

Neuronal Activity in Macaque Supplementary Eye Field During Planning of Saccades in Response to Pattern and Spatial Cues

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Olson, Carl R., Sonya N. Gettner, Valérie Ventura, Roberto Carta, and Robert E. Kass. Neuronal activity in macaque supplementary eye field during planning of saccades in response to pattern and spatial cues. *J Neurophysiol* 84: 1369–1384, 2000. The aim of this study was to determine whether neuronal activity in the macaque supplementary eye field (SEF) is influenced by the rule used for saccadic target selection. Two monkeys were trained to perform a variant of the memory-guided saccade task in which any of four visible dots (rightward, upward, leftward, and downward) could be the target. On each trial, the cue identifying the target was either a spot flashed in superimposition on the target (spatial condition) or a foveally presented digitized image associated with the target (pattern condition). Trials conforming to the two conditions were interleaved randomly. On recording from 439 SEF neurons, we found that two aspects of neuronal activity were influenced by the nature of the cue. 1) Activity reflecting the direction of the impending response developed more rapidly following spatial than following pattern cues. 2) Activity throughout the delay period tended to be higher following pattern than following spatial cues. We consider these findings in relation to the possible involvement of the SEF in processes underlying attention, arousal, response-selection, and motor preparation.

INTRODUCTION

The supplementary eye field (SEF) has been known since its discovery by Schlag and Schlag-Rey (1985, 1987) to play a role in oculomotor processes. Evidence for this role has arisen from studies involving both electrical stimulation and single-neuron recording. Electrical stimulation of the SEF at reasonably low currents (<50 μ A) elicits saccadic eye movements (Chen and Wise 1995b; Fujii et al. 1995; Lee and Tehovnik 1995; Mann et al. 1988; Mitz and Goldschalk 1989; Russo and Bruce 1993; Tehovnik and Lee 1993; Tehovnik and Sommer 1997; Tehovnik et al. 1994; Tian and Lynch 1995). Further, SEF neurons fire during the preparation and execution of saccades (Bon and Lucchetti 1992; Chen and Wise 1995a,b, 1996, 1997; Hanes et al. 1995; Mann et al. 1988; Mushiaké et al. 1996; Olson and Gettner 1995, 1999; Olson and Tremblay 2000; Russo and Bruce 1996; Schall 1991a,b; Schlag and Schlag-Rey 1985, 1987; Schlag-Rey et al. 1997).

Several observations, however, suggest that the SEF is in-

involved in processes distinct from the simple programming and execution of eye movements. For example, some SEF neurons are differentially active during the learning of arbitrary associations between visual patterns and eye-movement directions (Chen and Wise 1995a,b, 1996, 1997). Further, some neurons fire at different levels when the monkey is preparing saccades to the right or left side of an object, even under conditions such that the saccades' physical direction is constant (Olson and Gettner 1995, 1999; Olson and Tremblay 2000). Thus, the question remains open: to what degree is neural activity in the SEF related to processes antecedent to the final stages of oculomotor control?

One approach to answering this question is to study the SEF under conditions such that the same eye movements are selected according to different decision processes. Schlag-Rey et al. (1997), following this approach, recorded from the SEF in monkeys trained to make delayed prosaccades or antisaccades. They found that neuronal activity was higher overall during antisaccade than prosaccade trials, although the physical directions of the saccades were the same in both cases. This finding indicates that SEF neurons are sensitive to some nonmotor task variable; however, it leaves open several possibilities with respect to the nature of that variable. The higher rate of neuronal activity under antisaccade conditions might arise from the selection of the target by means of an abstract rule (move to a location diametrically opposed to the location of the cue). Alternatively, it might arise from the need for suppression of eye movements to the location marked by the cue. These two factors covary across prosaccades and antisaccades. However, by appropriate task design, they can be dissociated. Like humans (Klein et al. 1992), monkeys are able to select saccade-targets not only in response to peripheral cues presented at their location (Hikosaka and Wurtz 1983), but also in response to centrally presented patterns associated with them (Chen and Wise 1995a,b, 1996, 1997). Pattern-based target selection requires use of an abstract rule but imposes no need to suppress eye movements to the location marked by the cue because the cue is central. By comparing between spatial trials (in which the cue is a spot flashed at the target location) and pattern trials

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(in which the cue is a centrally presented image), one should be able to determine whether and in what manner neuronal activity depends on the target-selection rule in itself without regard to the need to suppress eye movements to the location marked by the cue. Neuronal activity elicited by performance of the two tasks has been compared previously in dorsolateral prefrontal cortex (Wilson et al. 1993) and the superior colliculus (Kustov and Robinson 1996). However, while SEF neurons are known to exhibit direction-selective activity in the context of both the pattern task (Chen and Wise 1995a,b, 1996, 1997) and the spatial task (Olson and Tremblay 2000; Olson et al. 1999), no direct comparison has previously been carried out in the SEF. Results obtained by direct comparison, as described in this paper, have been reported previously in an abstract (Olson and Gettner 1996).

METHODS

SUBJECTS. Two adult male rhesus monkeys were used (*Macaca mulatta*; laboratory designations Pk and Qu). Experimental procedures were approved by the Carnegie Mellon University Animal Care and Use Committee and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals.

PREPARATORY SURGERY. At the outset of the training period, each monkey underwent sterile surgery under general anesthesia maintained with isoflurane inhalation. The top of the skull was exposed, bone screws were inserted around the perimeter of the exposed area, a continuous cap of rapidly hardening acrylic was laid down so as to cover the skull and embed the heads of the screws, a head-restraint bar was embedded in the cap, and scleral search coils were implanted on the eyes, with the leads directed subcutaneously to plugs on the acrylic cap (Rommel 1984; Robinson 1963). Following initial training, a 2-cm-diameter disk of acrylic and skull, centered on the midline of the brain approximately at anterior 23 mm (Horsley-Clarke coordinates), was removed and a cylindrical recording chamber was cemented into the hole with its base just above the exposed dural membrane.

SINGLE-NEURON RECORDING. At the beginning of each day's session, a varnish-coated tungsten microelectrode with an initial impedance of several megohms at 1 KHz (Frederick Haer, Bowdoinham, ME) was advanced vertically through the dura into the immediately underlying cortex. The electrode could be placed reproducibly at points forming a square grid with 1-mm spacing (Crist et al. 1988). The action potentials of a single neuron were isolated from the multineuronal trace by means of an on-line spike-sorting system using a template matching algorithm (Signal Processing Systems, Prospect, Australia). The spike-sorting system, on detection of an action potential, generated a pulse the time of which was stored with 1-ms resolution.

BEHAVIORAL APPARATUS. All aspects of the behavioral experiment, including presentation of stimuli, monitoring of eye movements, monitoring of neuronal activity, and delivery of reward, were under the control of a 486-based computer running Cortex software provided by R. Desimone, Laboratory of Neuropsychology, National Institute of Mental Health. Eye position was monitored by means of a scleral search coil system (Rommel Labs, Ashland, MA, or Riverbend Instruments, Birmingham, AL) and the *X* and *Y* coordinates of eye position were stored with 10-ms resolution. Stimuli generated by an active matrix liquid crystal display projector (Sharp, XG H4OU) were rear-projected on a frontoparallel screen 25 cm from the monkey's eyes. Reward in the form of approximately 0.1 ml of water or juice was delivered through a spigot under control of a solenoid valve on successful completion of each trial.

PATTERN-SPATIAL TASK. Both monkeys were trained to perform a task requiring them to make eye movements to targets selected on the basis of a pattern cue (a foveally presented digitized image associated with the target) or a spatial cue (a spot flashed in superimposition on the target). Essential features of the task are summarized in Fig. 1. At the beginning of each trial, the monkey fixated a central $0.8^\circ \times 0.8^\circ$ white spot (Fig. 1A). After 400 ms, four potential targets ($0.8^\circ \times 0.8^\circ$ white spots) appeared at locations 20° rightward, upward, leftward, and downward from fixation (Fig. 1B). Then, for 100 ms, either a pattern cue (Fig. 1Cp: central $1.6^\circ \times 1.6^\circ$ digitized image) or a spatial cue (Fig. 1Cs: $1.6^\circ \times 1.6^\circ$ white square superimposed on one of the four targets) was presented. During a subsequent delay period (which varied randomly in duration across the range 550–750 ms), the monkey was required to maintain central fixation (Fig. 1D). Then offset of the fixation spot (Fig. 1E) signaled him to make an eye movement. If the monkey made a saccade directly to the target indicated by the earlier cue (Fig. 1F) and maintained fixation on the target for a variable period of 300–450 ms, he was rewarded with a drop of water and the display was simultaneously extinguished. There were eight trial conditions differentiated by the nature of the cue. The cue might be any of four standard, highly overlearned patterns or a white spot superimposed on any of the four targets. The eight conditions were presented in random sequence until 10–16 trials had been completed successfully under each condition.

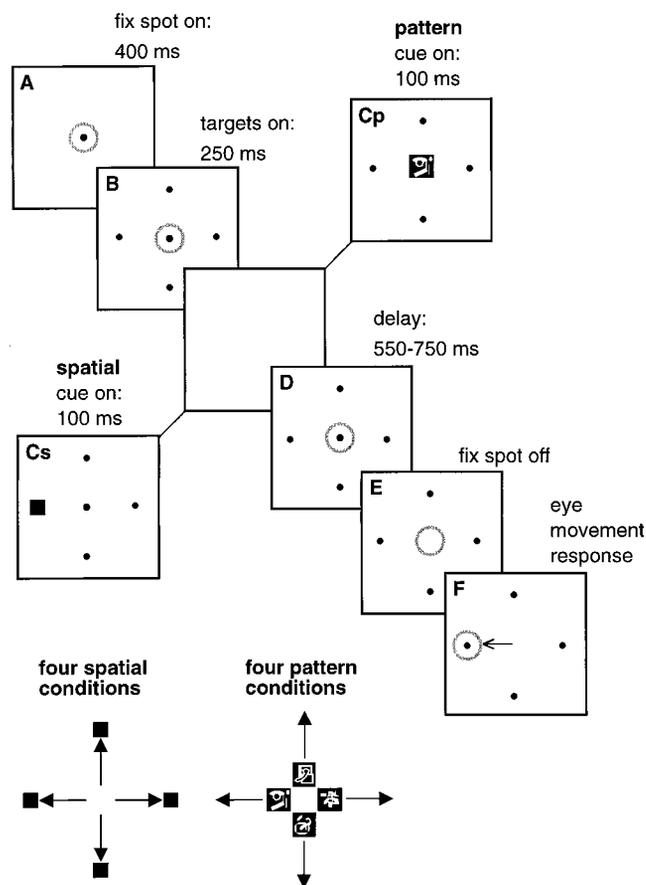


FIG. 1. Sequence of events during a representative behavioral trial. Panels A–F represent the screen in front of the monkey at successive stages during the trial. The center of the gray circle indicates the monkey's direction of gaze; the arrow indicates the direction of his eye movement. All other items are stimuli visible to the monkey. Pattern and spatial cues differed with respect to the nature of the stimulus presented during the cue period, either a central digitized image associated with one of the four targets (Cp) or a peripheral white spot superimposed on one of the four targets (Cs).

