppression of response in the preferred-color and the nonpreferred-target trials. In all the tested neurons, the magnitudes of their CT responses ($n = 17$)
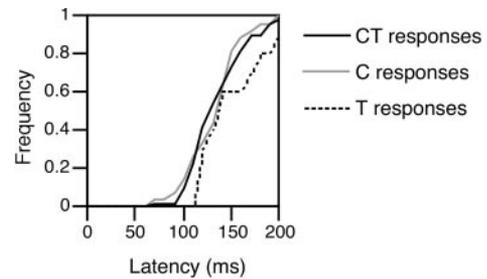
FIG. 19. Distribution of latencies of CT, C, and T responses. Cumulative summation curve of latencies of CT response ($n = 58$), C response ($n = 32$), and T response ($n = 12$) that were <200 ms.

during the preferred-color and preferred-target trials of the SPR task were not significantly ($P > 0.05$) different from those during the fixation task (Fig. 20*B*). The population activity of the CT responses also exhibited similar patterns during the preferred-color and preferred-target trials in the SPR task to those during the preferred-color trial in the fixation task (Fig. 20*C*).

Figure 20*D* shows the histograms of the T response during the SPR task and fixation task. The neuron showed no clear responses during the fixation task. All tested neurons with T response ($n = 6$) showed no responses during the fixation task (Fig. 20*E*). The population activity of the T responses also showed no responses during the fixation task (Fig. 20*F*).

Relationship between neuronal activities during color cue period and C1/C2 periods and D1/D2 periods

Of 139 neurons with a response during the color cue period, 45 neurons (CT responses, $n = 24$; C responses, $n = 16$; T responses, $n = 5$) showed an object-selective response during the C1 and/or C2 period (Table 2). We compared the object preference between the color cue period and the object cue period of the CT and T neurons. About one-third of the neurons (CT neurons, $n = 8$; T neurons, $n = 1$) showed the same object-preference during the color cue period and object cue period (Table 2). Figure 21*A* shows an example of responses of a neuron with the same preference during the color cue period and object cue period. This neuron responded to the circle stimulus during the C1 and C2 periods and also responded when the color cue was red and the target object was the circle during the color cue period. In contrast, the remaining two-thirds of neurons (CT neurons, $n = 16$; T neurons, $n = 4$) did not show the same object preference. Figure 21*B* shows an example of responses of a neuron with the different preference
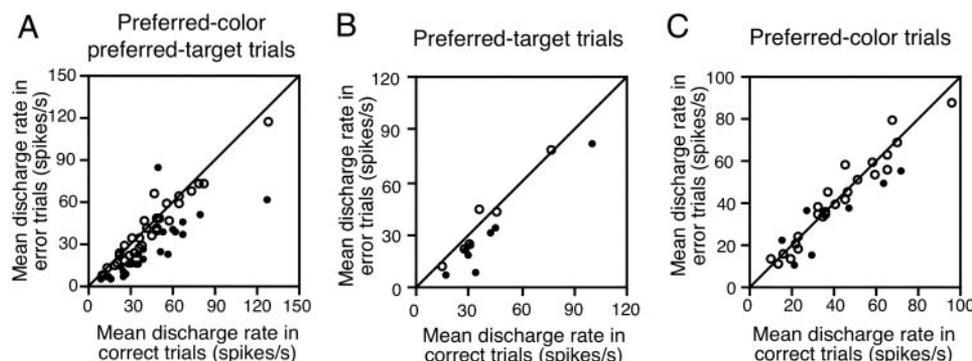
FIG. 18. *A*: comparison between CT responses during correct and error trials in preferred-color preferred-target trials. *B*: comparison between T responses during correct and error trials in preferred-target trials. *C*: comparison between C responses during correct and error trials in preferred-color trials. ○, discharge rate of neurons whose responses during correct and error trials were not significantly different (Mann-Whitney *U* test, $P > 0.05$); ●, discharge rate of neurons whose responses during correct and error trials were significantly different (Mann-Whitney *U* test, $P < 0.05$).
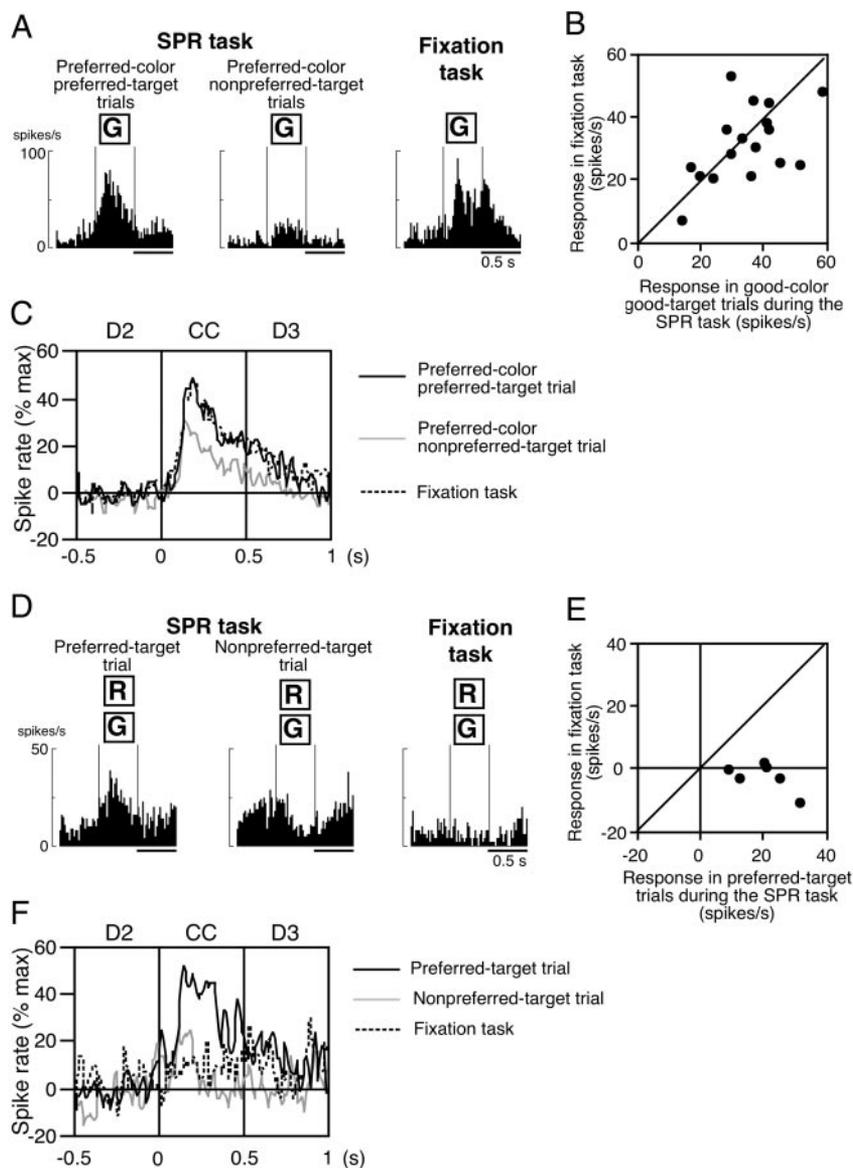
FIG. 20. Comparison of CT and T responses during the SPR task with response during fixation task. *A*: neuronal activities during SPR task and fixation task of a neuron with CT response. *B*: comparison between discharge rates during preferred-color preferred-target trials during the SPR task and fixation task. *C*: population activities for CT response (*n* = 17) during SPR task and fixation task. *D*: neuronal activity during SPR task and fixation task of a neuron with T response. *E*: comparison between discharge rates during preferred-target trials of SPR task and fixation task. *F*: population activities of T response (*n* = 6) during SPR task and fixation task.

during the color cue period and object cue period. The preferred object of this neuron was the circle during the C1 and C2 periods and the double cone during the color cue period. Indeed, the object selectivity was not clear in the population activity. We constructed the histograms of the population activities of the neurons with CT response that preferred red (Fig. 21*C, left*) and those that preferred green (Fig. 21*C, right*). We also constructed the histograms of the population activities of the neurons with T response when the color cues were red (Fig. 21*D, left*) and green (Fig. 21*D, right*). The left histograms show that the preferred target object was presented during the C1 period and the right histograms show that the preferred target object was presented during the C2 period. The fact that the population activities during the C1 period and C2 period were not different between the presentations of preferred target objects (black line) and nonpreferred target objects (gray line) implies that the object selectivity of the CT or T neurons could not be derived from the activities during the cue period.

