Mnemonic Coding of Visual Space in the Monkey’s Dorsolateral Prefrontal Cortex

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SUMMARY AND CONCLUSIONS

1. An oculomotor delayed-response task was used to examine the spatial memory functions of neurons in primate prefrontal cortex. Monkeys were trained to fixate a central spot during a brief presentation (0.5 s) of a peripheral cue and throughout a subsequent delay period (1–6 s), and then, upon the extinction of the fixation target, to make a saccadic eye movement to where the cue had been presented. Cues were usually presented in one of eight different locations separated by 45°. This task thus requires monkeys to direct their gaze to the location of a remembered visual cue, controls the retinal coordinates of the visual cues, and controls the monkey’s oculomotor behavior during the delay period, and also allows precise measurement of the timing and direction of the relevant behavioral responses.

2. Recordings were obtained from 288 neurons in the prefrontal cortex within and surrounding the principal sulcus (PS) while monkeys performed this task. An additional 31 neurons in the frontal eye fields (FEF) region within and near the anterior bank of the arcuate sulcus were also studied.

3. Of the 288 PS neurons, 170 exhibited task-related activity during at least one phase of this task and, of these, 87 showed significant excitation or inhibition of activity during the delay period relative to activity during the intertrial interval.

4. Delay period activity was classified as directional for 79% of these 87 neurons in that significant responses only occurred following cues located over a certain range of visual field directions and were weak or absent for other cue directions. The remaining 21% were omnidirectional, i.e., showed comparable delay period activity for all visual field locations tested. Directional preferences, or lack thereof, were maintained across different delay intervals (1–6 s).

5. For 50 of the 87 PS neurons, activity during the delay period was significantly elevated above the neuron’s spontaneous rate for at least one cue location; for the remaining 37 neurons only inhibitory delay period activity was seen. Nearly all (92%) neurons with excitatory delay period activity were directional and few (8%) were omnidirectional. Most (62%) neurons with purely inhibitory delay period activity were directional, but a substantial minority (38%) was omnidirectional.

6. Fifteen of the neurons with excitatory directional delay period activity also had significant inhibitory delay period activity for other cue directions. These inhibitory responses were usually strongest for, or centered about, cue directions roughly opposite those optimal for excitatory responses.

7. The distribution of preferred cue locations was examined across the population of PS neurons having directional delay period activity. All possible cue locations were represented (left, right, up, down, and obliques); however, preferred cue locations in the contralateral hemifield predominated.

8. Tuning curves were calculated by the Gaussian formula to determine the directional specificity of delay period activity. The mean tuning indices ($T_d$) of PS neurons were 26.8° for excitatory delay period activity and 43.5° for inhibitory delay period activity.

9. Delay period activity was examined on trials in which the monkey made large saccadic errors for cues in a neuron’s preferred direction. Delay period activity was either truncated or absent altogether on such trials.

10. Of the 31 FEF neurons examined, 22 exhibited task-related activity: 17 had delay period activity and 10 showed directional delay period activity. The mean tuning index ($T_d$) of excitatory directional delay period activity in the FEF was 27.4°.

II. These results indicate that prefrontal neurons (both PS and FEF) possess information concerning the location of visual cues during the delay period of the oculomotor delayed-response task. This information appears to be in a labeled line code: different neurons code different cue locations and the same neuron repeatedly codes the same location. This mnemonic activity occurs during the 1- to 6-s delay interval—in the absence of any overt stimuli or movements—and it ceases upon the execution of the behavioral response. These results strengthen the evidence that the dorsolateral prefrontal cortex participates in the process of working or transient memory and further indicate that this area of the cortex contains a complete “memory” map of visual space.

INTRODUCTION

The role of the prefrontal cortex, particularly the principal sulcal (PS) region, in spatial memory has been strongly supported by lesion and developmental studies over the past two decades (17, 28, 57). Studies of single neuron activity in monkeys during performance of delayed-response tasks have also provided strong evidence of a prefrontal contribution to memory (4, 5, 15, 16, 20, 22, 37, 41, 42, 46, 50–53). Although many types of neural activity have been found in the prefrontal cortex, neurons that show sustained activity during the delay period are particularly relevant to the issue of mnemonic processing. Usually these neurons increase their discharge rates following the brief cue presentation and continue firing tonically during the delay period until the response is executed (5, 15, 20, 22, 52, 53). Such delay activity is often “directional” (44, 50–52) i.e., dependent on the left-right location of the cue or response, with some neurons responding only in conjunction with “left” trials and others only with “right” trials. Because experimental lesions of the dorsolateral prefrontal cortex profoundly affect the ability of monkeys to perform spatial delayed-response tasks correctly (17, 28), this delay activity has been assumed to be the cellular expression of a mnemonic code for the left-right direction of the cue or, equivalently, of the impending response (17, 18, 28).
In the present study we have explored further the properties of neural activity in the prefrontal cortex of monkeys performing delayed-response tasks. We sought to determine if prefrontal neurons were capable of accessing and maintaining activity reflecting the location of a target stimulus or motor response in any part of the visual field or if they were particularly tuned to left-right categorization. Further, we were interested in finding out if prefrontal neurons code stimuli in both the contralateral and ipsilateral visual fields equally well. To answer these questions, it was necessary to precisely control the retinotopic location of the cues, a requirement that has not been met in most previous studies. Accordingly, in the present study, we used an oculomotor analogue of the classical, manual delayed-response task, in which the monkeys were trained to maintain fixation during the cue presentation, and the visual cue could be presented at multiple locations around the visual field. This method allowed us to record the monkey’s direction of gaze throughout the task, and consequently to know the precise retinotopic location of the peripheral visual cue. In addition, the fixation requirement during the delay period insured comparable behavior in this period on every trial and also made it difficult for the monkey to adopt postural rather than mnemonic strategies to perform the task. Similar oculomotor delay tasks have previously been used for neurophysiological experiments in the frontal eye fields (6), the posterior parietal cortex (30), the caudate nucleus (32), and the substantia nigra (33) as well as in the prefrontal cortex (37, 40). The present study, however, is the first to explore the full perimetry of visual space with this paradigm. Preliminary results from this study have previously been presented in abstract form (15).

METHODS

Subjects

Three adult rhesus monkeys (Macaca mulatta, 3.2–5.3 kg, one male and two females) served as subjects. Prior to surgery and training they were adapted to a primate chair for 5–10 days.