LOCALIZATION OF RECORDING SITES. In each monkey, recording was carried out in a pair of regions, each a few millimeters in extent, disposed approximately symmetrically across the interhemispheric midline. Following sacrifice with an overdose of sodium pentobarbital and transcardiac perfusion with 10% formalin, the brains were photographed. Marks indicating the location of the recording chamber were compared with gross anatomical landmarks, including the hemispheric midline and the arcuate and principal sulci. On the basis of the grid coordinates at which the electrode had been placed, recording sites were then projected onto the image of the cortical surface.

ANALYSIS OF DEPENDENCE OF FIRING RATE ON CONDITION IN INDIVIDUAL NEURONS. A set of identical procedures was applied to data collected from each neuron. The trial-epoch under consideration was defined as the period between two identifiable events. The mean firing rate during this period was computed for each trial completed successfully during recording from the neuron. Then an analysis of variance (ANOVA) was carried out to determine whether firing rate varied significantly across the trials as a function of cue type or direction.

ANALYSIS OF THE CORRELATION OF TRAITS ACROSS A NEURONAL POPULATION. Neurons in a population might exhibit trait a or b in one test and trait x or y in another test. In such cases, to test whether the distribution of neurons with respect to a and b was significantly correlated with the distribution with respect to x and y , we employed a Pearson chi-square test of association (Hayes 1988; Olson and Tremblay 2000).

ANALYSIS OF THE TIME COURSE OF NEURONAL ACTIVITY. The aim of this analysis was to determine the extent to which the type of cue (pattern or spatial) affected the time course of postcue neuronal activity. Three aspects of neuronal activity were considered: 1) the time at which firing attained its maximal rate, 2) the magnitude of the maximal rate, and 3) the average magnitude of activity 500–600 ms after presentation of the cue. To ensure that the results were robust, we applied two independent approaches. 1) *Regression splines and parametric analysis.* We assumed that the spike times followed an inhomogeneous Poisson process and obtained a smooth estimate of its intensity function using maximum likelihood (ML) estimation for Poisson regression splines, as described in the APPENDIX, with the statistical software S-PLUS (see Venables and Ripley 1997). We checked the Poisson assumption using exponential QQ plots of the interspike intervals on the integral transform scale. Statistical significance was based on standard asymptotic theory, which shows that for large samples, the characteristics of interest are normally distributed (Agresti 1990, Chapter 12). For population analysis, we used a normal hierarchical model (Gilks et al. 1996), which assumed that the three characteristics of interest were normally distributed across neurons; this was empirically verified via a normal probability plot. We determined the population means and standard deviations of the three characteristics using Bayesian analysis using Gibbs sampling (BUGS) (Spiegelhalter et al. 1996). Further details are given in the APPENDIX. 2) *Gaussian filtering and nonparametric bootstrap analysis.* Without making assumptions about the spike time distribution, we obtained a smooth estimate of firing intensity by use of kernel density estimation (Gaussian filtering) with bandwidth selected by methods indicated in the APPENDIX. Statistical significance was then based on a nonparametric bootstrap analysis (Davison and Hinkley 1997). This analysis made no distributional assumptions about the data or the test statistics used.

RESULTS

Behavior

Both monkeys performed the pattern-spatial task at a level well above chance. Across all runs of the task during which neuronal data were collected, *monkey 1* scored 94.6% on

pattern trials as compared with 99.8% on spatial trials, while the corresponding values for *monkey 2* were 94.9 and 99.1% (numbers based on trials in which the monkey completed an eye movement to one of the four targets). The difference between pattern and spatial percent-correct scores was highly significant in both monkeys (2-tailed paired t -test, $P < 0.0001$). The behavioral reaction time, measured as the interval between offset of the fixation spot and initiation of the saccadic eye movement on correct trials, also varied as a function of cue condition. In *monkey 1*, the mean behavioral reaction time was 225.5 ms on pattern trials as compared with 231.6 ms on spatial trials, while, in *monkey 2*, the corresponding values were 193.9 and 215.8 ms. The tendency for the behavioral reaction time to be shorter on pattern than on spatial trials was present for all four response directions in each monkey and attained significance for two directions in *monkey 1* and all four directions in *monkey 2* (2-tailed paired t -test, $P < 0.001$). Decision time was not a factor in this effect because a long delay intervened between the instructional cue and the imperative signal. In summary, both monkeys gave moderately faster but slightly less accurate responses under pattern as compared with spatial conditions.

Recording sites

Having centered the recording chamber over the approximate location of the SEF as determined in previous mapping studies (Tehovnik 1995), we proceeded to select recording sites according to the following strategy. We first placed exploratory penetrations at widely spaced locations in each hemisphere until we found neurons exhibiting robust task-related activity in the context of the pattern-spatial task. We then proceeded to record from neurons at these and adjacent sites, moving out in all directions from the initially identified loci until we reached the limits of the domain within which neuronal activity was robustly task-related. Using this approach, we collected data from 439 SEF neurons during performance of the pattern-spatial task (327 neurons in *monkey 1* and 112 neurons in *monkey 2*). The recording sites are projected onto dorsal views of the frontal lobes in Fig. 2, *A* and *B*, where they are shown in relation to a square marking the approximate limits of the SEF (Fig. 2*C*) as determined in studies summarized by Tehovnik (1995). The issue of the relation of recording sites in this study to the location of the SEF as determined by electrical stimulation in classic studies will be taken up at greater length in the DISCUSSION.

Conservation of preferred direction across cue conditions

The selectivity of each neuron for response direction was assessed by carrying out independent ANOVAs on data from pattern and spatial trials, with firing rate as the dependent variable and with response direction (right, up, left, or down) as the single factor. The results, summarized in Table 1, indicate that under both pattern and spatial conditions and during both the delay epoch (cue-onset to fix-spot offset) and movement epoch (fix-spot offset to 100 ms after target attainment) around 40% of the population exhibited significant ($P < 0.05$) direction selectivity. During the delay epoch, the proportion of neurons exhibiting direction selectivity under pattern conditions was slightly lower than the number exhibiting it

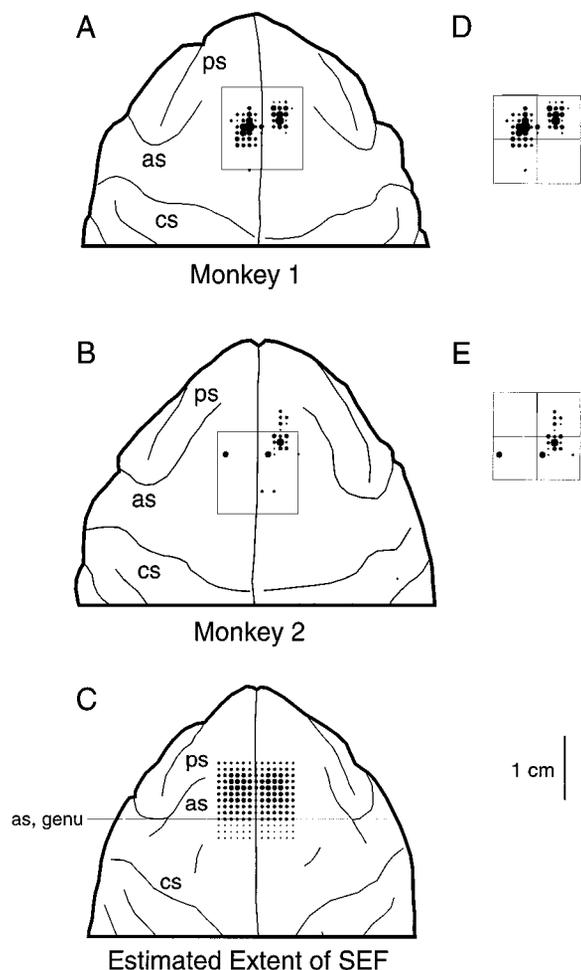


FIG. 2. *A*: recording sites superimposed on a dorsal view of the cerebral hemispheres of *monkey 1*. Each dot indicates a recording site. The area of each dot is proportional to the number of neurons at that site contributing data to the present paper. The largest dot, in the left hemisphere, represents 39 neurons, whereas the smallest dots represent one neuron each. The square corresponds to extent of SEF as estimated in Fig. 2*C*. *B*: recording sites superimposed on a dorsal view of the cerebral hemispheres of *monkey 2*. The largest dot, in the right hemisphere, represents 21 neurons, whereas the smallest dots represent 1 neuron each. The square corresponds to extent of SEF as estimated in Fig. 2*C*. *C*: extent of the SEF as defined by mapping with intracortical microstimulation in studies from 10 laboratories listed in Table 1 of Tehovnik (1995). The number of times a site was counted could range from 1 (smallest dots in this figure: sites implicated in only one study) to 10 (largest dots in this figure: sites implicated by all 10 studies). *D–E*: recording sites in *monkeys 1* and *2*, respectively, projected onto chamber-centered grids (cf. Fig. 9). as, arcuate sulcus; as, genu, genu of the arcuate sulcus; cs, central sulcus; ps, principal sulcus.

under spatial conditions (38 vs. 45%), an effect which just attained significance ($P = 0.047$). This difference may arise from the fact that direction selectivity developed later under pattern conditions (see *Time course of population-averaged cue-dependent activity*).