Of 139 neurons with a response during the color cue period, 44 neurons (CT response, *n* = 24; C response, *n* = 16; T

TABLE 2. *Number of neurons with responses during color cue period and other periods*

	Color Cue Period			
	CT response	C response	T response	Total
C1 and C2 period				
Order-nonselective	8 (3)	4	1 (1)	22
C1-dominant	8 (2)	5	3 (0)	33
C2-dominant	8 (3)	7	1 (0)	26
D1 and D2 period				
Order-nonselective	11 (3)	4	1 (0)	40
C1-coding (D1)	2 (0)	1	1 (0)	16
C1-coding (D2)	6 (3)	7	0 (0)	34
C2-coding	5 (3)	4	2 (1)	30
D3 period				
CT activity	23 (19)	5 (3)	2 (1)	102
C activity	8 (3)	4 (4)	0	61
T activity	5 (3)	0	4 (2)	38
Total	70	36	15	

Numbers in parentheses are the numbers of neurons with the same object or color preference during the color cue period and other periods.
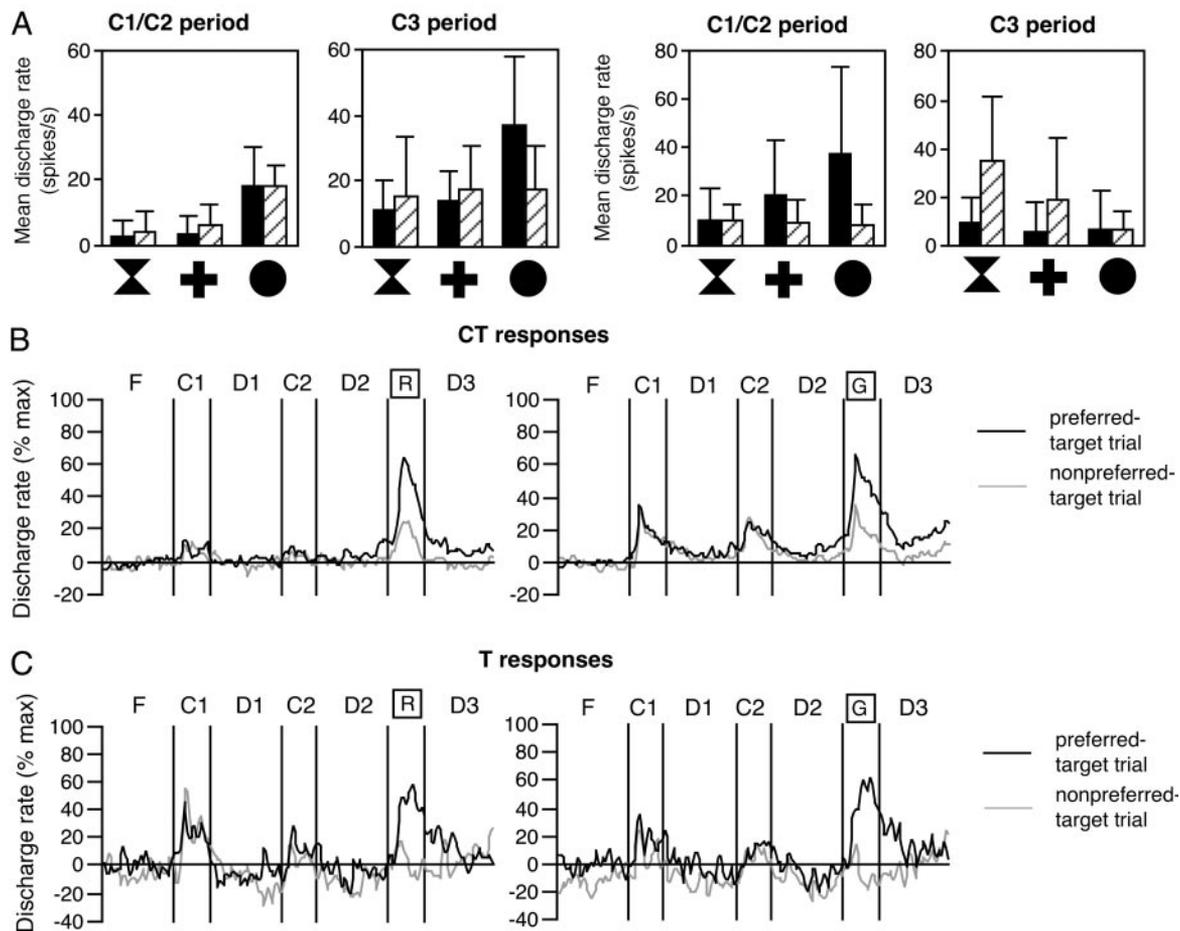
FIG. 21. *A*: example of response of neuron whose preferred object was the same during C1, C2, and color cue periods. *B*: example of response of neuron whose preferred objects were different between C1, C2, and color cue period. *Left*: solid bars indicate response during C1 period, and hatched bars indicate response during C2 period. *Right*: solid bars indicate response when color cue was red, and hatched bars indicate response when color cue was green during color cue period. Error bars indicate SD. *C*: histograms of population activity of CT neurons whose preferred colors were red (*left*) and green (*right*). Black line indicates population activity during preferred-color preferred-target trials, and gray line indicates population activity during preferred-color nonpreferred-target trials. *D*: histogram of population activity of T neurons when color cues were red (*left*) and green (*right*). Black line indicates population activity during preferred-target trials, and gray line indicates population activity during nonpreferred-target trials.

response, $n = 4$) also showed the object-selective delay-period activity during the D1 and/or D2 period. Ten neurons showed the same object selectivity during the delay period and the color cue period (Table 2). As shown in Fig. 21*C*, the population activities of the neurons with the CT response during the D1 period were not different between the preferred-target (black line) and nonpreferred-target trials (gray line). However, near the end of the D2 period, the population activity in the preferred-target trials was higher than that in the nonpreferred-target trials (Fig. 21*C*). Indeed, of six neurons with the CT response and C1-coding (D2) delay-period activity, three preferred red. Five neurons with the CT response also showed C2-coding delay-period activity, and all these five neurons preferred green. Population activities of the neurons with the T response did not show delay-period activity during the D1 and D2 periods (Fig. 21*D*).

Target- and/or color-selective delay-period activity during D3 period

During the D3 period, 260 neurons exhibited a significantly higher delay-period activity than the baseline activity during

the fixation period. Similar to the response during the color cue period, we could detect CT, C, and T delay-period activities during the D3 period. Figure 22*A* shows the histograms of the activities of a neuron that depended on both the color cue and the target object. The neuron was activated during the D3 period when the color cue was green and the target object was the double cone. However, when the target object was the cross or circle and the color cue was green, this neuron did not show a significant delay-period activity. When the color cue was red, this neuron did not show the activity during the D3 period. The response magnitude of this neuron was significantly different in terms of both the color factor [$F(1,144) = 31.07$, $P < 0.0001$] and the target factor [$F(2,144) = 18.88$, $P < 0.0001$]. Thus this activity during the D3 period depended on both the color cue and target object. This type of activity was classified as CT delay-period activity. One hundred two neurons were identified as having CT delay-period activity in this study.