Surgical procedures

Monkeys were prepared for chronic single-neuron recording using aseptic surgical technique and barbiturate anesthesia (pentobarbital sodium, intravenous to effect). For the purpose of recording eye movements (see below), a search coil was placed under the conjunctiva in one eye using the technique of Judge et al. (38). To secure the implant, stainless steel bolts with flattened heads were run along slots in the skull with the bolt head under the skull. The bolts, a connector for the search coil, and a stainless steel receptacle for attaching the monkey's head to the primate chair were bound together with dental acrylic. Because dura exposed during the lengthy training period (usually 3–4 mo) would thicken and impede the passage of electrodes, a second surgery to install the recording cylinder was performed only after the monkey became proficient on the oculomotor delayed-response task. Trephine holes (20 mm diam.) were made over the prefrontal region and a stainless steel recording cylinder placed over the hole. Additional acrylic was applied to bond the recording cylinder to the existing implant. Monkeys were given systemic antibiotics, fruits, and ad lib water and chow for 5–8 days following each surgery.

Behavioral techniques

The monkey sat in the primate chair during the experiment and his head was fixed to the chair by the restraining receptacle. Recording and training sessions usually lasted 2–3 h. A program on the PDP-11/23 computer presented the visual stimuli, sampled the monkey’s gaze coordinates as well as neuron activity, and delivered rewards.

Visual stimuli were presented on a monochrome CRT (19-in., RCA TC11119) subtending 48 × 38° in visual angle using a GRAPH-11 graphics card (Pacific Binary Systems). The fixation target was a small white spot (0.1° diam.), usually presented at the center of the CRT. The peripheral visual cues were filled white squares (0.7 × 0.7°).

Gaze coordinates were obtained with Robinson’s search coil method (56). The field coil and associated electronic equipment were made by C-N-C Engineering, Seattle, WA. Details concerning the sampling and storage of the eye and neural signals are given below.

The monkeys were rewarded with drops (0.2 ml) of lightly sweetened water via an electronic metering pump (A741, Waltham). Water was not available in the home cage; instead the monkeys worked to satiety (150–250 ml) each day in the laboratory. They were given monkey chow immediately upon return to their home cages and their intake of chow and body weight were closely monitored.

Oculomotor delayed-response task

Figure 1 shows schematic drawings of the oculomotor delayed-response task. Figure 1A depicts the timing of presentation of the fixation target, peripheral cues, and reward. Figure 1B illustrates records of horizontal and vertical eye movements and single neuron activity on a typical trial of the oculomotor delayed-response task.

Following a 5-s intertrial interval (ITI), the fixation target appeared at the center of the CRT. The monkey looked at the fixation target and maintained fixation for 0.75 s (the fixation period), whereupon the visual cue was presented for 0.5 s (the cue period) at one of four or eight peripheral locations (13° eccentric.

FIG. 1. A: temporal sequence of events in the oculomotor delayed-response task. B: eye movements and single neuron activity during an oculomotor delayed-response trial. ITI, intertrial interval; F, fixation period (0.75 s); C, cue period (0.5 s); D, delay period (3 s); R, response period (0.5 s).
All cue eccentricities were 13°. A crucial feature of the task was that the monkey had to maintain fixation throughout the cue period and also throughout the subsequent delay period. At the end of the delay period, the fixation target was extinguished; this was the "go" signal to make a saccade. If the monkeys made a saccadic eye movement within the next 0.5 s (the response period) to the location where the cue had been presented, they were rewarded with a drop of liquid. A correct response was defined as an eye movement that fell within a window (6° diam.) around the cue location.

We usually used one fixed delay interval (3 s) during recording, but longer delays (6 s) or combinations of two (3 and 6 s) or three (1.5, 3, and 6 s) different delays were sometimes used to examine activity across different delay intervals. Many of these neurons were also studied with other tasks (visual probe task, visually guided saccade task, etc.); these results will be presented in a future paper.

After analyzing the response properties of neurons, we sometimes employed microstimulation through the recording microelectrode to determine whether the recording site was in the frontal eye fields, based on the criteria of Bruce et al. (7).

Recording of single neuron activity

Single neuron activity was recorded with Parylene-coated tungsten microelectrodes (2–5 MΩ at 1 kHz, Micro Probe) that were advanced through the intact dura with a hydraulic microdrive (MO-95B, Narishige). Single neuron activity was amplified 10,000-fold by a differential amplifier (MDA-4, BAK). This signal passed through a low-pass filter to eliminate artifact from the search coil driver and then to a window discriminator (DIS-1, BAK) to isolate single neuron activity for the computer. We monitored both the raw activity signal and the window discriminator output simultaneously by an oscilloscope (5110A, Tektronix) and an audio monitor. Usually one electrode track was explored each recording session. Electrode tracks were separated on a 1-mm grid.

For the microstimulation, trains of pulses were generated by a biphasic pulse generator (BPG-1, BAK). Each pulse was 0.2 ms in duration, stimulation frequency was 330 Hz, and the train duration was 70 ms. The pulse generator output was connected to a constant-current stimulus isolation unit (BSI-1, BAK). Current was monitored by the voltage drop across a 1-kΩ resistor in series between the output of the isolation unit and the microelectrode. Current tested ranged up to 200 μA.

Data acquisition

The on-line computer system, in addition to carrying out the behavioral paradigms, sampled neural and ocular signals and stored these data in relation to task events on magnetic media. Voltages from the phase-sensitive detector representing the horizontal and vertical eye coordinates were digitized every 2 ms (500 Hz). These signals were also electronically differentiated to yield horizontal and vertical eye velocity. The velocity signals were also digitized and were used by the on-line computer program to identify each saccade that the monkey made via the algorithm of van Gisbergen et al. (25).

Two types of data storage files were stored. Event buffer files contained the time of every event that the computer had access to, including the time of each discriminated action potential, the time, duration, and amplitude of each saccade, and the time of events such as the appearance and disappearance of visual cues. Individual event buffer files usually contained 50–100 trials. Analogue buffer files contained multiple records (1–2 s epoches) of all of the analogue signals being sampled, together with the discriminated action potentials and a code representing progress through the task paradigm (see Fig. 1B).

Two types of computer-generated displays were monitored during the experiments. In one display, horizontal gaze, vertical gaze, and overall eye velocity were displayed as scrolling traces on a digital oscilloscope (1345A, Hewlett-Packard). Discriminated neuron activity was scrolled below these traces and ticks representing on-line saccade recognition were placed on the velocity trace. Superimposed on the scrolling display were two-dimensional representations of gaze, visual stimuli, and the fixation window. In the other display, rasters and histograms were viewed on the same oscilloscope to observe the overall neural data collection.