It was evident on casual inspection of histograms representing neuronal activity (Fig. 3) that the response directions eliciting strongest neuronal activity tended to be the same under pattern and spatial conditions. To assess this tendency quantitatively, we analyzed data from neurons exhibiting significant direction selectivity under both cueing conditions (125 during the delay period and 129 during the movement period). For each neuron, and for each cueing condition independently,

we estimated the best direction by summing vectors pointing toward the four targets after weighting them by the four associated firing rates. Then we computed the absolute angular difference between the best directions estimated on the basis of pattern and spatial data. The results, summarized in Fig. 4, indicate that the estimated best directions were within 20° of each other in a majority of cases. It might be objected that by testing with only four directions, we obtained poor estimates of the preferred directions of those SEF neurons possessing tuning curves narrower than 90° (Russo and Bruce 1996). It is true that estimates of preferred direction would have been inaccurate in these cases. However, the resulting inaccuracy could not have given rise spuriously to the observed tendency for preferred directions to match.

Dependence of firing rate on cue condition

In many neurons, the strength of activity during the period between presentation of the cue and the signal to respond appeared to depend on the type of the cue. For example, the neuron of Fig. 5 fired more strongly when any given direction had been signaled by a central pattern than when it had been signaled by a spatial cue, while the neuron of Fig. 6 showed the opposite pattern. To ascertain whether the type of cue systematically affected the strength of neuronal activity, we carried out ANOVAs on data from each neuron, with firing rate during the delay period as the dependent variable and with cue-type (spatial or pattern) and response-direction (right, up, left, or down) as factors. Independent analyses were carried out on data from the delay epoch (cue onset to fix-spot offset) and the movement epoch (fix-spot offset to 100 ms after target attainment).

During the delay period, there was a significant ($P < 0.05$) dependence on cue-type in 40% (176/439) of all tested neurons. Among 176 neurons showing significant dependence on cue-type during this period, 131 fired more strongly during pattern trials and 45 during spatial trials (Fig. 7). Each of these counts significantly (chi-squared test, $P < 0.0001$) exceeded the level of 2.5% expected by chance with the significance criterion ($P < 0.05$) employed in the ANOVA. We conclude therefore that the SEF contained at least two classes of neurons with cue-dependent activity: those more active on pattern and those more active on spatial trials. However, the number of cue-dependent neurons favoring pattern conditions (131/176)

TABLE 1. *Counts of direction selective neurons*

	Pattern Conditions		Spatial Conditions		All Neurons
	Delay period	Move period	Delay period	Move period	
<i>Monkey 1</i>	134	155	166	159	327
<i>Monkey 2</i>	35	35	32	32	112
Combined	169	190	198	191	439
Percent of all	38%	43%	45%	44%	100%

Numbers of neurons exhibiting significant dependence on direction for each combination of cue-type and epoch [4 single-factor analyses of variance (ANOVAs), $P < 0.05$]. Analysis based on successfully completed trials only. Combined, sum of counts from the two monkeys. Percent of all, combined count represented as a percentage of all neurons studied. All neurons, entries represent the number of neurons on which the test was carried out and thus represent the sum of all direction-selective and nondirection-selective neurons.

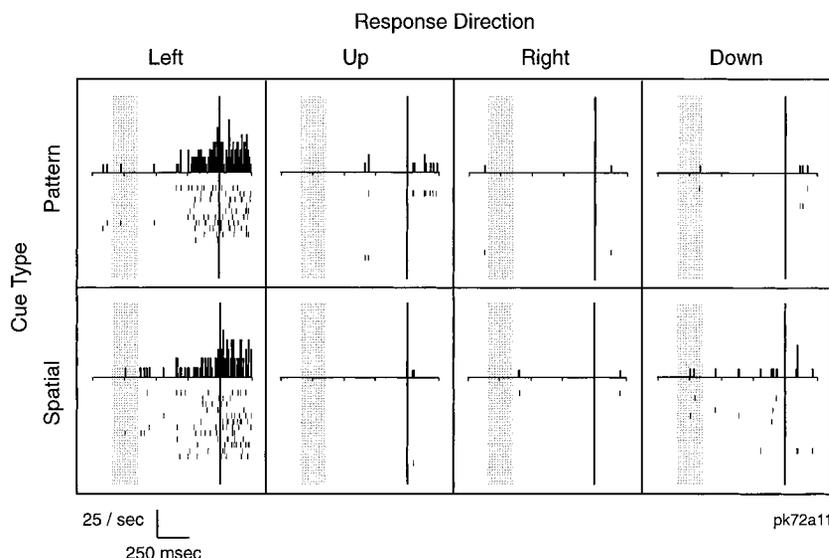


FIG. 3. Data from a single supplementary eye field (SEF) neuron with matching preferred directions under pattern and spatial conditions. The 8 histograms represent mean firing rate as a function of time during trial for the 8 possible combinations of cue-type (pattern or spatial) and target-location (left, up, right, or down). Each histogram is based on 10–16 successfully completed trials. Action potentials from successive trials were aligned on the time of fix-spot offset, which signaled the monkey to move (vertical line); the range of times of cue onset is indicated by the gray vertical bar. Tick marks demarcate 250 ms epochs.

exceeded the number favoring spatial conditions (45/176) by a large margin, with the ratio not significantly different between monkeys (chi-squared test, $P = 0.11$). The excess of neurons firing at a higher rate under the pattern condition was highly significant in each monkey and attained even higher significance in the combined data (chi-squared test, $P \ll 0.0001$).

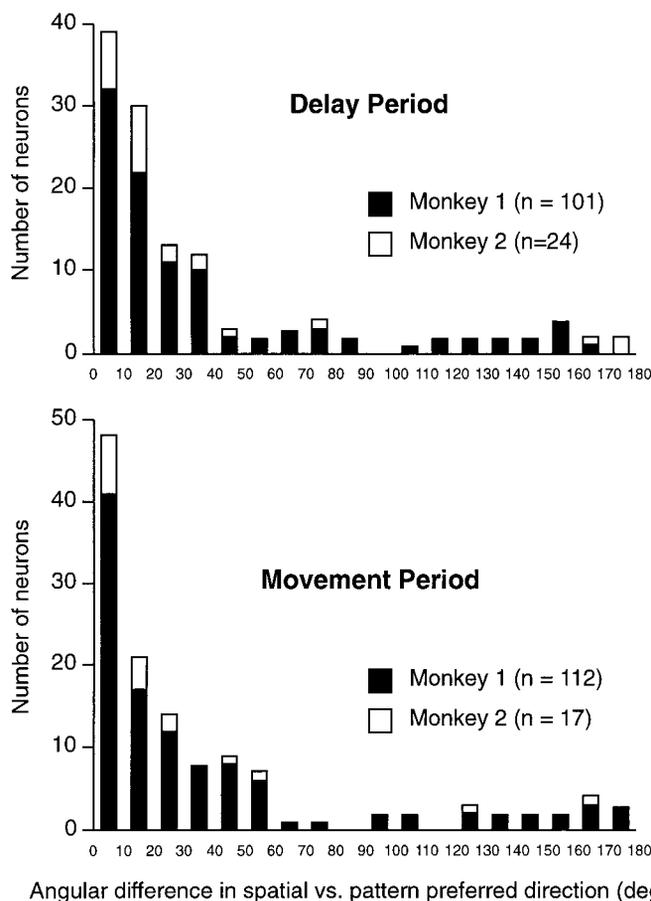


FIG. 4. Distribution of neurons with respect to the difference in degrees between the best direction estimated for spatial trials and the best direction estimated for pattern trials. Only neurons exhibiting significant direction selectivity under each cue condition independently were included in this analysis.

During the movement period, there was a significant ($P < 0.05$) dependence on cue-type in 27% (119/439) of all tested neurons. Among 119 neurons showing significant dependence on cue-type during this period, 105 fired more strongly during pattern trials and 14 during spatial trials (Fig. 7). The excess of neurons firing at a higher rate under the pattern condition was highly significant in each monkey, attained even higher significance in the combined data (chi-squared test, $P \ll 0.0001$) and was not different between monkeys (chi-squared test, $P = 0.14$). That the number of neurons exhibiting a significant main effect of cue type was lower during the movement than during the delay period might reflect a genuine decline in cue-dependent activity or, alternatively, might reflect the fact that noise was higher due to the shorter sampling interval (approximately 300 vs. approximately 750 ms).

To investigate this issue, we computed, for each neuron during each task epoch, a nonstatistical index of cue-dependent activity: $i = (p - s)/(p + s)$, where p and s were the mean firing rates on pattern and spatial trials, respectively. The distributions for both task epochs (Fig. 8, A and B) had means significantly different from zero (One Group t -test, $P < 0.0001$). Further, the mean was actually greater during the movement period (0.060) than during the delay period (0.043) and this difference was significant (paired 2-tailed t -test, $P = 0.02$). The average rate of firing on pattern trials, expressed as a percentage of the average rate of firing on spatial trials [$100 * (1 + i)/(1 - i)$], was 113% during the movement period, as contrasted to 109% during the delay period. Despite this moderate difference between task epochs, neurons exhibiting cue-dependent activity during either epoch in general did so during the other epoch as well. This is indicated by the fact that indices based on activity during the two epochs (Fig. 8C) were significantly and positively correlated ($P < 0.0001$; r -squared = 0.246).