Figure 22*B* shows the histograms of activities of a neuron that depended on the color cue. The neuron exhibited delay-period activity when the color cue was red regardless of the target object. The response magnitudes were significantly different in terms of the color factor [$F(1,150) = 83.36$, $P <$
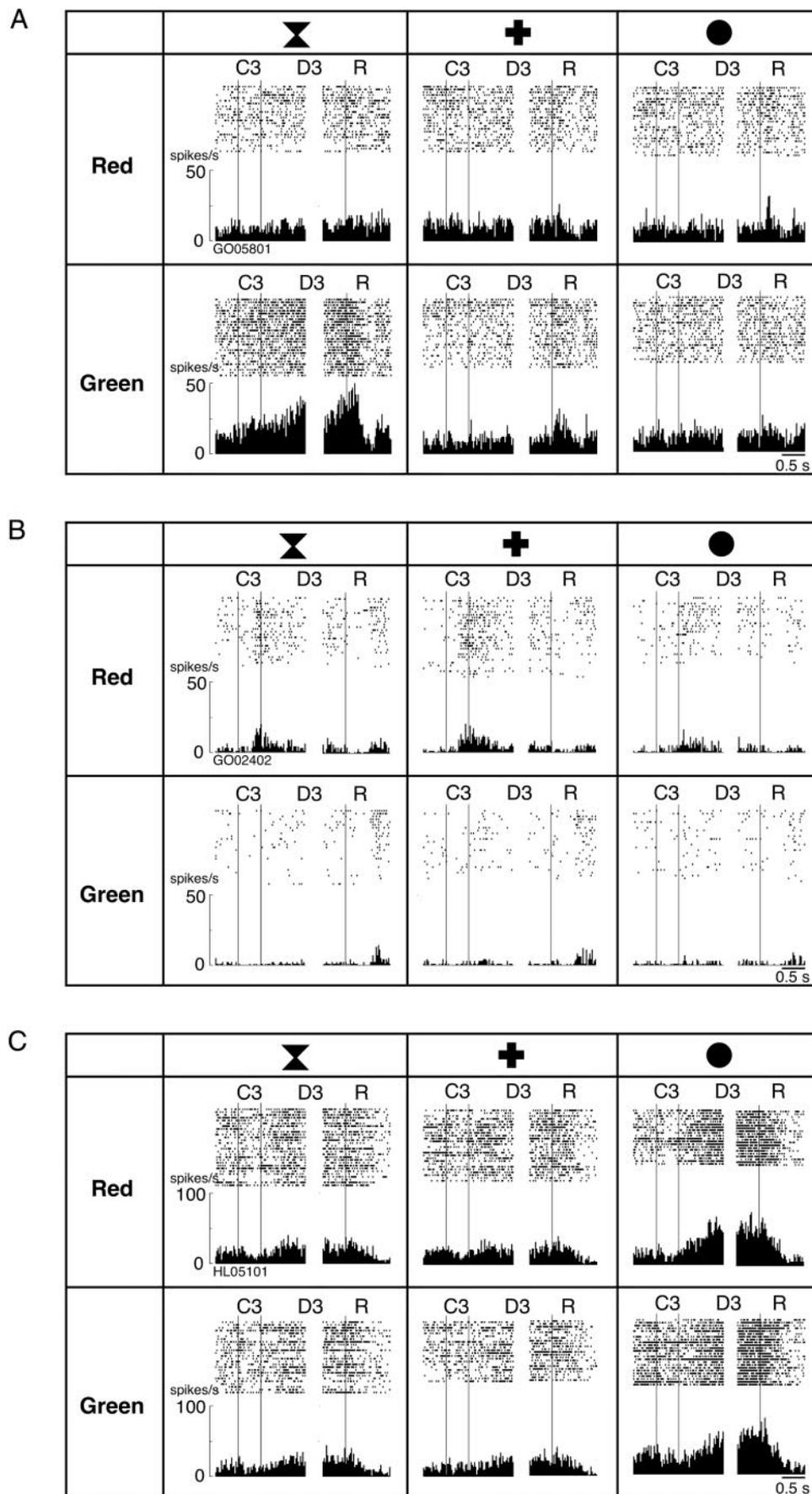
FIG. 22. *A*: histograms of CT delay-period activity of a neuron. Because duration of D3 period was randomly selected from 1 to 1.5 s, histograms were aligned to onset of color cue presentation and onset of target stimulus presentation. *Top* and *bottom histograms* correspond to neuronal activities when color cues were red and green, respectively. *Left, middle,* and *right histograms* correspond to neuronal activities when the monkey had to perform a saccade to the double cone, cross, and circle, respectively. Three vertical lines in each histogram indicate onset and offset of color cue presentation and onset of target stimulus presentation. This neuron was activated when color cue was green and target object was the double cone. Bin width is 50 ms. *B*: histograms of C delay-period activity of a neuron. This neuron was activated when color cue was red. Activities did not depend on target object. *C*: histograms of T delay-period activity of a neuron. This neuron was activated when target object was the circle. These activities did not depend on color.

0.0001] but not significant in terms of the target factor [$F(2,150) = 2.32$, $P > 0.05$]. Thus this delay-period activity during the D3 period depended on the color cue. This type of activity was classified as C delay-period activity. Sixty-one neurons were identified as having C delay-period activity in this study.

Figure 22*C* shows the histograms of activities of a neuron that depended on the target object. The neuron was activated when the target object was the circle and was not activated when the target object was the double cone or cross. These activities that depended on the color itself were not significantly different. The response magnitudes were significantly different in terms of the target factor [$F(2,139) = 20.22$, $P < 0.0001$] but not significant in terms of the color factor [$F(1,139) = 2.43$, $P > 0.05$]. Thus the delay-period activity of this neuron during the D3 period depended on the target object but not on the color. This type of delay-period activity was classified as T delay-period activity. Thirty-eight neurons were identified as having T delay-period activity in this study.

Response during D3 period in error trials

During the D3 period, the CT delay-period activities (Fig. 23*A*) during the error trials were significantly weaker than those during the correct preferred-color and preferred-target trials (Wilcoxon signed-rank test, $z = -4.07$, $P < 0.0001$, mean = 25.30 spikes/s in correct trials, mean = 21.99 spikes/s in error trials). Similarly, the T delay-period activities (Fig. 23*B*) during the error trials were significantly weaker than those during the correct preferred-target trials ($z = -2.14$, $P < 0.05$, mean = 22.81 spikes/s in correct trials, mean = 20.14 spikes/s in error trials). In contrast, neurons with C delay-period activity (Fig. 23*C*) did not show a significantly different response magnitude between the correct and error preferred-color trials ($z = -1.63$, $P > 0.05$, mean = 19.61 spikes/s in correct trials, mean = 19.01 spikes/s in error trials).

Relationship between neuronal activities during color cue period and D3 periods

Of 139 neurons with response during the color cue period, 51 neurons (CT response, $n = 36$; C response, $n = 9$; T response, $n = 6$) also showed delay-period activity during the D3 period. Of 36 neurons with the CT response during the color cue period, 23 neurons exhibited CT delay-period activity, 8 neurons exhibited C delay-period activity, and 5 neurons exhibited T delay-period activity during the D3 period. Of nine neurons with the C response during the color cue period, five

neurons showed CT delay-period activity, four neurons showed C delay-period activity, and no neurons showed T delay-period activity during the D3 period. Of six neurons with the T response during the color cue period, two neurons showed CT delay-period activity, four neurons showed T delay-period activity, and no neurons showed C delay-period activity during the D3 period (Table 2).

Recording sites

All neurons with the object-selective response during the C1 and/or C2 period were recorded from the VLPFC (Fig. 24*A*; Table 3). We could not find a difference between the distributions of neurons with the order-nonselective response and those with the order-selective response (Fig. 24*A*). In the neurons with object-nonselective response during the C1 and/or C2 period, all neurons were recorded from the VLPFC, except for one neuron that was recorded from the DLPFC (Fig. 24*B*; Table 3). We could not find a difference in the distribution between neurons with the order-nonselective response and those with the order-selective response (Fig. 24*B*).

During the D1 and D2 periods, all neurons with object-selective delay-period activity were recorded from the VLPFC (Fig. 24*C*; Table 3). We could not find a difference in distribution between neurons with order-nonselective activity and those with order-selective delay-period activity (Fig. 24*C*). Object-nonselective delay-period activity during the D1 and D2 periods was recorded from both the DLPFC and VLPFC (Fig. 24*D*; Table 3). Of the neurons recorded from DLPFC, six neurons were activated during both the D1 and D2 periods.

The neurons with a response during the color cue period were recorded from both the DLPFC and the VLPFC (Fig. 25*A*; Table 3). Although the proportions of neurons with CT, C, and T responses among neurons activated during the color cue period in the DLPFC were not different from those in the VLPFC, the proportion of neurons activated during the color cue period was much smaller in the DLPFC (10%). Thus the neurons activated during the color cue period were mainly located in the VLPFC (90%). In addition, the response latencies of all DLPFC neurons were >200 ms (mean = 289 ms). In contrast, the response latencies of most of the VLPFC neurons (80%) were <200 ms (mean = 163 ms) as observed in Fig. 25*B*. This difference was statistically significant ($z = 4.62$, $P < 0.0001$).