Data analysis

Using the stored event buffer files, we examined rasters and histograms of neuron activity for each cue location. These rasters and histograms were made with different alignment points including 1) the onset of cue, 2) the start of the delay period, 3) the end of the delay period, 4) the initiation of the saccadic eye movement during the response period, and 5) the appearance of the fixation target. Rasters and histograms were examined on the digital oscilloscope and copies were made using a digital plotter (7470A, Hewlett-Packard).

Neural activity during the delay period was also analyzed quantitatively for all neurons recorded. The average discharge rate...
during the delay period was calculated for each trial, and then overall mean discharge rates and standard deviations for each cue location were computed. We tested for significant delay period activity by comparing the mean discharge rate during the delay period for all trials having a given cue direction versus the mean discharge rate during the intertrial interval over all trials, using a two-tailed unpaired Student's t statistic and an alpha level of 0.05. Differences in delay period activity across different cue locations were evaluated using an analysis of variance (ANOVA).

**Histological analysis**

After 2–8 mo of nearly daily recording sessions the monkeys were killed with an overdose of pentobarbital sodium and perfused with saline followed by buffered Formalin. The brains were photographed. Frozen coronal sections were taken and stained with thionin.

Individual recording sites that had been marked with electrolytic lesions (20 μA, 10–15 s, tip negative) were identified. How-
ever, the long duration of recording and large number of electrode penetrations precluded identification of most penetrations, and their locations in the brain were estimated from their microdrive coordinates.

RESULTS

Task performance

All monkeys performed the oculomotor delayed-response task proficiently and the percentage correct was usually 90% or better for all cue locations. Figure 2 shows the distribution of saccade end points of one monkey in a visually guided saccade task (Fig. 2A) and in the 3-s (Fig. 2B) and 6-s delay conditions (Fig. 2C) of the oculomotor delayed-response task. Although the distribution of saccade end points is wider in the delay task than in the visually guided saccade task, nearly all saccades end near the appropriate location, even with 6-s delays.

The mean latencies for saccadic eye movements in the response period were 216.4 ± 33.0 (SD) ms in the visually guided saccade task, 298.3 ± 34.4 ms in the 3-s delay task, and 293.0 ± 37.4 ms in the 6-s delay task. The difference in

FIG. 4. Directional delay period activity of a principal sulcus neuron during the oculomotor delayed-response task. This neuron (5111, right hemisphere) exhibited directional delay period activity (F = 25.23, df = 7, 56, P < 0.001), responding only when the cue had been presented at locations in the upper quadrant of the contralateral visual field (90, 135, and 180°). The strongest delay period activity occurred at the 135° location. Visual cues were randomly presented at 1 of the 8 locations indicated in the center diagram. All cue eccentricities were 13° and all delay periods were 3 s.
mean latency between the visually guided saccade task and each of the delay tasks was statistically significant (3-s delay: \( t = 25.93, df = 454, P < 0.001 \); 6-s delay: \( t = 24.08, df = 493, P < 0.001 \)), whereas that between the 3-s and the 6-s delay tasks was not significant (\( t = 1.60, df = 477, P > 0.05 \)).

The mean duration of saccadic eye movements was 46.2 ± 8.5 (SD) ms in the visually guided saccade task, 44.9 ± 7.6 ms in the 3-s delay task, and 46.2 ± 8.2 ms in the 6-s delay task. There were no significant differences in mean saccade duration among the three tasks (ANOVA, \( F = 1.982; df = 2, 706; P > 0.1 \)).

Neural data base

We recorded from 319 neurons in the prefrontal cortex of three rhesus monkeys while they performed the oculomotor delayed-response task. As discussed in detail below, 288 of these neurons were from cortex within and surrounding the caudal half of the principal sulcus. We term these PS (principal sulcus) neurons and most of this report concerns their activity. The other 31 neurons were located within and near the anterior bank of the arcuate sulcus and were classified as frontal eye field (FEF) neurons. At some sites this FEF classification was confirmed by low microstimulation thresholds (<50 μA) for the elicitation of sac-

![FIG. 5. Directional delay period activity of a principal sulcus neuron. This neuron (5050, right hemisphere) showed tonic inhibitory delay period activity only when the cue was presented at 90° (\( F = 4.870; df = 3, 39; P < 0.025 \)). Visual cues were randomly presented at 1 of the 4 locations indicated in the center diagram. All cue eccentricities were 13° and all delay periods were 3 s.](http://jn.physiology.org/Downloaded from)
cadic eye movements. Data concerning these 31 FEF neurons is separately presented at the end of the RESULTS.

Of the 288 PS neurons thoroughly analyzed, most (170 neurons, 59% of total sample) had task-related activity in that their average discharge rate during at least one phase of the delayed-response task differed significantly ($P < 0.05$, $t$ test) from their ITI (InterTrial Interval) rate. Of these 170 neurons, 87 neurons (30% of total sample, 51% of total task-related neurons) had task-related activity.

For 33 (38%) of these neurons the delay period activity was the only significant task-related activity, but most (54 neurons, 67%) also had significant activity in the task segments immediately preceding or following the delay period (delay and cue periods: 11 neurons, 13%; delay and response periods: 32 neurons, 36%; delay, cue, and response periods: 11 neurons, 13%). The remaining 83 task-related neurons exhibited significant activity only in the cue period ($n = 12$), only in the response period ($n = 55$), in both cue and response periods ($n = 10$), or at reward presentation ($n = 6$).

**Directional specificity of delay period activity**

Most PS neurons with delay period activity showed a significant increase or decrease in this activity relative to their base-line discharge rate only when the cue had been...
FIG. 7. Directional tuning of 6 principal sulcus neurons with delay period activity. In each radial plot, the neuron's average discharge rate during the delay period for each cue location is depicted by the radial eccentricity of the plot in that direction, the standard deviation of this rate is depicted by the radial line, and the neuron's average IT1 discharge rate is the radius of the circle. Asterisks (*) indicate cue directions with statistically significant (t test, \( P < 0.05 \)) differences between delay period activity and the IT1 rate. A and B: 2 principal sulcus neurons (A: 5041, right hemisphere; B: 5211, left hemisphere) with very specific directional delay period activity (A, \( F = 10.12; df = 7, 54; P < 0.001 \); B, \( F = 48.35; df = 7, 68 \); \( P < 0.001 \)). They have a significant elevation of delay period activity for only 1 direction. Notice that there is significant inhibition of delay period activity for cue directions roughly opposite the excitatory directions. C and D: 2 principal sulcus neurons (C: 5111, right hemisphere; D: 5066, right hemisphere) with directional, but broadly tuned, delay period activity (C, \( F = 25.23; df = 7, 56; P < 0.001 \); D, \( F = 3.80; df = 7, 71; P < 0.005 \)). Notice that for C the responses are excitatory relative to the IT1 rate whereas for D the only significant responses are inhibitory. E and F: 2 principal sulcus neurons (E: 5011, right hemisphere; F: 5008, right hemisphere) with omnidirectional delay period activity (E, \( F = 0.63; df = 7, 63 \); \( P > 0.1 \); \( F = 1.26; df = 7, 65 \); \( P > 0.1 \)). One of these is excitatory (E) and the other inhibitory (F).
presented at one or a few among the 4 or 8 locations tested. Of the 87 PS neurons with delay period activity, 69 (79%) were directional, i.e., a statistically significant difference \((P < 0.05)\) in delay period discharge rates across different cue locations.