To determine whether dependence on cue-type was related to dependence on response-direction, we analyzed data from the delay period in both monkeys. In each monkey, neurons exhibiting direction selectivity also tended to display dependence on cue-type (Pearson chi-square test of association, $P = 0.0016$ and $P = 0.0011$ in monkey 1 and 2, respectively). Among neurons exhibiting a main effect of direction, the

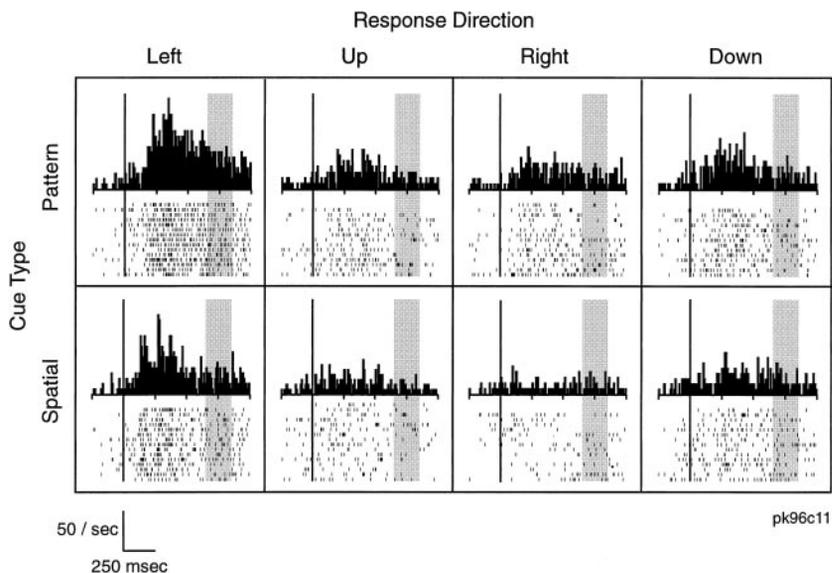


FIG. 5. Data from a single SEF neuron more active under pattern than spatial conditions. Conventions as for Fig. 3 except that action potentials from successive trials were aligned on the time of cue-onset (vertical line); the range of times of fix-spot offset, which signaled the monkey to move, is indicated by the gray vertical bar.

proportion exhibiting a significant main effect of cue-type was 51% (116/227) during the delay period and 52% (99/189) during the movement period (as contrasted to 40 and 27% among all neurons). In contrast to the presence of a cue-type effect, the sign of the effect (pattern greater than spatial or vice versa) was not correlated with the presence of direction selectivity.

Cortical location of neurons with cue-dependent activity

To determine whether neurons exhibiting a significant main effect of cue type were distributed systematically with respect to the cortical surface, we constructed maps showing the locations of neurons that exhibited specific forms of task-related activity during the delay period. These are shown in Fig. 9, with data from *monkey 1* in the left column and data from *monkey 2* in the right column. It is evident from these maps that neurons whose activity was significantly elevated (Fig. 9, C and D) or suppressed (Fig. 9, E and F) on pattern compared with spatial trials were not systematically segregated from each other. Nor were these neurons, as a group, segregated systematically from neurons exhibiting selectivity for saccade direction (Fig. 9, A and B).

Relation of cue-dependent activity to the frequency of behavioral errors

The tendency for neurons to fire more strongly on pattern trials, although documented through an analysis of data from correct trials, might nevertheless have arisen from the fact that the monkeys made more errors under the pattern condition. Pattern cues, due to their more frequent association with errors, might have elicited phasic arousal and this, in turn, might have produced an enhancement of neuronal activity. To test this possibility, we took advantage of the fact that the percent-correct score under pattern conditions varied from run to run of the task (the standard deviation was 7.1% in *monkey 1* and 5.2% in *monkey 2*). This permitted us to ask whether the tendency for neuronal activity to be elevated on pattern trials was correlated, across runs of the task, with the tendency for errors to occur more frequently on pattern trials. For each session during which neuronal data were collected, we computed four values: the mean firing rate on successful pattern trials (PR), the mean firing rate on successful spatial trials (SR), the frequency of errors on pattern trials (PE), and the frequency of errors on spatial trials (SE). We then assessed the correlation across

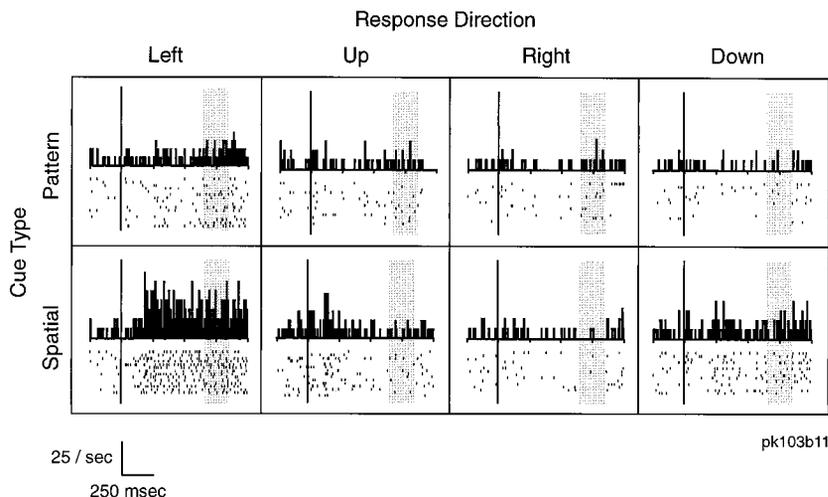


FIG. 6. Data from a single SEF neuron more active under spatial than pattern conditions. Conventions as in Fig. 5.

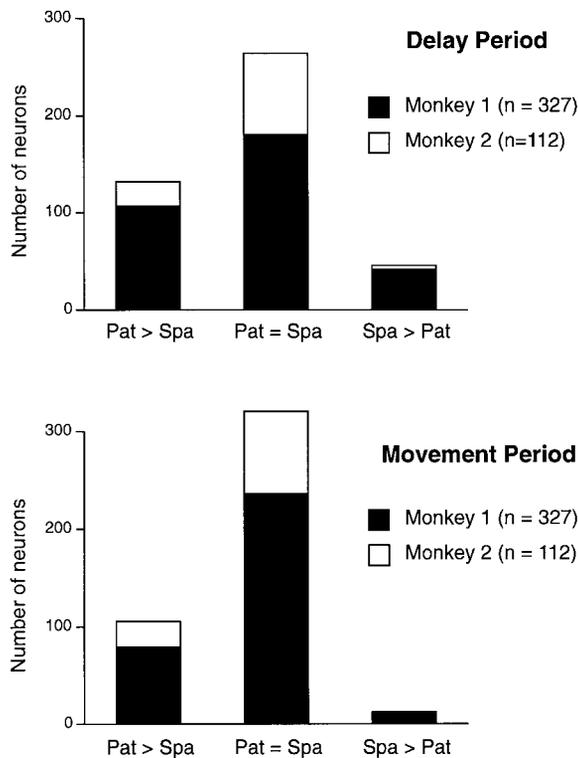


FIG. 7. Distribution of neurons with respect to the dependence of firing rate on cue type. Pat > Spa: neurons firing significantly more strongly on pattern than on spatial trials. Spa > Pat: neurons firing significantly more strongly on spatial than on pattern trials. Pat = Spa: neurons in which the level of activity was not significantly different under the two conditions.

sessions between an index of higher pattern-trial firing rate, $(PR - SR)/(PR + SR)$, and an index of higher pattern-trial error rate, $(PE - SE)/(PE + SE)$. The two indices were not significantly correlated and the trend was negative. Thus, if task difficulty did underlie the enhancement of activity on endogenously cued trials, the critical variable must have been some aspect or consequence of task difficulty other than the higher rate of errors in itself.

Relation of cue-dependent activity to behavioral reaction time

Both monkeys, as described in an earlier section, showed a significant tendency to respond more swiftly following offset of the fixation light under pattern than under spatial conditions. Perhaps presentation of a pattern cue elicited some state which gave rise both to stronger firing on pattern trials and to faster behavioral responses. If so, then insofar as the tendency of pattern cues to elicit this state varied from run to run of the task, we would expect to observe, across runs, covariation of 1) the tendency for firing to be stronger on pattern trials and 2) the tendency for behavioral reactions to be swifter on pattern trials. The difference between pattern and spatial reaction times indeed varied from run to run of the task (the standard deviation of the difference between the reaction times was 27 and 14 ms in *monkey 1* and 2, respectively). Accordingly, we asked whether the tendency for neuronal activity to be elevated on pattern trials was correlated, across runs of the task, with the tendency for behavioral reaction times to be shorter on pattern trials. For

each session during which neuronal data were collected, we computed four values: the mean firing rate on successful pattern trials (PR), the mean firing rate on successful spatial trials (SR), the reaction time on pattern trials (PT), and the reaction time on spatial trials (ST). We then assessed the correlation across sessions between an index of higher pattern-trial firing rate, $(PR - SR)/(PR + SR)$, and an index of faster pattern-trial reaction times, $(ST - PT)/(ST + PT)$. In

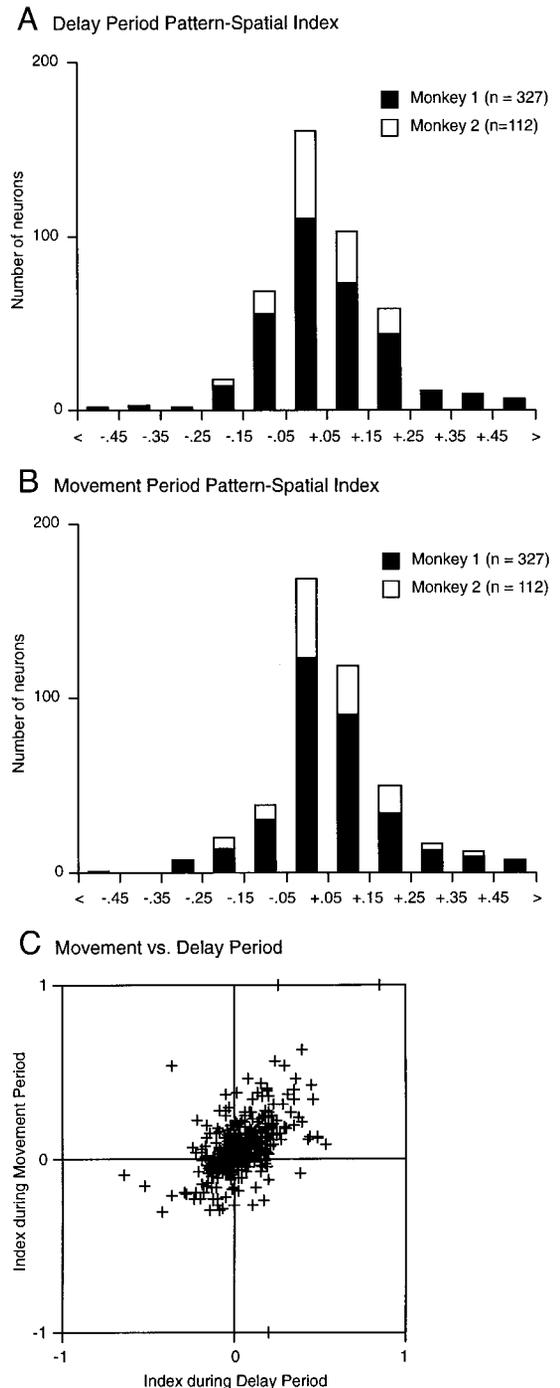


FIG. 8. Distribution of neurons with respect to an index of the difference between firing rates on pattern and spatial trials: $(p - s)/(p + s)$. A: indices based on activity during the delay period. B: indices based on activity during the movement period. C: movement-period indices versus delay-period indices.