The neurons with delay-period activity during the D3 period were recorded from both the DLPFC and the VLPFC (Fig. 25*C*; Table 3). Similar to the response during the color cue
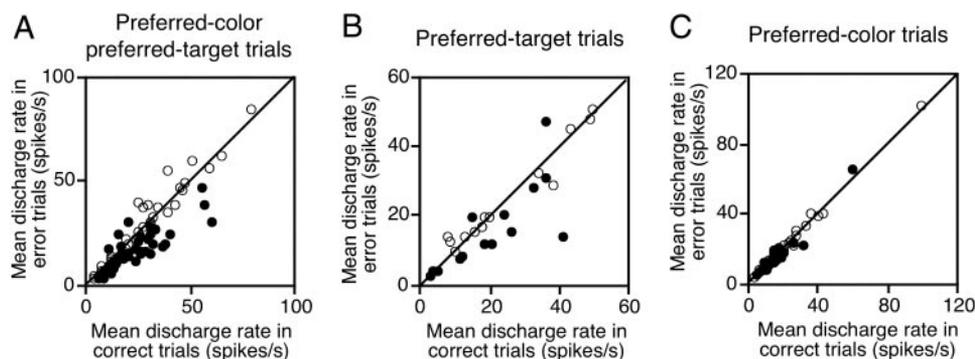
FIG. 23. *A*: comparison between CT delay-period activities during correct and error trials in preferred-color preferred-target trials. *B*: comparison between T delay-period activities during correct and error trials in preferred-target trials. *C*: comparison between C delay-period activities during correct and error trials in preferred-color trials. ○, discharge rate of neurons whose responses during correct and error trials were not significantly different (Mann-Whitney *U* test, $P > 0.05$); ●, discharge rate of neurons whose responses during correct and error trials were significantly different (Mann-Whitney *U* test, $P < 0.05$).
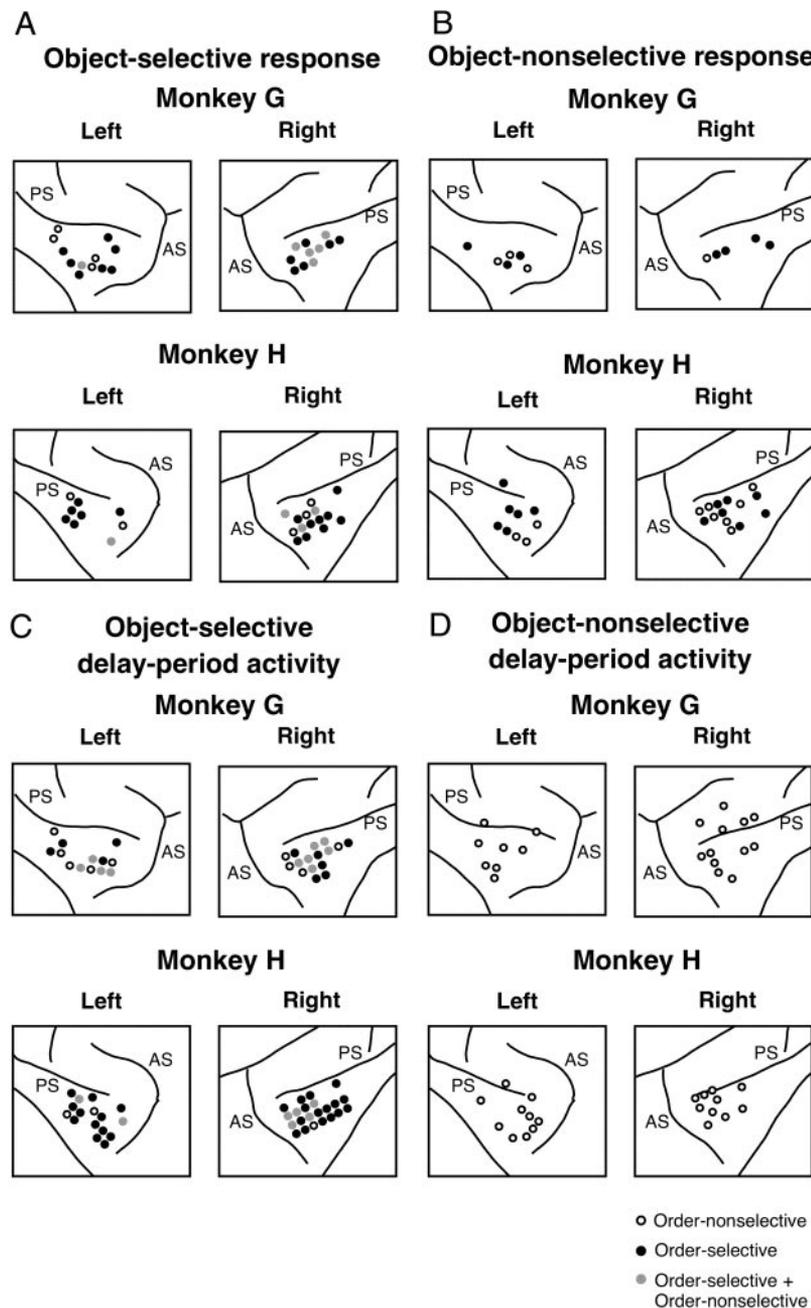
FIG. 24. Surface location of neurons with object-selective response (*A*) and object-nonselective response (*B*) during C1 and/or C2 period. Recording area of neurons with object-selective delay-period activity (*C*) and object-nonselective delay-period activity (*D*) during the D1 and/or D2 period. ○, surface locations where order-nonselective response was recorded; ●, surface locations where order-selective response was recorded. Gray circles indicate surface locations where both order-nonselective and order-selective responses were recorded. AS, aracuate sulcus; PS, principal sulcus.

period, the neurons with delay-period activity during the D3 period were mainly located in the VLPFC.

DISCUSSION

To study the neuronal mechanisms for the encoding, mnemonic, and retrieval processes of the working memory dealing with multiple objects and the order of object presentation, we recorded neuronal activity from the lateral prefrontal cortex of monkeys performing the SPR task. We found order-selective activities during the cue and/or the delay period. Because our task does not contain motor aspects before the color cue presentation, these order-selective activities must be a part of the sensory processes rather than the preparation of sequential action. In addition, neurons with order-selective delay-period activity did not exhibit object-selective delay-period activity during the DMS task. This means that there are different groups of neurons being responsible for the order of object information and its memory. During the color cue period, we recorded object-selective activities (CT and T responses), although the target object was not presented during this period.

Coding object and temporal order of object presentation during cue period

Seventy-three percent of neurons with the object-selective response and 55% of neurons with the object-nonselective response showed the order-selective response. In these neurons, although the visual stimulus was physically identical, response magnitudes during the C1 and C2 periods were significantly different.

TABLE 3. *Classification of responses in DLPFC and VLPFC*

Type	DLPFC	VLPFC
C1/C2 periods		
Object-selective		
Order-nonselective	0	22
C1-dominant	0	33
C2-dominant	0	26
Object-nonselective		
Order-nonselective	0	17
C1-dominant	1	20
C2-dominant	0	0
D1/D2 period		
Object-selective		
Order-nonselective	0	40
C1-coding (D1)	0	16
C1-coding (D2)	0	34
C1-coding (D1 and D2)	0	2
C2-coding	0	30
Object-nonselective	7	54
Color cue period		
CT response	9	61
C response	3	33
T response	2	13
Nonselective	0	18
D3 period		
CT activity	6	96
C activity	11	50
T activity	5	33
Nonselective	18	41

DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

The modulation of the visual response of prefrontal neurons has been described in many previous reports (Asaad et al. 2000; Everling et al. 2002; Funahashi et al. 1990; Hasegawa et al. 2000; Iba and Sawaguchi 2002; Kobayashi et al. 2002; Mikami et al. 1982; Rainer et al. 1998b; Sakagami and Niki 1994a,b; Sakagami and Tsutsui 1999; Sakagami et al. 2001; Watanabe 1981, 1986, 1990, 1992). Previous results and these results confirmed that not only the physical property but also the behavioral significance of a sensory stimulus is a factor critical to the activation of prefrontal neurons.