Figure 3 shows directional activity in a PS neuron tested with eight cue locations. Strong tonic excitatory activation appeared throughout the delay period only when the cue was presented at the downward \((270^\circ)\) location. This response began \(\sim 100\) ms after the cue presentation and ceased \(130\) ms after the initiation of the saccadic eye movement. Moreover, activity during the delay period was suppressed relative to the ITI discharge rate for the three cue locations in the upper (opposite) visual field \((45^\circ, t = 2.350, df = 84, P < 0.025; 90^\circ, t = 3.451, df = 85, P < 0.001; 135^\circ, t = 2.607, df = 84, P < 0.025)\). This phenomenon of an excitation of delay period activity for one set of cue locations and an inhibition of delay period activity for other directions is discussed further below.

Figure 4 shows another PS neuron with directional activity that exhibited broader tuning than the neuron shown in Fig. 3. The delay period activity was significantly elevated for the three locations that span the upper quadrant of the contralateral visual field \((90, 135, and 180^\circ)\), with the highest rate on \(135^\circ\) trials. The activity ceased abruptly 170 ms after the initiation of the saccadic eye movement. For the three cues spanning the opposite quadrant (lower ipsilateral, \(270, 315,\) and \(0^\circ\)) this neuron’s activity was depressed below its ITI rate (see also Fig. 7C), although this depression was not statistically significant for any individual direction.

Neurons with only inhibitory activity during the delay period could also be directional. The neuron shown in Fig. 5 was suppressed during the delay period only when the cue had been presented at the upper location \((90^\circ, t = 6.036, df = 53, P < 0.001)\), there was no significant change in activity during the delay period for the three other cue locations tested.

The remaining 18 neurons \((21%)\) with significant delay period activity were classified as omnidirectional because they responded similarly during the delay period regardless of cue locations and the ANOVA criterion for directional selectivity was not met. Figure 6 shows an example of a PS neuron with omnidirectional delay period activity. The tonic excitatory delay period responses for all locations was significantly above the ITI rate by individual \(t\) test and the slight differences between locations were not statistically significant.

To more concisely show directional specificity of directional delay period activity, we constructed polar plots that depict the delay period discharge rate of a neuron as a function of polar direction by plotting discharge rate as a function of polar eccentricity. The base-line (ITI) rate of the neuron is shown on the plots by the radius of a circle, and the standard deviations of the delay period discharge for each direction are shown by radial bars, and statistically significant departures from the ITI rate are indicated by asterisks. Figure 7, B, C, and E, show polar plots for the narrowly tuned, broadly tuned, and omnidirectional

<table>
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<th>TABLE 1.</th>
<th>Response type of directional and omnidirectional delay period activity of principal sulcus neurons</th>
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<tr>
<td></td>
<td>Directional</td>
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<tr>
<td>Excitation</td>
<td>46</td>
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<td>Inhibition</td>
<td>23</td>
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<td>Total</td>
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neurons whose histograms were illustrated in the previous three figures (Fig. 3, Fig. 4, and Fig. 6, respectively), whereas Fig. 7, A, D, and F, show three additional examples: another PS neuron with narrowly tuned directional delay period activity is shown in Fig. 7A. For this PS neuron, the preferred cue direction was leftward (180°), whereas for most other cue directions, the discharge rate during the delay period was suppressed below baseline. A neuron with directional delay period activity that was suppressed below baseline when the to-be-remembered cues were in the upper-left quadrant of the visual field is shown in Fig. 7D. Finally, Fig. 7F shows a neuron with omnidirectional inhibition of delay period activity: comparable inhibition occurred for all eight cue locations.

Excitatory and inhibitory delay period activity

As evident from the polar plots in Fig. 7, we observed instances of both elevation and depression of delay period activity relative to a neuron’s baseline rate. To further understand the relation between the “sign” of this activity and directional specificity, we classified each neuron as having either excitatory or inhibitory delay period activity by the statistical criteria previously described. A neuron was classified as excitatory (or inhibitory) if delay period rate for any cue direction was significantly elevated (or only reduced) relative to the neuron’s ITI.

Table 1 shows the incidence of neurons for the different combinations of delay period response sign and directionality. As is evident from examining the Table, neurons having excitatory delay period activity were more likely to be directional (92%) than neurons with solely inhibitory responses (62%). Furthermore, we observed that directional tuning for inhibitory delay period activity was usually broader than that for excitatory directional activity.

The phenomenon of a single neuron having both an elevation of delay period activity for one set of directions and depression of delay period activity for another set was frequently encountered. Usually the best cue directions for...
eliciting inhibitory responses were opposite to the best directions for eliciting excitatory responses. For 15 neurons the criteria for having a statistically significant elevation of delay period activity for at least one direction and a statistically significant inhibition of activity for at least one other direction was met. However, several other neurons, such as the ones illustrated in Figs. 4 and 7C, had delay period discharge rates below baseline for one or more directions that did not meet our statistical criteria yet seemed genuine because the inhibition was present for two or more adjacent directions opposite to the excitatory direction.

**Distribution of preferred directions**

To determine the distribution of directional preferences of delay period activity, we used the largest t statistic to classify the preferred direction of each neuron as the cue location where it showed the most prominent excitation or inhibition. For analytical and graphic purposes, the preferred directions of left-hemisphere neurons were transformed into mirror-image directions, as if all neurons were recorded from the right hemisphere. Among the 69 PS neurons with directional delay period activity, 30 were studied in the 4-cue condition and 39 were studied in the 8-cue condition. As shown in Fig. 8, the majority of neurons with excitatory directional delay period activity had preferred directions on the side contralateral to the hemisphere recorded from. This contralateral bias was statistically significant by a chi-square test (X^2 = 8.758, df = 1, P < 0.01). There was no statistical significance in the directional preference of inhibitory directional delay period activity (X^2 = 1.667, df = 1, P > 0.1), although most inhibitory directions were also contralateral.