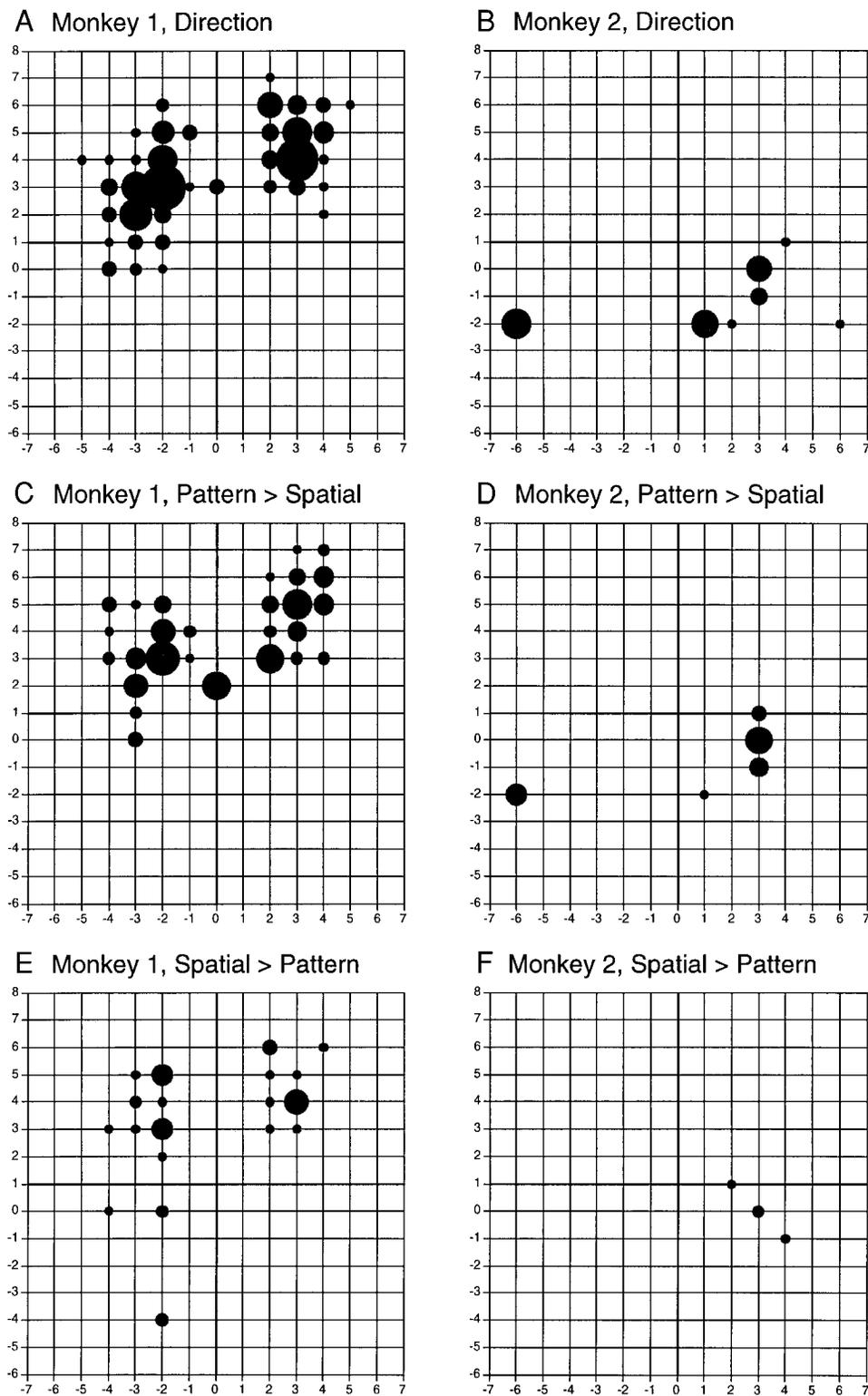


FIG. 9. Distribution across the cortical surface of neurons exhibiting specific patterns of task-related activity. The square frames in the left column (*monkey 1*) correspond to the square frame shown in Fig. 2D. The square frames in the right column (*monkey 2*) correspond to the square frame shown in Fig. 2E. Two recording sites in *monkey 2*, located posterior to the area demarcated by the square, contained only neurons without task-related activity. The numbers on the axes denote displacement in millimeters from the center of the recording chamber. Anterior is represented upward and right is represented to the right. The area of each dark circle is proportional to the number of neurons at that site exhibiting, at a statistically significant level, the indicated form of task-related activity. The smallest circles represent 1 neuron each while the largest circle, at $(-2, 3)$ in A, represents 28 neurons. A and B: neurons exhibiting a significant main effect of saccade direction. C and D: neurons firing significantly more strongly under pattern versus spatial conditions. E and F: neurons firing significantly more strongly under spatial versus pattern conditions.

monkey 1, the two indices were positively (slope = 0.47 [sp/s]/ms) and significantly ($P = 0.0015$) correlated ($r = 0.175$). In *monkey 2*, the trend was opposite (slope = -0.43 [sp/s]/ms) but not significant ($P = 0.13$, $r = 0.145$). A simple description of the effect observed in *monkey 1* is that,

during runs in which firing on pattern trials was especially strong, behavioral reaction times on pattern trials were especially short. This result is intriguing but failure to observe it in the second monkey leaves its significance in doubt.

TABLE 2. Counts of neurons by pattern of cue-direction interaction

	Interaction:		Interaction: Sds > Pds	Total
	Pds > Sds	No Interaction		
<i>A. Delay period</i>				
<i>Monkey 1</i>	34	248	45	327
<i>Monkey 2</i>	7	100	5	112
Combined	41	348	50	439
Percent of total	9%	79%	11%	100%
<i>B. Move period</i>				
<i>Monkey 1</i>	27	279	21	327
<i>Monkey 2</i>	8	103	1	112
Combined	35	382	22	439
Percent of total	8%	73%	5%	100%

Numbers of neurons exhibiting significant interaction effects between cue-type and direction (1 2-factor ANOVA for each task epoch, $P < 0.05$). Neurons showing a significant interaction effect are broken down according to whether directional modulation (as determined by a variance measure described in the text) was greater for pattern cues (Pds > Sds) or for spatial cues (Sds > Pds). Analysis based on successfully completed trials only. Combined, sum of counts from the two monkeys; Percent of total, combined count represented as a percentage of all neurons studied.

Strength of directional signals in relation to cue-dependent activity

Having analyzed whether the *mean firing rate* depended on cue-type (as indicated by a main effect of cue-type), we next asked whether the *strength of the directional signal* depended on cue-type (as indicated by an interaction between cue-type and direction). The ANOVA described in the preceding section revealed interaction effects in 91/439 neurons during the delay period and 57/439 neurons during the movement period. In each of these cases, we measured the strength of direction-selectivity (the variance in mean firing rate across the 4 directions) under both pattern and spatial conditions during the corresponding epoch. Then we classified neurons with a significant interaction effect into two categories: those in which direction-selectivity was stronger (as indicated by higher variance) under the pattern condition (Pds > Sds) and those in which direction-selectivity was stronger (as indicated by higher variance) under spatial condition (Sds > Pds). The counts in these two categories, as given in Table 2, were not significantly different. We conclude that neurons carrying stronger directional signals under the pattern condition were no more common than those exhibiting the opposite pattern.

It might still be the case that the impact of cue-type on the

strength of the directional signal was correlated with its impact on mean firing rate. To determine whether this was so, we considered all cases in which, during a given epoch, a neuron exhibited both a main effect of cue-type and an interaction of cue-type with direction (Table 3). We then asked whether the property of firing more strongly on pattern (or spatial) trials was correlated with the property of carrying stronger directional signals on pattern (or spatial) trials. We found that this tendency was present at a highly significant level (Pearson chi-square test of association, $P = 0.0008$ and $P = 0.0001$ during the delay and movement periods, respectively). We conclude that neurons firing at a higher level under a given condition (pattern or spatial) tend to carry stronger directional signals under that condition.

Time course of population-averaged cue-dependent activity

Given that SEF neurons tended to be more active following pattern than spatial cues, by a measure based on mean firing rate during the delay period as a whole, we next asked at what time during the delay period the enhancement was present. To do so, we employed a population measure, the mean firing rate as a function of time during the trial, computed independently for trials in which the required eye movement was in the neuron's preferred direction and those in which it was in the opposite direction. This analysis was performed on data from all neurons that exhibited statistically significant main effect of direction during the delay period (ANOVA, $P < 0.05$). There were 189 such neurons in *monkey 1* and 38 in *monkey 2*. The results are shown in the form of population histograms in Fig. 10, A and B. Several general features are apparent in these histograms. 1) The mean firing rate increased steadily from the starting point of the analysis, 125 ms before cue onset until around 75 ms after cue onset (activity thus anticipating the appearance of a task-relevant cue is common in premotor areas: Mauritz and Wise 1986; Vaadia et al. 1988). 2) Following the cue, activity became stronger during trials in which the required response was in the neurons' preferred direction (thick curves, "pref") as compared with trials when it was in the antipreferred direction (thin curves, "anti"). 3) This difference emerged earlier on spatial trials (gray curves: directional signal fully developed at around 150 ms following cue presentation) than on pattern trials (black curves: directional signal fully developed at 300–500 ms following cue presentation). 4) At a variable time following cue-presentation, on the order of several hundred milliseconds, activity became stronger on pattern than on spatial trials, both when the required movement was in the preferred direction (thick black curve, "pat," higher than

TABLE 3. Main effects of cue-type vs. interactions of cue-type with direction

Main Effect	Interaction Effect	Delay Period			Move Period		
		<i>M1</i>	<i>M2</i>	Both	<i>M1</i>	<i>M2</i>	Both
Pat > Spa	Pds > Sds	23	5	28	13	8	21
Pat > Spa	Sds > Pds	13	2	15	3	1	4
Spa > Pat	Pds > Sds	4	0	4	0	0	0
Spa > Pat	Sds > Pds	15	1	16	5	0	5

Numbers of neurons exhibiting the various possible combinations of main effect of cue type (column 1) and interaction between cue-type and direction (column 2). A main effect could be manifest as a higher mean rate of activity on pattern trials (Pat > Spa) or on spatial trials (Spa > Pat). An interaction effect could be manifest as stronger directional signals on pattern trials (Pds > Sds) or on spatial trials (Sds > Pds). Analysis based on successfully completed trials only. *M1* and *M2*, *monkey 1* and *2*. Both, sum of counts from the 2 monkeys.