How are the object- and order-selective responses elicited? One possible mechanism may be that neurons with the object- and order-selective visual responses receive the object information and the order information separately and integrates them. However, our data do not support this mechanism. Latencies were not different among these responses. In addition, in some neurons the C2-dominant response during the C2 period depended on the cue object presented during the C1 period. Furthermore, we could not find the object-nonselective C2-dominant response. These findings suggest that neurons with the object- and order-selective responses are not receiving object information and order information separately. That is, our monkeys may be processing order information individually for each object and in parallel with order-nonselective object information.

When response magnitudes during the C1 and C2 periods were significantly different, the response was regarded as order-selective. This difference could be caused by the enhancement or suppression of sensory responses during the C1 or C2 period. To test this hypothesis, we compared responses during the SPR task and the DMS task. In 75% of neurons with the C1-dominant response, the response magnitude during the

C1 period was similar to that during the cue period of the DMS task, and the response magnitude during the C2 period was significantly smaller than that during the cue period of the DMS task. This result suggests that the C1-dominant response must be elicited by the suppression of sensory responses during the C2 period. Thus the C1-dominant response was actually generated by the same sensory input as in the order-nonselective response, but suppressed during the C2 period. That is, the C1-dominant response may be considered as a C2-dominant suppression rather than a C1-dominant activation. On the other hand, in about two-thirds of neurons with the C2-dominant response, the response magnitude during the C1 period was similar to that during the cue period of the DMS task, and the response magnitude during the C2 period was significantly larger than that during the cue period of the DMS task. In one-third of neurons with the C2-dominant response, the response magnitude during the C1 period was significantly smaller than that during the cue period of the DMS task, and the response magnitude during the C2 period was similar to that during the cue period of the DMS task. Thus the C2-dominant response was based on either C2-dominant enhancement or C1-dominant suppression.

To generate the object- and order-selective responses during the C2 period, object-selective delay-period activity during the D1 period could contribute by enhancing or suppressing the response during the C2 period. In fact, just before the C2 presentation during the last phase of the D1 period, population activity was slightly higher in the trials when the preferred object was presented during the C2 period than in the trials when the nonpreferred object was presented during the C2 period (Fig. 4*A*) or the preferred object was presented during the C1 period (Fig. 16*F*).

The object-selective and C2-dominant response magnitudes in the error trials were significantly smaller than those in the correct trials. This finding will support the behavioral significance of the C2-dominant response in the performance of the SPR task. The order-nonselective and C1-dominant response magnitudes during the C1 period were not significantly different in the error trials. One possible interpretation of these results may be that these neurons have no significant roles in the performance of the SPR task. However, because we defined error trials as those in which the monkeys made wrong choices at the end of trials, most of the errors of this complex task may be caused by activity during the later periods of the task rather than firing rate at the beginning of each trial.

Recently, Ninokura et al. (2004) have examined prefrontal neuronal activity while monkeys performed a task in which the monkey had to memorize three objects and their order of presentation. They found visual responses that depended on the object, order, or both object and order. Although this result is similar to our result, there are differences. One major difference is the distribution of neurons with object-nonselective and order-selective responses. We recorded almost all neurons with this type of response from the VLPFC, but Ninokura et al. recorded such neurons from the DLPFC and not from the VLPFC. Although both of these tasks look similar in terms of visual objects and their sequence, the nature of memory may be different. In Ninokura's task, monkeys were required to do the sequential action toward the stimuli in the same sequence presented during the cue periods. In contrast, our monkeys were required to select one object at the time of color stimulus
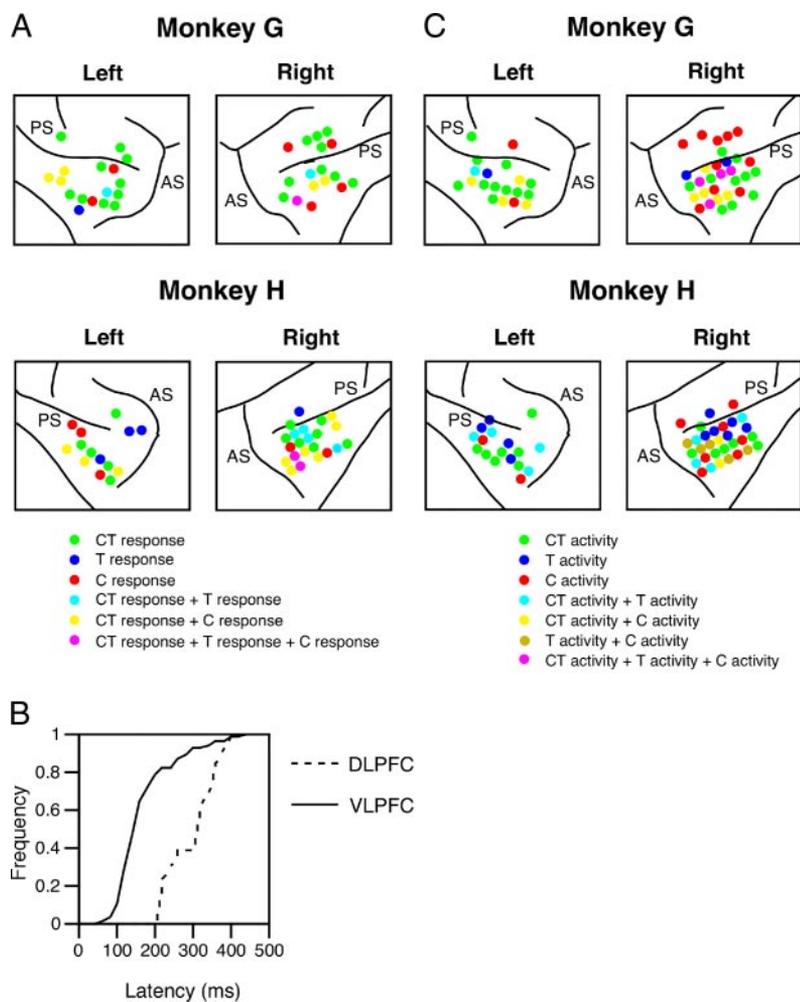
FIG. 25. *A*: surface locations of neurons with response during color cue period. AS, aracuate sulcus; PS, principal sulcus. *B*: cumulative summation curve of response latencies of DLPFC neurons (*n* = 14) and VLPFC neurons (*n* = 125). *C*: surface locations of neurons with delay-period activity during D3 period. AS, aracuate sulcus; PS, principal sulcus.

and that selected object became the target of action. Before this epoch our monkey did not know what the target of action would be. Thus in the task of Ninokura et al., memory of objects and their order contained motor aspect or preparation of action. In contrast, in our task, memory of objects and their order did not contain motor aspect before the presentation of color cue. This difference may explain why Ninokura et al. found object-nonselective and order-selective response in the DLPFC. Recently, Hasegawa et al. (2004) found neuronal activity that was modulated according to the step of a self-ordered task from the DLPFC; this result indicates that the DLPFC could contribute to the processing of order information of action.

Ninokura et al. recorded object-nonselective and order-selective response to the first, second, and third cues. In contrast, we recorded object-nonselective and order-selective responses to the first cue, not to the second cue. These differences could be caused by the difference in the number of memorized objects. In our SPR task, monkeys had to memorize two objects and the order of its presentation. To recognize whether a cue is the first or second cue, monkeys could pay attention to the presence of the first cue. If not, the cue is the first one, and if yes, the cue is the second one. However, this simple strategy might not be sufficient for performing the task used by Ninokura et al., because there were three memorized objects. To recognize whether a cue is the first cue, second cue,

or third cue, a more complex neuronal mechanism may be necessary.

Order-selective delay-period activities

In 67% of neurons with object-selective delay-period activity, delay-period activity depended on both the object and temporal order of its presentation (C1-coding and C2-coding delay-period activities). Most neurons (90%) with order-selective delay-period activity did not exhibit object-selective delay-period activity during the DMS task. In addition, neurons with order-selective delay-period activity showed decreased discharge rates during the delay period of the error trials. These results suggest that neurons with order-selective delay-period activity specialized to participate in the storing of information regarding both the object and the temporal order of its presentation during the SPR task.