**Tuning of directional delay period activity**

To determine the directional specificity of delay period activity, tuning curves were estimated using the Gaussian function

\[ f(d) = B + R \cdot e^{-(d-D)^2/2T_d^2} \]

where \( f(d) \) is discharge frequency, \( d \) is cue direction, and the remaining terms are constants: \( B \) is the discharge rate during the ITI, \( D \) is the best direction, \( R \) indexes delay period response strength, and \( T_d \) indexes tuning with respect to cue direction. The function was implemented by fixing \( B \) at the average background discharge rate, and then iteratively converging to the best least-squares solution for \( R, D, \) and \( T_d \). This Gaussian approach has previously been used to describe visual receptive fields and presaccadic movement fields in the FEF (6).

We applied this Gaussian formula to all 69 PS neurons that exhibited directional delay period activity. However, we omitted 42 PS neurons because 30 PS neurons were only studied with 4 cue directions and the Gaussian fits to 8 data points for 12 PS cells were poor. The remaining 27 PS neurons had good fits based on 8 cue locations. Figure 9 shows the tuning curves obtained for two of these PS neurons, one with narrowly tuned excitatory delay period activity (\( T_d = 19.7^\circ \), Fig. 9A) and another with broadly tuned excitatory delay period activity (\( T_d = 48.4^\circ \), Fig. 9B). Excitatory delay period activity tended to have narrower tuning than inhibitory delay period activity. The mean tuning index (\( T_d \)) was 26.8 ± 14.2° (SD) (n = 22) for neurons with significant excitatory delay period activity versus 48.2 ± 43.5° (n = 5) for neurons with only inhibitory delay period activity. These means are not significantly different (t = 1.985; df = 25; 0.05 < P < 0.1) proba-

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**FIG. 11** Directional delay period activity of a principal sulcus neuron (5018, right hemisphere) for 2 different delay durations (3-s delay in A and 6-s delay in B), examined sequentially (3 s first, then 6 s). For each set of histograms the visual cues were presented randomly at 1 of 4 locations indicated (0° = right, 90° = up, 180° = left, and 270° = down). All cue eccentricities were 13°.
bly because of the small number of inhibitory neurons that could be fit and the large SD of inhibitory tunings.

**Time course of delay period activity**

To further characterize the overall activity of PS neurons during the oculomotor delayed-response task, we made histograms that summed activity across our sample of neurons, selecting for each neuron the trials with cues in that neuron's preferred direction. Figure 10 shows these composite histograms. Neurons with excitatory \((n = 46)\) and inhibitory \((n = 23)\) directional delay period activity were summed separately to prevent these activities from canceling each other. The left pair of histograms (Fig. 10, A and C) depict excitatory and inhibitory composite activities during the 3-s delay period, as well as during the fixation, cue, and response periods, and part of the ITI. For the excitatory composite histogram the overall delay period activity was 13.9 spikes/s, in comparison to 7.6 s/ during the first 1.5 s of the histogram (the ITI and fixation interval). For the inhibitory composite histogram the overall delay period discharge rate was 4.5 s/ in comparison to 8.1 s/s during the ITI and fixation interval. Thus PS neurons with typical excitatory directional activity discharge at approximately twice their base-line rate during the delay period, whereas PS neurons with typical inhibitory directional activity discharge at approximately one-half their base-line rate.

The composite histograms also indicate the time course of PS neuron activity during the delay period. Although individual neurons have a variety of temporal changes during the delay period, these composite histograms indicate that overall PS neuron activity is well-maintained during a 3-s delay. In fact, there is an increase in discharge rate over the 3-s delay period in the excitatory composite histogram \((12.4, 14.9, \) and \(14.5 \text{ s/s in the first, second, and third second, respectively} \) and a decrease in the inhibitory composite histogram \((4.8, 4.7, \) and \(3.9 \text{ s/s}.\)

A phasic response is evident during the 0.5-s cue period in the excitatory composite histogram (Fig. 10A). The earliest indication of this response begins \(\sim 70 \text{ ms} \text{ following cue onset} \) (all latencies were estimated using a cumulative histogram of the same data, which is not shown); but individual neurons had a wide variety of latencies, and many did not respond at all during the cue period. It should be noted that many PS neurons having strong visual responses, but lacking delay period activity, were not included in these composite histograms.

Finally, the composite histograms depict a phasic increase in activity during the response period for both the excitatory and inhibitory activity. The latency of this activity is 180 ms following the disappearance of the fixation target for the excitatory activity and 300 ms for the inhibitory activity. Since the typical saccade latency during the oculomotor delayed-response task is \(\sim 290 \text{ ms} \), it would appear that the excitatory burst leads the saccade in the excitatory composite histogram but follows the saccade in the inhibitory composite histogram. Histograms aligned at the saccade initiation (Fig. 10, B and D) support this interpretation: the additional burst of activity in the excitatory composite begins \(\sim 30 \text{ ms} \) prior to the saccade initiation and ends \(\sim 40 \text{ ms} \) after the saccade initiation (Fig. 10B). In contrast, the increased discharge in the inhibitory composite begins \(\sim 40 \text{ ms} \) following the saccade initiation (which is approximately at the saccade termination) and continues for \(\sim 0.5 \text{ s} \) (Fig. 10D).

**Effects of different delay durations**

Eighteen PS neurons that exhibited directional delay period activity were tested either with two \((3 \text{ and } 6 \text{ s})\) or three \((1.5, 3, \text{ and } 6 \text{ s})\) different delay durations. The monkeys had little difficulty with any of these delay times and maintained a high level \(\text{(}>80\%)\) of correct performance at all delays tested.

Varying the delay length over this range of values had little effect on delay period activity. In particular, the directional preference was unchanged and the duration of excitation or inhibition expanded with longer delays. For example, Fig. 11A shows a neuron with tonic excitation during a 3-s delay period only when the cue was presented at the \(180^\circ\) location. Figure 11B shows the same neuron's activity.
activity during the delayed-response task with a 6-s delay. The tonic excitation still appeared only when the cue was presented at 180° and was maintained during the entire 6-s delay period. With both delays, the tonic excitation ceased at the initiation of the response. Eight other PS neurons with tonic delay period activity were similarly tested with different delay durations; all showed similar results, that is, the response expanded to fill the entire delay.