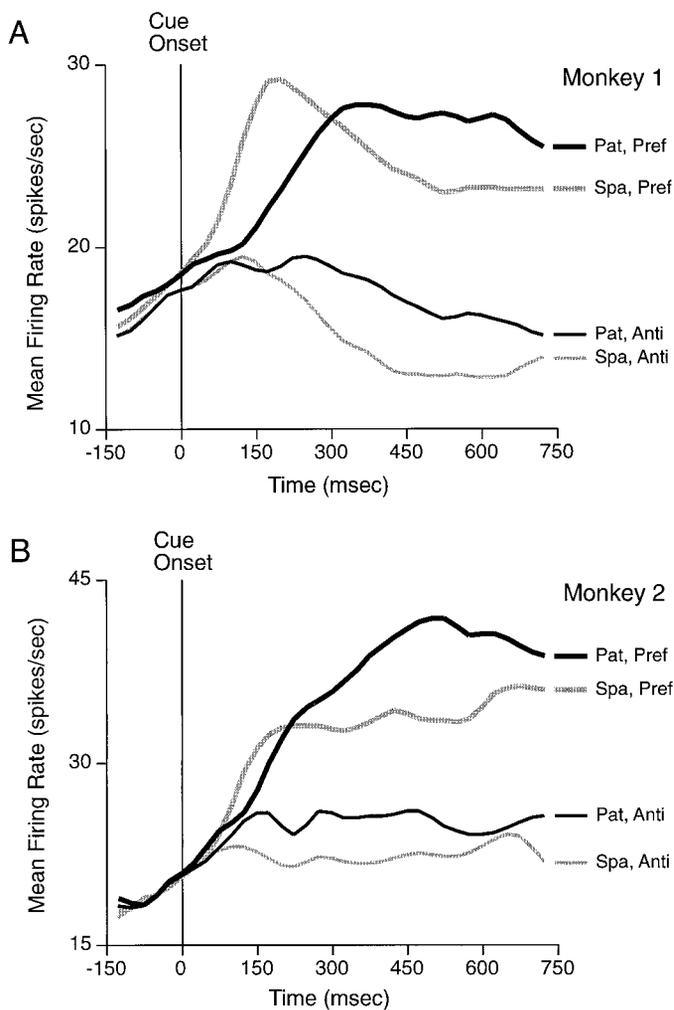


FIG. 10. Mean firing rate as a function of time for all neurons exhibiting significant direction selectivity. Trials were subdivided into spatial (gray) and pattern (black) categories. Within each category, trials were further subdivided according to whether the instructed response was in the neuron's preferred direction (thick curve) or in the opposite direction (thin curve). Trials in which the response deviated 90° from the neuron's preferred direction were not considered.

thick gray curve, "spa") and when it was in the antipreferred direction (thin black curve, "pat," higher than thin gray curve, "spa"). 5) This elevation of activity on pattern compared with spatial trials persisted to the end of the delay period, which occurred, at the earliest, 650 ms following onset of the cue.

We next assessed how the time course of neuronal activity differed between neurons that fired significantly more strongly on pattern trials and those that fired significantly more strongly on spatial trials. This analysis was performed on data from all neurons from *monkey 1* that exhibited statistically significant main effects of both direction and cue-type during the delay period (ANOVA, $P < 0.05$). In this sample were 67 neurons that fired significantly more strongly on pattern trials and 32 that did so on spatial trials. No meaningful analysis was possible in *monkey 2* because only one direction-selective neuron exhibited enhanced activity on spatial trials. The results for *monkey 1* are shown in the form of population histograms in Fig. 11, A and B. Comparison of data from neurons firing more strongly on pattern trials (Fig. 11A) and those firing more strongly on spatial trials (Fig. 11B) suggests the following

general conclusions. 1) In both pattern-enhanced (Fig. 11A) and spatial-enhanced (Fig. 11B) neurons, just as in the entire population (Fig. 10A), the directional signal (thick curve minus thin curve) attained a maximum earlier on spatial (gray) than on pattern (black) trials. 2) In pattern-enhanced neurons (Fig. 11A), the directional signal on pattern trials (thick black curve minus thin black curve) was stronger than the directional signal on spatial trials (thick gray curve minus thin gray curve). In spatial-enhanced neurons (Fig. 11B), the reverse was true. Thus, in each population there was a linkage between conditions that induced higher firing rates and those that induced a stronger dependence on direction. This reinforces the finding, described above, that, in neurons exhibiting both a main effect of cue-type and an interaction between cue-type and direction, the cue-type eliciting stronger activity tended also to elicit deeper modulation by direction. 3) Pattern enhancement (Fig. 11A) was present both on trials when the response was in the neuron's preferred direction (thick black curve minus thick gray curve) and when the response was in the opposite direction (thin black curve minus thin gray curve). In contrast, spatial enhancement (Fig. 11B) was strong on preferred-direction trials (thick gray curve minus thick black curve) but nearly

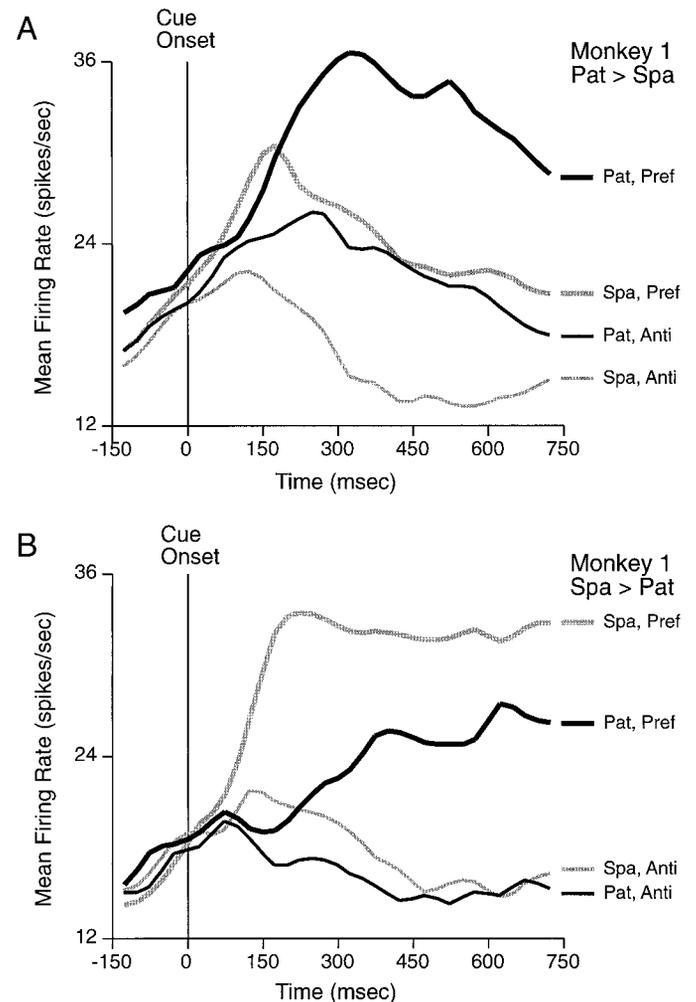


FIG. 11. Mean firing rate as a function of time for all direction-selective neurons firing significantly more strongly under (A) pattern as compared with spatial conditions and (B) spatial as compared with pattern conditions. Other conventions as in Fig. 10.

absent on opposite-direction trials (thin gray curve minus thin black curve). 4) On preferred-direction trials (thick black and gray curves), the mean level of activity tapered off during the second half of the delay period in pattern-enhanced neurons (Fig. 11A) but remained constant or rose in spatial-enhanced neurons (Fig. 11B). These observations suggest a general contrast between pattern-enhancement (which occurs regardless of response direction) and spatial enhancement (which arises because of stronger activity on preferred-direction trials). They also suggest a general contrast between cells exhibiting pattern enhancement (whose rate of activity declines during the delay period) and those exhibiting spatial enhancement (whose rate of activity remains high to the end of the delay period).

Time course of cue-dependent activity: single-neuron analysis

Population histograms are potentially misleading in that they represent the mean rate of firing of neurons which, considered individually, might exhibit quite different patterns of activity. Accordingly, we tested the general conclusions of the population-averaged analysis by analyzing the time course of activity following pattern and spatial cues in individual neurons. We restricted this analysis to a subset of neurons in which we judged that the signal-to-noise ratio was sufficiently high to permit a cell-by-cell analysis. In particular, we considered neurons with the following traits: 1) from *monkey 1*; 2) no fewer than 10 spikes per trial on average; 3) a significant main effect of direction; 4) preferred direction (right, up, left, or down), as judged on the basis of firing rate 300–600 ms after cue onset, identical under pattern and spatial conditions; 5) the fitted curves obtained by regression spline analysis (see APPENDIX) possessed maxima between onset of the cue and the signal to move. These criteria were met by 84 neurons. We analyzed data from each neuron by means of a regression spline approach. Firing rates were fitted with a piecewise cubic polynomial function (Fig. 12). Then comparisons between pattern and spatial conditions were carried out based on the assumption that the binwise spike counts conformed to Poisson distributions (see METHODS and APPENDIX for details).