Previous studies showed that some delay-period activities depended on both the cue and its order of presentation. Barone and Joseph (1989) recorded prefrontal neuronal activity while a monkey performed a delayed-response task in which the monkey was required to retain information regarding three target positions and the temporal order of presentation and to respond by performing sequential saccades and hand-reaching movements toward the targets in the same temporal order. They found that one class of neurons exhibited tonic activity

with spatial and temporal selectivity, such that tonic activity was observed only when the first visual cue was presented at one particular position out of three. Funahashi et al. (1997) recorded prefrontal neuronal activity while a monkey performed a delayed sequential reaching task, in which the monkey is required to retain information on two of three target positions and the temporal order of presentation, and to respond by performing hand-reaching movements toward the targets in the same temporal order. They found position-dependent activity elicited when a cue was presented at a particular position in a particular temporal order. Ninokura et al. (2003) found that 43% of neurons with delay-period activity was selective for the sequence in which visual objects were presented during the cue period. Previous studies (Barone and Joseph 1989; Funahashi et al. 1997; Ninokura et al. 2003) showed the presence of delay-period activities coding both the item (spatial position or object) and the order of presentation. Our data are comparable to those of previous studies in a sense that we found object- and order-selective delay-period activities in the prefrontal cortex. The previous results suggest that the lateral prefrontal cortex contributes to the memorization of the temporal order, and our results suggest that the VLPFC participates in retaining not only object information but also temporal information.

However, our results are different from previous results in several points, and we believe that these differences provide us useful knowledge about the functions of the prefrontal cortex. In this study, we could not find delay-period activity that was elicited in only one of six sequences. In previous studies (Funahashi et al. 1997; Ninokura et al. 2003), some neurons were activated during the delay period in only one sequence. In these previous experiments, the monkeys memorized multiple spatial locations or objects and the order of their presentation, and during the response period, the monkeys had to respond sequentially for each spatial location or object in the same order of presentation. To execute a sequential response on the basis of the memorized items presented sequentially, the existence of delay-period activity specific for one sequence may have an advantage. In contrast, in our SPR task, the monkeys had to memorize the first and second cue objects and retrieved one object on the basis of the color cue. The monkeys selected one of three objects at the time of color cue appearance. They do not need to memorize each combination separately, because they were not required to repeat that sequence afterward. During the color cue period, the existence of delay-period activity that depended on the specific sequence of cue presentation has no advantage. This could be the reason why we did not detect delay-period activity that was elicited in only one of six sequences.

Order-nonselective delay-period activity

Thirty-three percent of neurons with object-selective delay-period activity did not exhibit dependence on the temporal order of cue presentation (order-nonselective delay-period activity). In these neurons, delay-period activity followed the presentation of the preferred object and continued until the presentation of the next object cue or the color cue.

In these neurons, delay-period activity during the correct trials was not significantly different from that during the error trials in the SPR task. In most of the neurons (95%) with the

order-nonselective delay-period activity, object-selective delay-period activity was also found during the DMS task. In addition, during the DMS task, these delay-period activities significantly decreased during the error trials. Thus order-nonselective delay-period activity may participate in the mnemonic process in the DMS task.

Order-nonselective delay-period activity ended when an intervening stimulus was presented. This is inconsistent with previous results (di Pellegrino and Wise 1993; Miller et al. 1996), in which the delay-period activity of the prefrontal cortex was maintained throughout the trial even when other intervening stimuli were presented during the delay. These differences could be caused by the nature of the intervening stimulus. In previous studies (di Pellegrino and Wise 1993; Miller et al. 1996), the intervening stimuli were distractors, so the monkey neglected the intervening stimuli. On the other hand, in our study, the monkey had to recognize and memorize the visual stimulus during the C2 period. These differences could account for the difference in delay-period activity between our present and previous studies.

Neuronal response related to retrieval of remembered object

Two-thirds of the neurons with a response during the color cue period showed target object selectivity (CT and T responses), although the target object was not presented during this period. These CT and T responses could play a critical role in the retrieval of an item among items in the working memory.

The LPFC participates in selecting a relevant target among several distractors (Hasegawa et al. 2000; Iba and Sawaguchi 2002) and in selecting the forthcoming movement (Hasegawa et al. 1998; Hoshi and Tanji 2004; Hoshi et al. 2000; Kim and Shadlen 1999; Sakagami and Niki 1994a,b; Sakagami and Tsutsui 1999; Sakagami et al. 2001; Watanabe 1986). The results of these experiments confirmed the importance of the active maintenance of information for the subsequent use and response selection or decision-making. In these experiments, however, either a target was selected before it was memorized or a target was selected among the visible objects. Here in our task, when the monkey attempted to select a target during the color cue presentation, the objects were not visible and the monkey was required to retrieve memorized objects from the working memory. This is actually one of the typical processes of the working memory that we usually encounter in our daily life. In this study, the VLPFC neurons showed responses that depended on the target object retrieved from the working memory (CT and T responses). In addition, the neurons with CT and T responses showed lower activities during the error trials than those during the correct trials. These neurons can participate in the retrieval of a target object from two objects in the working memory. In contrast, the C response showed color selectivity but not target object selectivity. The neurons with the C response showed a similar activity during the correct and error trials. These results suggest that the C response is not affected by the retrieval of the target object.

In the DLPFC, we could detect the neurons with a response to the color cue. However, the number of neurons was small, and the response latencies of these neurons were >200 ms. These results suggest that the DLPFC could not contribute to the retrieval process. The proportions of neurons with the CT, C, and T responses in the DLPFC were not significantly

different from those in the VLPFC. The DLPFC receives input from the VLPFC (Barbas and Pandya 1989). These anatomical data suggest that neurons with the CT, C, and T responses in the DLPFC receive information from neurons with the CT, C, and T responses in the VLPFC.

Neuronal response related to mnemonic process of retrieved object

During the D3 period, we found the delay-period activities with CT, C, or T properties (CT, C, and T delay-period activities). During this period, monkeys had to memorize the target object retrieved during the color cue period. Because CT and T delay-period activities depended on the target object retrieved during the color cue period, and the neurons with the CT and T delay-period activities showed lower activities during the error trials than those during the correct trials, these neurons may participate in the mnemonic processing of the target object retrieved during the color cue period.

Although, monkeys did not have to memorize the color in our task, some neurons showed C delay-period activity during the D3 period. This delay-period activity is not necessary for performing the SPR task, and the functional role of this C delay-period activity is unclear. Similar delay-period activities were recorded from the lateral prefrontal cortex in previous studies (Funahashi et al. 1993b; Takeda and Funahashi 2002). In these studies, monkeys had to perform a memory-guided saccade to the opposite direction of the visual cue (Funahashi et al. 1993b) or 90° clockwise direction from the cue direction (Takeda and Funahashi 2002). Although monkeys had to memorized target direction but not had to memorize the cue location during the delay period, the directional delay-period activity of about two-thirds of neurons depended on the cue location.

Contribution of the VLPFC in SPR tasks

In this study, we found the object-selective response during the C1 and/or C2 period and delay-period activity during the D1 and/or D2 period in the VLPFC, not in the DLPFC. This suggests that the VLPFC contributes to the memorization of object information during the delay period. This is supported by previous anatomical, neuropsychological, and neurophysiological data. The DLPFC receives projections from the inferior parietal association cortex (Andersen et al. 1985; Barbas and Mesulam 1985; Cavada and Goldman-Rakic 1989; Petrides and Pandya 1984), which is involved in visuospatial processing (Barash et al. 1991a,b; Chafee and Goldman-Rakic 1998; Snyder et al. 1997). In contrast, the VLPFC receives dense projections from the inferotemporal association cortex (Barbas 1988; Seltzer and Pandya 1989; Ungerleider et al. 1989; Webster et al. 1994), which is involved in the representation of visual objects (Bruce et al. 1981; Desimone et al. 1984; Fuster 1990; Fuster and Jervey 1981; Miller et al. 1991, 1993; Perret et al. 1982). Lesions of the DLPFC, and more specifically those restricted to the principal sulcus or the middle third of its sulcus, produce a deficit in the performance of spatial delayed-response and spatial delayed-alternation tasks (Butters and Pandya 1969; Butters et al. 1971, 1972; Funahashi et al. 1993a; Mishkin 1957). Lesions of the VLPFC cause impairments in the performance of tasks based on the

identity or features of object rather than spatial location. This impairment is observed in a delayed object alternation task (Mishkin and Manning 1978) and object/color delayed-matching or nonmatching-to-sample tasks (Iversen and Mishkin 1970; Kowalska et al. 1991; Mishkin and Manning 1978; Passingham 1975). In neurophysiological studies, it appears that neurons tuned specifically to the identity or features of an object are much fewer in the DLPFC than in the VLPFC (Fuster et al. 1982; O'Scalaidhe et al. 1997, 1999; Wallis and Miller 2003; Wilson et al. 1993). These previous results and our present results suggest that the VLPFC plays an important role in encoding and retaining information regarding the features of an object. In contrast, the contribution of the DLPFC to the encoding and retaining information regarding the feature of an object is small.