Figure 12 shows another PS neuron tested across different delay durations. In this case, four cue locations (0, 90, 180, and 270°) at three different delay durations (1.5, 3, and 6 s) were randomly intermixed. The rasters and histograms in Fig. 12 show neural activity during three different delay durations for cues presented at 180°, the preferred direction for this neuron. Notice that the activity in the first 1.5 s of the delay is very similar in all three conditions, that is little or no change in activity relative to the preceding fixation interval. Furthermore, the activity in the next 1.5 s of the delay period is the same in the 3-s and 6-s delay conditions, both showing a gradual rise in activity. This result was obtained in six other PS neurons that increased discharge rate during the delay. Likewise, two PS neurons with gradually decreasing discharge rates during the delay showed analogous patterning of activity when the delay duration was changed.

**Directional delay period activity in error trials**

Analysis of activity in error trials often aids the interpretation of delay period activity (5, 53, 54, 58, 64–66). Therefore, we examined the activity when the monkeys made errors on trials with the preferred cue direction for the neuron being studied. For this analysis, failure to saccade and misdirected saccades (i.e., ending outside the window) were counted as errors; however, nearly all errors were misdirected saccades. Premature saccades made during the delay period did not count as errors. Of 69 PS neurons

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**FIG. 13.** Discharges of 2 principal sulcus neurons with directional delay period activity during correct performance of the oculomotor delayed-response task and during trials with errors. For each trial depicted, discharge traces are shown on the left and cue locations and saccade directions are shown on the right. Top: this neuron's (5018, right hemisphere) strongest delay period activity was associated with leftward cue presentations. On the error trial, its discharge ceased about midway through the delay period. Bottom: this neuron's (5111, right hemisphere) strongest delay period activity was associated with cue presentations in the upper-left visual field. On the error trial, its discharge in the delay period was absent.

**FIG. 14.** Comparison of delay period activity for correct trials with activity for error trials. The first correct trial and the first error trial were taken from each of the 9 principal sulcus neurons that had excitatory directional delay period activity and for which the monkey made at least 1 error on a trial in the neuron's preferred direction. The top histogram sums the 9 correct trials and the bottom histogram sums the 9 error trials.
exhibited directional delay period activity, only 13 PS neurons (9 excitatory and 4 inhibitory) had one or more such error trials. Nevertheless, these data indicate that the responses of PS neurons during the delay period were significantly weaker on trials where the monkey made an error during the response period.

Figure 13 shows examples of neural activity in both correct and error trials for two neurons with directional delay period activity. The neuron shown at the top of the figure had its strongest delay period activity with leftward (180°) cue presentations. For trials on which the monkey’s eventual saccade was to this location the neuron responded tonically throughout the delay period. However, on the one trial in which an error was made (saccade to upper right) the neuron’s discharge ceased about midway through the delay period. The neuron at the bottom of Fig. 13 showed a similar pattern except that its delay period activity was absent altogether on the one trial in which an error was made.

To examine the error data as a whole we summed the first error trial (usually the only one) across the nine excitatory neurons with an error trial in the neuron’s preferred direction. This histogram was compared to a histogram composed of the first correct trial (from the same event buffer) of these nine neurons at their preferred direction. Figure 14 shows these two histograms. The delay period activity on the correct trials was significantly greater than activity on the error trials by a paired t test (t = 2.76, df = 8, P < 0.025).

Directional and omnidirectional delay period activity in the frontal eye fields

Of the 319 examined neurons, 31 were recorded from the frontal eye fields (FEF), where low- (<50 μA) and intermediate-threshold (between 50 and 100 μA) microstimulation generated saccadic eye movements (7). Of these 31 neurons, 22 showed task-related activity during the oculomotor delayed-response task, with 17 (54.8%) having significant responses during the delay period (10 excitatory and 7 inhibitory).

Of these 17 FEF neurons, 10 exhibited directional delay period activity. Figure 15 provides an example of a neuron with a preferred direction at 90°; this FEF neuron showed tonic excitation during the delay period (see Fig. 15B) and also exhibited presaccadic excitation at the time of response when the monkey made saccadic eye movements to the cue location which was the neuron’s preferred direction for delay period activity (see Fig. 15C). Like some PS neurons, the delay period activity was suppressed when the cue was presented at roughly opposite directions to its preferred direction (135, 180, and 225°).

Of the 10 FEF neurons with directional delay period activity, 5 had preferred directions into the contralateral hemifield, 4 preferred upward directions, and 1 preferred ipsilaterally directed stimuli. The mean tuning index (Td) was 27.4 ± 20.0° (n = 7) for FEF neurons with excitatory directional delay period activity. The three FEF neurons with inhibitory directional delay period activity were very broadly tuned.

FIG. 15. Directional delay period activity (F = 29.582, df = 7, 33, P < 0.001) of a frontal eye fields neuron. This neuron (5035, right hemisphere) had significant tonic excitatory delay period activity only when the cue was presented at the 45 and 90° locations and was suppressed during the delay when the cue was presented at roughly opposite locations (135°, t = 2.647, df = 43, P < 0.025; 180°, t = 3.138, df = 42, P < 0.005; 225°, t = 3.739, df = 46, P < 0.001). Visual cues were presented randomly at 1 of the 8 locations. All cue eccentricities were 13° and all delay durations were 3 s. 4: radial plot showing the directional tuning of delay period activity. B and D: neuron’s delay period activity on the 90° trial and the 225° trial, respectively. C and E: activity aligned at the start of saccadic eye movements at the response period on the 90° trial and the 225° trial, respectively. Note that this neuron had presaccadic activity for 90° saccades and postsaccadic activity for 225° saccades.
Cortical distribution of neurons with directional and omnidirectional delay period activity in the prefrontal cortex

Recording sites in each hemisphere were located on reconstructions of the dorsolateral prefrontal region. Most electrode penetrations were in the dorsal and ventral banks of the medial and posterior part of the principal sulcus and also in the surrounding regions of the principal sulcus [Walker's area 46 (63)]; however, in one hemisphere nine penetrations were made in the prearcuate region bordering the anterior bank of the arcuate sulcus where the frontal eye fields are located.

Figure 16 illustrates the location of all penetrations and also shows the location of neurons with directional and omnidirectional delay period activity in each of five hemispheres studied. We were unable to discern any clear localization or clustering of neurons with directional delay period activity and neurons with omnidirectional delay period activity.