TIME TO PEAK. We asked, for each neuron, whether its firing rate achieved a maximum significantly ($P < 0.05$) later under the pattern than under the spatial condition or vice versa. Regression spline analysis revealed a “pattern later” effect in 41/84 neurons (49%) and a “spatial later” effect in 3/84 neurons (3.6%). The population mean difference in maximal firing rate (the mean delay in achieving maximal rate under the pattern condition as compared with the spatial condition as estimated from the hierarchical model) was 137 ms (SE 18 ms), which was significantly different from zero. The distribution of values was fit well by a normal distribution; thus neurons form a continuum with respect to the difference in time-to-peak between pattern and spatial conditions. In conclusion, the cell-by-cell analyses supported the population-averaged analysis in indicating that firing on preferred-direction trials tended to peak later under pattern than under spatial conditions.

PEAK RATE. We asked, for each neuron, whether the maximal firing rate attained between cue onset and the signal to respond was significantly ($P < 0.05$) greater under the pattern than

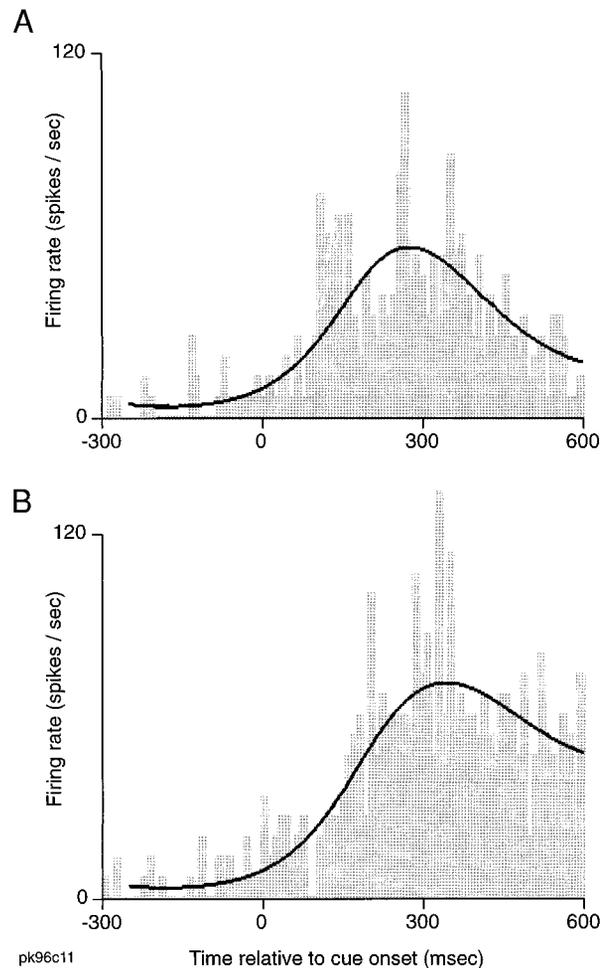


FIG. 12. Regression spline analysis of firing rate as a function of time for one neuron (pk96c11; see Fig. 5) during trials in which the response was in the preferred (leftward) direction and the cue was either spatial (A) or pattern (B). The parameters of the functions obtained for this neuron by polynomial curve fitting (shown superimposed on histograms) were peak firing rate, 55 (A) versus 70 (B) spikes/s; time to peak, 274 (A) versus 350 (B) ms; late firing rate, 22 (A) versus 52 (B) spikes/s. Regression analysis following the polynomial curve fit revealed significant ($P < 0.01$) tendencies for the peak firing rate to be higher, for the time to peak to be later, and for the late rate to be higher under the pattern condition.

under the spatial condition or vice versa. Regression spline analysis revealed a “pattern greater” effect in 21/84 neurons (25%) and a “spatial greater” effect in 24/84 neurons (30%). The mean difference between the maximal rates on pattern and spatial trials as estimated from the hierarchical model was -1.15 spikes/s (SE 2.06), which was not significantly different from zero; the distribution of differences was fit well by a normal distribution. In conclusion, these analyses revealed only an insignificant trend toward greater maximal activity on spatial than on pattern trials. This trend is consonant with population data from *monkey 1* (Fig. 10A, thick gray curve versus thick black curve) but not from *monkey 2* (Fig. 10B, thick gray curve versus thick black curve). We conclude that the maximal firing rate did not exhibit a strong or consistent dependence on cue condition.

LATE RATE. We asked, for each neuron, whether the mean firing rate attained late in the delay period (500–600 ms following cue onset) was significantly ($P < 0.05$) greater under

the pattern than under the spatial condition or vice versa. Regression spline analysis revealed a pattern greater effect in 44/84 neurons (52%) and a spatial greater effect in 9/84 neurons (11%). The mean difference between the late rates on pattern and spatial trials as estimated from the hierarchical model was 9.67 spikes/s (SE 1.59), which was significantly different from zero. The distribution of differences was fit well by a normal distribution. In conclusion, this analysis revealed a significant trend toward greater late-delay-period activity on pattern than on spatial trials, in agreement with population-averaged data from both monkeys.

To establish that these results were not an artifact of statistical methodology, we repeated the analysis using a bootstrap approach (see METHODS and APPENDIX for details). In this approach, firing rates were fitted with a Gaussian smoothing function and the validity of the subsequent comparisons did not rest on assumptions concerning the distribution of values. The results were in close agreement with those of the regression spline analysis.

DISCUSSION

Overview

The central finding of this study is that neuronal activity in the SEF was influenced by the nature of the cue that signaled the direction of an eye movement to be performed later in the trial. Differences between spatial trials (in which the cue marked the target location) and pattern trials (in which the cue was a central pattern associated with the target location) were evident during both early and late task epochs. 1) *Early activity*: activity reflecting the direction of the impending response developed more rapidly on spatial than on pattern trials. 2) *Late activity*: the mean level of activity throughout the delay period was higher on pattern than on spatial trials.

Early activity: differential timing

On spatial trials in which the stimulus was in the neuron's preferred direction (Fig. 10, thick gray curves), there was an early increase in activity at the latency of previously described visual responses (Schall 1991a,b; Schlag and Schlag-Rey 1987). On pattern trials, there was no comparable early increase. This difference could be accounted for in at least three different ways.

VISUAL RESPONSIVENESS. The occurrence of early activity on spatial but not pattern trials could be accounted for by assuming that SEF neurons possess eccentric visual receptive fields spatially congruent with the targets of eye movements in their preferred directions, as reported previously (Schall 1991a; Schlag and Schlag-Rey 1987), and that these receptive fields do not encroach on the fovea, contrary to one previous report (Schall 1991a), or are weaker at the fovea. However, even visual stimuli presented during passive fixation probably trigger automatic responses: shifts of spatial attention and the incipient programming of eye movements. Additional research will be required to distinguish between passive visual responses, on one hand, and, on the other hand, neuronal activity correlated with attentional and motoric processes elicited automatically by visual stimulation.

SPATIAL ATTENTION. In studies of spatial attention, a fundamental distinction is made between exogenous and endogenous cueing (Egeth and Yantis 1997; Posner 1980). Exogenous cueing occurs when a peripheral stimulus of sudden onset draws attention to its location, whereas endogenous cueing results when a symbolic cue at one location (e.g., an arrow at fixation) directs attention to another location (e.g., the peripheral site to which the arrow points). Either type of cue can elicit a shift of attention, as reflected by improved detection and discrimination for stimuli presented at the cued location and reduced reaction time. However, shifts elicited by exogenous and endogenous cues occur with different time courses. Monkey and human studies have indicated that the reaction-time and accuracy benefits conferred by an exogenous cue peak at around 100 ms following its presentation, whereas the benefits conferred by an endogenous cue peak at around 300 ms (Bowman et al. 1993; Cheal and Lyon 1991; Müller and Rabbit 1989). Lateralized scalp potentials correlated with the direction of attention also develop more rapidly in response to exogenous cues (Yamaguchi et al. 1994). The low speed with which attention is shifted in response to an endogenous cue might reflect the time required for recognition or for implementing the arbitrary association between the stimulus and the response. On spatial trials, the monkey's attention presumably was drawn to the target location by an exogenous process (an automatic tendency to attend to the location of the cue) as well as by an endogenous process (a deliberate effort to attend to the cued location), whereas, on pattern trials, an endogenous process alone was active. It is reasonable therefore to speculate that the earlier appearance of directional activity on spatial trials reflected the greater speed with which attention was allocated under exogenous control.

OCULOMOTOR PROGRAMMING. Early direction-selective activity in the SEF, as observed on spatial trials, might have been correlated with the rapid programming of oculomotor responses. Preparedness to make an eye movement to a cued location, as measured in monkeys with a technique based on electrical stimulation, peaks at around 100 ms following an exogenous cue but rises steadily over several hundred milliseconds following an endogenous one (Kustov and Robinson 1996). To distinguish definitively between activity related to saccade programming and activity related to the spatial allocation of attention is a formidable challenge because the two processes are very tightly yoked and may rely on substantially overlapping neural substrates (Corbetta 1998; Kustov and Robinson 1996; Rizzolatti et al. 1994; Sheliga et al. 1994). This challenge is faced by any study that attempts to establish a relation between neural activity in the SEF and spatial attention (Bon and Lucchetti 1997).

Late activity: differential strength

The finding that population activity late in the delay period was higher on pattern than on spatial trials fits with a growing body of literature indicating that activation of some frontal areas is elevated during the performance of tasks which, because they are not automatic, require a high degree of endogenous control. The observation that population activity in the SEF is greater on antisaccade than on prosaccade trials (Schlag-Rey et al. 1997) can be accounted for in these terms. Further, human imaging studies have demonstrated enhanced

frontal-lobe functional activation under several conditions requiring greater engagement of voluntary resources, including response-selection based on novel versus familiar associations (Paus et al. 1993; Raichle et al. 1994), attention to multiple versus single visual-feature dimensions (Corbetta et al. 1991; Rees et al. 1997), comprehension of syntactically complex versus simple sentences (Just et al. 1996), performance of tasks placing a higher versus lower load on short-term memory (Cohen et al. 1997), execution of the Stroop task with incongruent versus congruent conditions (Carter et al. 1995; Pardo et al. 1990), and performance of the antisaccade versus prosaccade task (Sweeney et al. 1996).