Neurons with the CT, C, and T response during the color cue period were recorded from both the DLPFC and VLPFC. However, larger population of these neurons was recorded from the VLPFC. In addition, the response latencies were shorter in the VLPFC. These results indicate that the neurons in the VLPFC were activated earlier than those in the DLPFC. A similar temporal difference in response between the DLPFC and VLPFC was found in human event-related functional MRI (fMRI) studies (Leung et al. 2000; Wagner et al. 2001) and a monkey neurophysiological study (Hoshi and Tanji 2004). These results suggest the greater contribution of the VLPFC in the retrieval of an object from multiple objects in the working memory. This is supported by human neuroimaging data. Human fMRI and PET studies showed that increases in activity are observed in the mid-VLPFC when human subjects retrieve one of the spatial and nonspatial aspects of an encoded stimulus on the basis of the color stimulus (Cadoret et al. 2001; Kostopoulos and Petrides 2003).

Neurons with delay-period activity during the D3 period were also recorded from both the DLPFC and VLPFC. However, large proportion of these neurons was recorded from the VLPFC. These results suggest the greater contribution of the VLPFC in the memorization of a target object. On the other hand, the fact that a small number of delay-period activities in the DLPFC was target object-selective and/or color-selective suggest some contribution of the DLPFC when the monkeys had to memorize what to respond.

Our results suggest the contribution of the VLPFC in performing this SPR task. However, some other cortical regions also could contribute to the performance of the SPR task. One possible cortical region is the inferotemporal cortex (IT). The IT is connected with the VLPFC (Barbas 1988; Seltzer and Pandya 1989; Ungerleider et al. 1989; Webster et al. 1994) and is involved in the representation of visual objects (Bruce et al. 1981; Desimone et al. 1984; Fuster 1990; Fuster and Jervey 1981; Miller et al. 1991, 1993; Perret et al. 1982). Many studies showed that IT neurons exhibited selective delay-period activity during the performance of a visual short-term memory task (Fuster 1990; Fuster and Jervey 1981, 1982; Mikami and Kubota 1980; Miller et al. 1993; Miyashita and Chang 1988). In addition, the contextual modulation of a visual response in the IT has been reported (Eskandar et al. 1992; Miller et al. 1993; Mikami and Kubota 1980). These results suggest that the IT could contribute to the encoding, mnemonic and retrieval processes of the SPR task. However, because the difference in

the roles between the VLPFC and the IT is unclear, further experiments that compare neuronal activity in the IT with that in the VLPFC are necessary.

Information flow in the SPR task

Information flows proposed on the basis of our results are shown schematically in Fig. 26. We draw this schema based on the following hypotheses. At first, when a single neuron responds during the adjacent periods and maintains its response properties during these periods, the neuron carries the information from the first period to the second period; e.g., continuous activation from the cue period to the delay period. Second, when two neurons activated during adjacent periods share the same kind of response properties, and the timing of the activation-end of neuron 1 response and the timing of the activation-start of neuron 2 activation were synchronized, neuron 1 can send the information to neuron 2.

During the C1 period, the VLPFC receives the object information from the visual association cortex, probably from the IT. This object information elicits the object-selective response in the order-nonselective and C1-dominant responses. It also elicits a small response in some of the neurons with the C2-dominant response.

Activity during the D1 period actually started during the C1 period. The object information travels from the neurons with the order-nonselective visual response to the neurons with either the order-nonselective delay-period activity or the C1-

coding (D1) delay-period activity. This information flow was suggested by the following results. Among neurons with the order-nonselective object-selective response during the C1 period, 36% (8/22) also exhibited the object-selective delay-period activity. The delay-period activities of these neurons was either the order-nonselective or C1-coding (D1) activity (Table 1). At the population level, neurons with the order-nonselective visual response exhibited the object-selective delay-period activity (Fig. 16*B*).

Neurons with the C1-dominant response showed the object-selective response during the C1 period but they were not activated during the delay period (Fig. 16*D*). This result suggests that neurons with the C1-dominant response could not code visual information during the delay period. However, because the object-selective properties of the C1-dominant response are similar to those of the C1-coding (D1) delay-period activity, and the end of the C1-dominant response synchronized with the start of the C1-coding (D1) delay-period activity, the C1-dominant response may contribute to generating the C1-coding (D1) delay-period activity. In addition, when the C1 object was presented, the difference between the preferred-object trials and nonpreferred-object trials was detected earlier for the order-nonselective delay-period activity than for C1-coding (D1) activity (Fig. 13*E*). This result suggests that the C1 object information encoded by the neurons with the order-nonselective delay-period activity is conveyed to the neurons with the C1-coding (D1) delay-period activity.
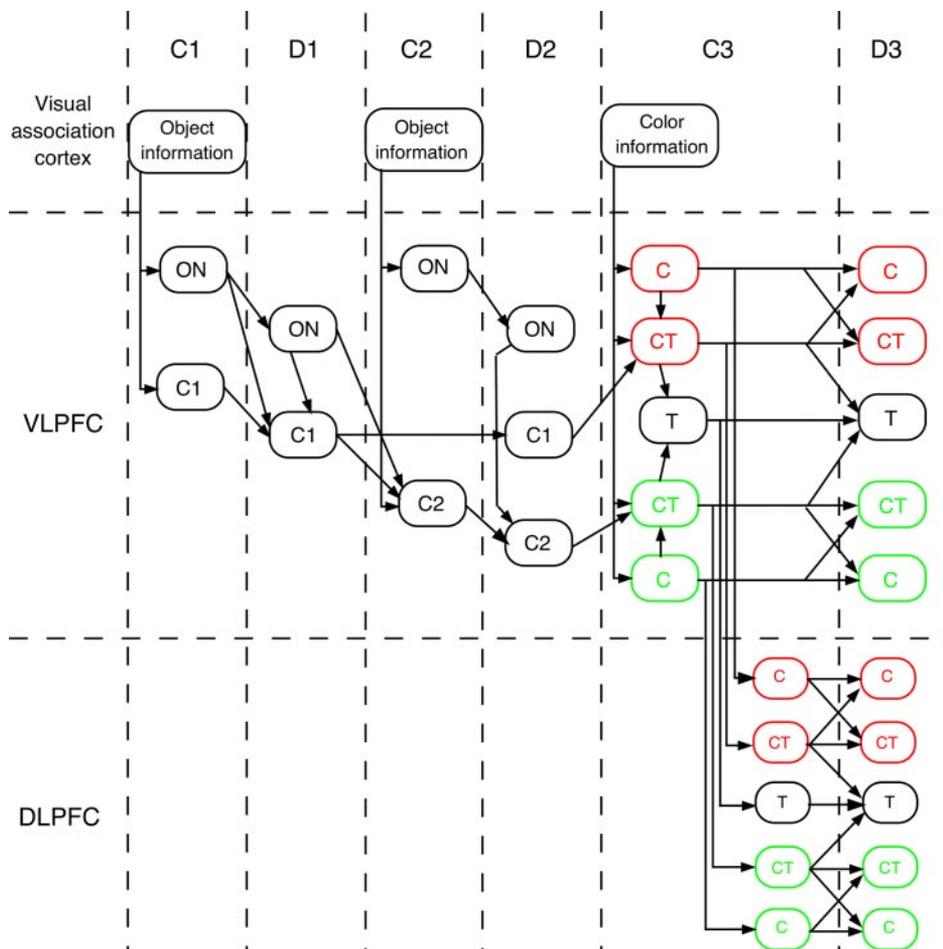

FIG. 26. Schema of information flow based on results of this experiment.

During the C2 period, the VLPFC receives object information from the visual association cortex, probably from the IT. It also elicits the order-nonselective and the C2-dominant responses. As described already, to generate the C2-dominant responses during the C2 period, object-selective delay-period activity during the D1 period could contribute by enhancing the response during the C2 period.