DISCUSSION

Memory fields of prefrontal neurons

Prefrontal neurons with directionally selective delay period activity were first described in conjunction with the classical manual version of the delayed-response task (50) and a related task, spatial delayed alternation (51, 52). Prefrontal neurons in previous studies were characterized as directionally selective because their delay period activity was specific for the left- or right-of-center locations of the cues or the left or right direction of the manual response (50–52). Similar selective delay period activity has been observed in prefrontal neurons during performance of delayed discrimination (22, 47, 58) and conditional response (64) tasks. Although the overall percentage of neurons with directionally selective delay period activity in previous studies of the prefrontal cortex was small [i.e., 6% of total “task-related” neurons in Niki (50); 13% in Niki (51); 19% in Niki and Watanabe (53); 10% in Fuster et al. (22)], these neurons are nevertheless reflective of central mnemonic processes guiding the correct choice at the end of delay (18, 28, 50).

The present study differs from previous recording efforts in that we employed fixation and perimetry in order to extend the analysis of delay-related activity beyond the traditional two-choice (left and right) paradigms (5, 16, 20, 22, 37, 40–42, 45, 50, 53, 54, 58, 67). We found that the delay period activity of prefrontal neurons codes the spatial coordinates of visual cues during a delayed-response task and thus provides a mnemonic code for direction over the full perimetry of visual space, not for left-right direction alone. Each neuron with directional delay period activity had a “mnemonic” receptive field. Only when the cue was presented in that field did the neuron show excitation or inhibition during the subsequent delay period. Moreover, directional delay period activity expanded when the delay was lengthened and faltered on occasional trials when errors were made. Therefore, we propose that this area of the visual field be termed the memory field of the neuron analogous to the receptive fields of visual neurons or the movement fields of oculomotor neurons. Memory fields may be the cellular expression of a working memory process (3) that allows mnemonic information to guide behavior.

The mechanisms by which a memory field is constructed are not known at present. It is highly relevant that the caudal prefrontal areas around the principal sulcus and prearcuate cortex are heavily interconnected with the posterior parietal cortex (2, 9, 11, 35, 36, 55, 59), which is a major center for processing of spatial vision (1, 49). Our recent anatomic studies of the posterior parietal cortex (10) indicate that visuotopic information may be transmitted to posterior parietal areas from a recently described visual area on the medial surface of the occipital lobe (area PO) which receives a direct input from the striate cortex (12) and where neurons are responsive to peripheral stimuli (13). The posterior parietal cortex also receivesafferents from the superior temporal sulcus, from area MT, from the inferotemporal cortex, and from other prestriate areas (10). Thus we speculate that prefrontal neurons may access visuotopic information via the parietoprefrontal pathway, although that information may be also available from other cortical and subcortical sources.
clude the posterior parietal cortex (5, 30, 39), the infero-temporal cortex (23, 24), the cingulate cortex (34), the basal ganglia (32, 33), the mediodorsal nucleus of the thalamus (21), and the hippocampus (67). Interestingly, almost all of these structures are reciprocally connected with the prefrontal cortex (17, 29, 62). These data are compatible with the idea that the mnemonic information in the prefrontal cortex reflected by neurons with directional delay period activity may be a result of the neural interaction among these cortical and subcortical structures (28, 29) and that many of these structures may be part of a distributed network of cortical and subcortical structures dedicated to spatially guided behavior (29, 61).

Laterality of memory fields

Previous studies of prefrontal cortex in delay tasks have not emphasized the laterality (left or right, contralateral versus ipsilateral) of neuronal activity. In contrast, our study found a predominance of neurons preferring contralateral cues for their delay period activation. Among the 69 PS neurons with directional delay period activity, one half (49.3%) had memory fields centered in the visual field contralateral to the hemisphere where the neurons were located, only 17.4% had ipsilateral memory fields, and 17.4 and 15.9% had memory fields in upward and downward directions, respectively. This result indicates that, although the population of neurons in each hemisphere may be capable of coding cues over the entire visual field, the prefrontal neurons within each hemisphere code mainly contralateral locations. Accordingly, these results provide evidence that memory for spatial location is lateralized, with memories for locations in the right visual field coded mainly in the left hemisphere and memories for left field locations coded in the right hemisphere.

This physiological evidence of lateralization of spatial memory is supported by results from lesion studies. Fuster and Alexander (19) observed a higher proportion of errors to the contralateral side in monkeys with unilateral cryogenic depression of the dorsolateral prefrontal cortex. In a study using the oculomotor delayed-response task (15), we found that monkeys with a unilateral surgical ablation in the principal sulcus had marked difficulty making correct saccadic eye movements to remembered visual targets which had been presented in the visual field contralateral to the lesioned hemisphere and only mild or no difficulty making saccades to remembered targets which had been presented in the ipsilateral visual field. A similar result was obtained by Deng et al. for a unilateral lesion of the frontal eye fields on a task requiring memory over a 100-ms time interval (14). Because the monkeys with unilateral prefrontal lesions made normal saccadic eye movements to targets in both fields when their eye movements were visually guided, the difficulty of making saccades to remembered targets in the oculomotor delayed-response task seems to reflect a mnemonic deficit, which we have termed a "mnemonic hemianopia" (15) or "mnemonic scotoma."

Incidence and specificity of delay period activity

More research is still needed to know if the principal sulcus region has one population of neurons with delay period activity specific for the oculomotor delayed-response task and a separate population specific for manual types of delay tasks. We saw no indication of an anatomic subregion of the prefrontal cortex particularly dense in neurons with directional delay period activity for the oculomotor task, and our sampling area largely overlapped with the regions where neurons with directional activity on manual types of delay tasks have been found (16, 22, 50, 51, 53). Thus it is possible that the same region of the prefrontal cortex codes mnemonic representations across different types of delay tasks, and may even generalize across both sensory (visual versus auditory) and response (hand versus eye) modality. Some evidence favors such a type of generalized coding by individual prefrontal neurons, primarily the relatively high incidence of neurons with directional delay period activity during the oculomotor task (40.5% of total "task-related" neurons) obtained in the present study. If there were separate populations of prefrontal neurons for mnemonic representations in conjunction with eye movements and hand movements, then both populations would be active during the conventional, manual types of delayed-response tasks because primates invariably first direct their gaze with a saccade to stimuli that are to be touched or grasped with the hand. Therefore, previous studies should have found an even higher proportion of prefrontal neurons with delay period activity than we found with the oculomotor delay task. In fact, the reverse is the case, with 6–19% being the incidence of directional delay neurons from previous studies using the manual task, as reviewed earlier. Thus it is possible that the same prefrontal neurons code delay period representations for both oculomotor and manual response systems. On the other hand, there is no anatomic evidence in primates that would indicate that single neurons in the prefrontal cortex have axon collaterals to both eye- and hand-movement centers. Therefore, the question of "supramodal" neurons in the prefrontal cortex must remain open for future evaluation.

The higher proportion of prefrontal neurons with directional delay period activity may be explained by two other differences between our study and most previous ones. First, our use of four or eight cue locations increases the number of responsive neurons relative to studies employing only two (left and right) cue locations; many of our neurons with directional delay period activity responded best to cues above or below the fixation point (see Figs. 3 and 4) and would have been classified as nondirectional or nonresponsive if only the histograms for the left and right cue locations are considered. Another important reason is that other observers seem reluctant to attend to inhibitory responses; however, neurons with only inhibitory responses account for nearly one-half of our sample of neurons with significant delay period activity and slightly over one-third of the population of directional delay period neurons.

Inhibitory delay period activity

Inhibitory delay period activity was much more prevalent than previous studies have indicated. Nearly one-half of the neurons with significant delay period activity were solely inhibitory. Inhibitory responses were less likely to be
directional than excitatory ones; even so, nearly one-third of the directional responses were classified as directional because of selective inhibitory responses in the delay period. In addition, some neurons with excitatory delay period activity for particular cue locations had inhibitory activity for other cue locations, usually such inhibition being strongest for, or centered about, cue directions opposite to those optimal for excitatory responses.

These inhibitory responses may have several functions. First, neurons with inhibitory omnidirectional delay period activity comprised 16% of all the PS cells with significant delay period activity. We suggest that a tonic reduction in activity over this prefrontal pathway during the delay period may help the monkey suppress all saccadic eye movements for the duration of the delay period. There is an intense projection from the prefrontal cortex to the intermediate and deeper layers of the superior colliculus, the collicular zones responsible for saccadic eye movements (27, 48). A tonic reduction in activity over this pathway may provide a mechanism whereby the prefrontal cortex may prevent inappropriate saccades; patients with frontal lobe lesions have difficulty withholding responses to salient sensory stimuli (31). Another role for the inhibitory delay period activity is suggested by the neurons with inhibitory activity for directions opposite the excitatory cues. For these neurons inhibitory activity may be sharpening the spatial tuning of excitatory delay period activity. Opposing patterns of activity are reminiscent of the complex response patterns of neurons in sensory and motor centers that respond with excitation to one parameter of stimulation but are inhibited by the opposite or complementary stimulation, e.g., the opponent vector organization of parietal neurons, the color opponency of visual cortical neurons, and the reciprocal activation of motor cortex neurons by extension and flexion. Our findings indicate that mnemonic coding is organized on a common physiological principle.

Comparison between the principal sulcal area and the frontal eye fields

We recorded neurons with memory fields from both the principal sulcal (PS) region [Walker's area 46 (63)] and from the frontal eye fields (FEF) region in and near the anterior bank of the arcuate sulcus. Although the number of FEF neurons sampled was small, several had directional delay period activity similar to that of PS neurons and the tuning of directional delay period activity was comparable (mean $T_d = 26.8^\circ$ in PS and 27.4$^\circ$ in FEF). Furthermore, the directional tuning of delay period activity in PS is comparable to the directional tuning of presaccadic movement fields in FEF (mean $T_d$ of visuomovement neurons = 31.3$^\circ$. The primary pathway of mnemonic information pertinent to saccadic eye movements in the frontal lobe may be from the PS to the FEF. We suggested in the previous section that PS neurons could code mnemonic representations of previous stimuli and impending responses across different delayed-response tasks. The FEF may construct appropriate saccadic commands based on these inputs from the PS region. Other cortex, such as the supplementary motor area, may fabricate hand movements based on similar PS inputs, with the context of the task potentiating one or both of these motor-specific cortical zones. Indeed, Goldberg and Bushnell (26) found that FEF visual activity was only enhanced in the context of eye movements, but Bushnell et al. (8) found that the visual activity on the surface of the inferior parietal lobule, which projects to the PS region, was enhanced in the context of both eye and hand movements. On the other hand, the PS and FEF regions also could function independently with respect to the delayed-saccade task. Both areas receive visual inputs from the temporal and parietal cortices (17, 62) and both have direct projections to the superior colliculus (27, 34, 43, 48) as well as indirect projections there via the corticostriatal system (60, 61). The actual circuit for memory guided behavior is probably complex, and at present, we can only postulate that the PS region handles delay information for both saccades and arm movements whereas the FEF are specific for eye movements.

Oculomotor delayed-response task

We used an oculomotor delayed-response task to examine the functions of the primate prefrontal cortex, whereas most information about previous studies of spatial delayed-response have been conducted in a Wisconsin General Test Apparatus (WGTA), in which freely moving monkeys reach through the bars of a small cage to retrieve a food reward manually after an imposed delay. Testing in a WGTA precludes precise experimental control over the animal's regard of visual stimuli as well as its behavior during the delay period. In neurophysiological experiments using behaving monkeys, modified versions of the WGTA-based task, such as two-choice (left and right) paradigms, have been used. Although the monkey's head is fixed and stimulus presentations and response movements are more controlled in this situation, the monkey's behavior during the delay period, especially its eye movements, have still not been controlled. The question could be raised as to whether, under these testing conditions, a monkey really needs memory to perform correctly, because he could maintain an ocular or postural orientation to the appropriate response key throughout the delay period. Obviously, if a monkey looked at the prospective response window continuously during this period, he would not need to remember the correct cue location. Although investigators have sometimes recorded electrooculographic data during task performance (21, 22, 37, 40, 65, 66), they

1 All $T_d$ estimates of Bruce and Goldberg (6) are inflated by a factor of 1.4142 because of a program error discovered while completing the present study. Thus their average $T_d$ of 44.2$^\circ$ for visuomovement neurons should be 31.3$^\circ$. 
have not usually continuously monitored or controlled eye movements during the collection of single neuron activity. In this respect, the oculomotor delayed response paradigm that we used has several advantages. First, the monkey's behavior can be controlled more precisely during the performance of the delayed-response task. Because the monkey must maintain fixation of the center spot of light during the delay period, and as there is no clue available during this period to indicate the direction of the correct response, the monkey is required to use working memory to achieve a high level performance. Second, this paradigm allows the use of multiple cue locations in the monkey's visual field in order to more rigorously test whether directionally selective activity of prefrontal neurons reflects coding of specific spatial information rather than just a general preparatory set. Finally, recording eye position during the delay as well as the latency, direction, and amplitude of the eye movement at the time of response allows a more accurate analysis of correlations between prefrontal single neuron activity and behavior. Thus the oculomotor delayed-response task may be a powerful tool for analyzing the mnemonic functions of the prefrontal cortex in both neurophysiological and ablation experiments.

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REFERENCES


33. HIKOSAKA, O. AND WURTZ, R. H. Visual and oculomotor functions...