Activity during the D2 period actually starts during the C2 period. The individual neurons with order-nonselective visual response do not share the same object preference during the D2 period at the population level as seen in Fig. 16*B*. At the same time, the individual neurons with order-nonselective delay-period activity during the D2 period do not share the same object preference with the phasic component of activity during the C2 period at the population level as seen in Fig. 13*A*. These results suggest that individual neurons cannot participate in transmitting the C2 object information from the C2 period to the D2 period. However, different neurons can contribute to transmission of this information. Neurons with order-nonselective visual response can send C2 object information to neurons with the order-nonselective delay-period activity during the D2 period. This is because both neurons share the same properties.

Neurons with the C2-dominant response showed activity during the D2 period at the population level (Fig. 16*F*). However, the object preferences of these neurons were also different between the cue period and the delay period at the individual neuron level (Table 1) and at the population level (Figs. 16*F* and 13*D*). Thus these neurons cannot transfer object-selective information by themselves from the cue period to the delay period. Instead, neurons with the C2-dominant response probably transfer object-selective information to neurons with the C2-coding delay-period activity, because both types of neurons shared the same type of selectivity and the activation-end and -start were synchronized.

Neurons with order-nonselective delay-period activity during the D2 period can also send information to neurons with C2-coding delay-period activity. This can be seen in the population activity related to C2-object information which starts earlier in order-nonselective neurons than in C2-coding neurons (Fig. 13*E*).

As seen in Fig. 13*E*, when the C2 object was presented, the C1-object-selective activity of order-nonselective neurons ended first, and the activity of C1-coding (D1) neurons ended. This was synchronized with the start of the activation in C1-coding (D2) neurons. These results suggest that the C1 object information is conveyed from the C1-coding (D1) neuron to the C1-coding (D2) neuron during the C2 period.

During the color cue period, the neurons with the CT response received color information because these neurons were activated by color stimuli during the fixation task. This result also suggests that the target selectivity of the CT response is achieved by suppressing the visual response to a color cue when the nonpreferred object was selected from the working memory. On the other hand, neurons with the T response did not respond to color stimuli during the fixation task. This result indicates that neurons with the T response do not receive color information. Although some of the neurons with CT and T responses showed the object-selective response during the C1 and/or C2 period, their object selectivity was often different from that during the color cue period. Thus the individual neuron may have multiple functions. For instance, it could code object A during the C1 and/or C2 period and code object B during the color cue period. Some neurons with the CT response were also activated during the delay period. Those delay-period activities also differed from the typical delay-period activity. In these neurons, the delay-period activity was observed only near the end of D2 period. The neurons with the T response were not activated during the D1 and D2 periods. This observation suggests that the neurons with T response are a different class of neuron. At the end of the delay period, the neurons with the CT response whose preferred color was red exhibited C1-coding delay-period activity; the neurons with the CT response whose preferred color was green exhibited C2-coding delay-period activity.

These results suggest that the neurons with the C response and CT response receive color information from the visual association cortex, probably from the IT. At the same time, neurons with the CT response receive object and temporal order information from neurons with delay-period activity, combined color, and object information. This combined information is then integrated into object information in neurons with the T responses to perform the future saccade.

During the color cue period, color information and retrieved target object information were conveyed from neurons with the visual response to those with the D3 delay-period activity. During the D3 period, most of neurons with the CT response also exhibited the delay-period activity with the CT property, and several neurons with the CT response exhibited the delay-period activity with the C or T property. Neurons with the T response exhibited the delay-period activity with the CT or T property. Neurons with the C response exhibited the delay-period activity with the C or CT property. These results suggest that both color information and target information are conveyed from neurons with the CT response during the color cue period to neurons with D3 delay-period activity carrying the CT property. Color information was conveyed from neurons with the CT or C response to neurons with the D3 delay-period activity carrying the CT or C property, and target information was conveyed from neurons with the CT or T response to neurons with the D3 delay-period activity carrying the CT or T property.

Most of the object-selective, order-selective, and color-selective neurons during the C1, D1, C2, D2, color cue, or D3 periods were mainly recorded from the VLPFC. Also, the latencies of the response of the VLPFC neurons were shorter than those of the DLPFC neurons. This suggests that the object and order information of our task are processed mainly in the VLPFC. During the color cue period, the retrieval process of an object is also processed mainly in the VLPFC. In the DLPFC, neurons with CT, C, or T responses receive information from neurons with the CT, C, or T responses in the VLPFC. The DLPFC uses this information for future execution of behaviors, such as saccade.

Prefrontal cortex and working memory

Neuronal activity during the delay period has been examined repeatedly while monkeys performed various types of working memory task (Chafee and Goldman-Rakic 1998; Constantinidis et al. 2001; di Pellegrino and Wise 1991, 1993; Funahashi et al. 1989, 1993b; Fuster 1973; Fuster et al. 1982; Kubota and Niki 1971; Kubota et al. 1974; Miller et al. 1996; Niki 1974;

Niki and Watanabe 1976; Rainer et al. 1998a; Rao et al. 1997; Sawaguchi and Yamane 1999; Takeda and Funahashi 2002; Watanabe 1981; Wilson et al. 1993). The sustained delay-period activity with directional preference or object preference has been considered to be a neuronal correlate of a mechanism that temporarily stores spatial or object information (Funahashi and Kubota 1994; Fuster 1997; Goldman-Rakic 1987).

Working memory involves both a short-term storage capacity for maintaining mental representation and a capacity for manipulating stored information (Baddeley 1986; Baddeley and Logie 1999). It has been suggested that the prefrontal cortex plays a critical role in working memory (Baddeley 1986; Funahashi and Kubota 1994; Fuster 1997; Goldman-Rakic 1987). This has been shown by both neurophysiological studies on monkey and neuroimaging studies on human. However, in most studies of monkeys, neuronal activities were examined during a delayed-response task or a delayed-matching-to-sample task, in which the monkey had to memorize single spatial or object information but did not have to manipulate stored information. In this study, monkeys had to memorize two objects and the order of their presentation and manipulate these pieces of information to select a target object. The order-selective delay-period activity found in this experiment was object- and order-selective as well as task period–specific. That is, most of the order-selective neurons were activated either during the D1 or D2 period but not both. These results suggest that prefrontal neurons operate in a way similar to the registers in the CPU of a microcomputer. Three major types of order-selective neurons [C1-coding (D1), C1-coding (D2), and C2-coding] are registers that perform the SPR task, and temporally stored information must be manipulated during the color cue presentation to select the correct target. Thus our results indicate that the prefrontal cortex participates in the manipulation and integration of stored information and suggest that the prefrontal cortex plays a critical role in working memory.

Our SPR task contains several components of the working memory process; the encoding and maintenance processes of objects and temporal order and retrieval processes from the working memory. During the C1 and C2 periods, the object information and temporal order information must be encoded in the working memory. During these periods, different groups of neurons were found to encode the presentation of objects to those presented without order. This was in addition to the object-nonselective response neurons. During the D1 and D2 periods, the object information and temporal order information must be maintained in the working memory. During these periods, there were neurons that memorized the ordered presentation of objects in addition to the nonselective delay-period activity. Although there were some overlaps, neurons in each epoch were specialized. Logically it is possible the same neuron is responsible for coding C1 object and memorizing it during the D1 and D2 periods until the color cue period. However, neurons in the VLPFC of our monkeys did not work this way. Instead, C1 object information seemed to travel from the C1-coding (D1) delay-period activity to the C1-coding (D2) delay-period activity. In other words, functional units in the monkey VLPFC seem fragmented and specialized. In addition, there were neurons with order-nonselective or object-nonselective activities. These neurons may contribute to the SPR task by carrying object information.

During the color cue period, an object must be retrieved from two objects in the working memory. During this period, there were neurons encoding color and/or object retrieval. During the D3 period, retrieved object information must be maintained in the working memory. There were neurons related to these processes. In addition there were neurons carrying color information during the D3 period, although the color information is not necessary during this period. The VLPFC is participating to perform the SPR task using the various types of neurons described above. However, the VLPFC may also prepare for unexpected situations by keeping some information in reserve even if it is not directly related to performing the current task.

Thus there were neurons corresponding to each process of the SPR task. In other words, each process could be defined as a group of neurons that exhibits a particular function. These functions include encoding, maintenance and retrieval processes of the working memory, although there were some overlapping functions. These results suggest that the working memory is clearly fractionated into a number of different aspects.

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