On one hand, these findings might be accounted for by supposing that frontal areas including, in particular, medial premotor areas such as the SEF, contribute preferentially to self-generated as opposed to stimulus-driven behavior (Passingham 1993; Tanji and Shima 1996). Under neither the pattern nor the spatial conditions is behavior strictly speaking self-generated, for, in both, a sensory stimulus provides the directional cue. However, the rule linking the stimulus to the response is entirely arbitrary and unnatural in pattern trials. In that sense, the rule, if not the response, is self-generated. Wise et al. (1996) captured this distinction in proposing that premotor cortex is selectively responsible for behaviors requiring “nonstandard” sensorimotor mappings.

On the other hand, explanations based on arousal cannot be ruled out. For example, pattern-based target-selection, being slower and more difficult than the process set in motion by a spatial cue, might give rise to phasic arousal manifest in a higher rate of neuronal activity (for a similar argument as applied to functional imaging studies of anterior cingulate cortex, see Paus et al. 1998). An arousal-based mechanism could account for the fact that enhanced firing persists past the point at which target selection is complete, as marked by the advent of robust direction-selective activity. It is also consonant with the fact that population activity on pattern trials differed from population activity on spatial trials primarily with respect to a nonspecific signal (mean rate) rather than with respect to a motorically relevant signal (the difference in rate between neurons representing the preferred and antipreferred directions).

Recording location

Although we did not map out the SEF by observing electrically stimulated eye movements, we feel confident that all or nearly all of the neurons in this study were in the SEF. Our confidence is based on two factors: the functional properties of the neurons and their location relative to the SEF as mapped out in other studies. 1) *Functional properties*: neurons exhibiting significant effects of cue-type (Fig. 9, C–F) were intermingled with neurons exhibiting selectivity for saccade direction (Fig. 9, A and B), the latter a functional signature of the SEF. Further, on analysis of trends across the neuronal population, we found that selectivity for saccade direction and significant effects of cue-type showed a significant tendency to occur together. 2) *Location relative to standard maps*: to compare recording sites in this study to the location of the SEF as characterized in classic studies based on electrical stimulation, we constructed the map shown in Fig. 2C, which is based on Table 1 of a review by Tehovnik (1995). Tehovnik sum-

marized the results of 10 studies in which electrical stimulation was used to map out the SEF, indicating, for each study, the area’s mediolateral extent (ML, defined relative to the inter-hemispheric midline) and anterior-posterior extent (AP, defined relative to the genu of the arcuate sulcus). These results are translated, in Fig. 2C, into a graph in which the area of each dot corresponds to the fraction of the 10 studies in which electrical stimulation at the dot’s location elicited eye movements. Loci at which electrical stimulation elicited eye movements extend from 3 mm posterior to 9 mm anterior to the level of the genu of the arcuate sulcus and from the midline to 6 mm lateral. In recent mapping studies, this general pattern has been confirmed. For example, Fig. 8A of Chen and Wise (1995b) show sites positive for elicitation of eye movements as extending 2–6 mm anterior to the genu, while Fig. 1 of Fujii et al. (1995) show such sites at levels 1–8 mm anterior to the genu. The anterior limit of the SEF as demarcated in these studies coincides approximately with the posterior limit (10 mm anterior to the genu) of an area from which ear movements can be elicited (Fig. 2A of Bon and Lucchetti 1994). To facilitate comparison of recording sites in this study to the limits of the SEF as defined in other studies, the zone marked by dots in Fig. 2C is represented by a square in Fig. 2, A and B. All recording sites in both *monkey 1* and *monkey 2* were within 6 mm of the hemispheric midline and thus were within the mediolateral limits of the SEF as defined in preceding studies. With respect to anterior-posterior location, the following conclusions can be drawn. In *monkey 1*, all recording sites, with one exception, were between 0 and 8 mm anterior to the genu of the arcuate sulcus (Fig. 2A) and thus were clearly within the confines of the SEF as demarcated in mapping studies. The exceptional site was approximately 3.5 mm posterior to the genu of the arcuate sulcus and thus was at the border of this zone. In *monkey 2*, recording sites extended from approximately 0 mm to approximately 13 mm anterior to the genu of the arcuate sulcus (Fig. 2B); however, recording sites at which neurons exhibited direction selectivity or fired differentially as a function of cue type extended anteriorly no farther than 9 mm (Fig. 9, B, D, and F). Neurons rostral to this level may well have been outside the confines of the SEF. Given the impossibility of drawing a precise line between the SEF and adjacent areas, we chose to include them in our sample at the cost of slightly reducing the percentage of neurons exhibiting task-related activity in *monkey 2*. Their inclusion had no impact on our major conclusions, which concerned the relative frequency of different forms of task-related activity.

Comparison to dorsal premotor cortex

Kurata and Wise (1988) recorded from the dorsal premotor cortex of monkeys during the performance of tasks similar to the spatial and pattern ones used here with the exception that the nonspatial cues were differentiated by color and the responses were reaching movements. Neurons exhibiting a significant effect of cue-type were significantly less frequent in their sample than in ours (19 vs. 30%, $P < 0.0001$, chi-squared test). However, among neurons exhibiting an effect of cue-type, there was in premotor cortex, as in the SEF, an approximately 3:1 preponderance of cells firing more strongly under the nonspatial condition. Making allowance for uncertainty arising from methodological differences, we conclude that the

effects of cue-type in the SEF and dorsal premotor cortex are qualitatively similar although quantitatively different.

Comparison to dorsolateral prefrontal cortex

Neuronal activity in the dorsolateral prefrontal cortex surrounding the principal sulcus has been monitored under conditions closely approximating the ones used in this study (Asaad et al. 1998; Wilson et al. 1993). However, there has been no report of phenomena equivalent to the ones described here (a slower rise of directional signals or a higher net level of sustained activity on pattern trials). Some prefrontal neurons fire more strongly on pattern trials simply because they are selective for particular patterns (Hasegawa et al. 1998; Hoshi et al. 1998; Miller et al. 1996; Ó Scalaidhe et al. 1997; Rao et al. 1997; White and Wise 1999; Wilson et al. 1993). This cannot be the mechanism of pattern-trial enhancement in the SEF because SEF neurons are not selective for patterns. At least three observations support this point. First, in monkeys performing an object-centered eye movement task, SEF neurons are unaffected by marked changes in the visual properties of cues (Olson and Gettner 1999). Second, in monkeys performing a chromatic delayed-match-to-sample task, SEF neurons are insensitive to the colors of the samples and probes (Olson and Tremblay 1997). Third, in the present study, the pattern selectivity of SEF neurons was predictable from the directions associated with the patterns and so was a simple extension of their spatial selectivity. Even when factors such as pattern selectivity are ruled out as a cause, some prefrontal neurons fire at different levels when the monkey is following a pattern or spatial rule (White and Wise 1999; Wilson et al. 1993). Further, neurons more active under pattern or spatial conditions may be regionally segregated (White and Wise 1999; Wilson et al. 1993). However, within prefrontal cortex as a whole, neither population is obviously more numerous.

Recording in the context of pattern and spatial working memory tasks has provided some evidence that prefrontal neurons as a population are more active during the processing of pattern than of spatial information. Hoshi et al. (1998), studying movement-period activity in prefrontal neurons of monkeys performing a delayed match to sample task, found that the activity of some neurons varied as a function of whether the monkey had selected the target on the basis of its form or location. Further, they found that neurons firing more strongly on pattern-match trials outnumbered those firing more strongly on spatial-match trials by a factor of around two to one. Although the tasks of Hoshi et al. are quite different from ours, this phenomenon could be interpreted as analogous to pattern-trial enhancement in the SEF.

APPENDIX

Regression splines

Let t_{ij} denote the j th spike time on the i th trial. To fit regression splines, we aggregate the spikes $\{t_{ij}\}$ into bins B_k of width δ centered at t_k^* . The Poisson regression likelihood function is

$$L^*(\theta) = e^{-\delta N \sum_{k=1}^K \lambda(t_k^*)} \prod_{k=1}^K \lambda(t_k^*)^{y_k}$$

where y_k is the number of spikes in the k th bin, which, for small δ provides a good approximation to the likelihood function of the inhomogeneous Poisson process. We have used a bin width of $\delta = 10$ ms. The intensity $\lambda(t)$ is specified by a loglinear model with cubic splines

$$\log \lambda(t) = \beta_0 + \beta_1(t - \xi_1)_+ + \beta_2(t - \xi_1)_+^2 + \beta_3(t - \xi_1)_+^3 + \beta_4(t - \xi_2)_+^3$$

where $\xi_1 = -250$ ms and $\xi_2 = 200$ ms. Note that this particular form assumes the intensity is constant until 250 ms prior to the cue. To implement the Poisson regression, we created appropriate basis vectors and applied the generalized linear model function (glm) in S-PLUS (see Venables and Ripley 1997). Because the trials ended at varying times, we pooled all counts after 580 ms into a single bin and then adjusted for this by weighting the resulting count by (the reciprocal of) the number of 10-ms intervals included in this last interval.

To compare formally the temporal evolution of the firing rates in the two tasks, we define features of interest. We denote by λ_{\max} the maximal firing rate, by τ_{\max} the time at which this maximum occurs, and by λ_{end} the mean end firing rate, that is, the firing rate averaged over the interval [500, 600] ms after presentation of the cue. Supercripts s or p distinguish their values for spatial and pattern tasks. For each neuron, we consider the differences $\tau_{\max}^p - \tau_{\max}^s$, $\lambda_{\max}^p - \lambda_{\max}^s$, and $\lambda_{\text{end}}^p - \lambda_{\text{end}}^s$. We test whether these differences are greater than (or less than) zero by evaluating their ML estimates and SE using standard asymptotic theory (the delta method, e.g., Agresti 1990, Chapter 12), comparing estimate/SE to a standard normal distribution to obtain a P value.

Kernel smoothing and the bootstrap

For a given neuron and condition, we use a Gaussian kernel estimator of the intensity function $\lambda(t)$, having the form

$$\hat{\lambda}(t) = R^{-1} h^{-1} \sum_{i,j} K\{(t - X_{ij})/h\}$$

where R is the number of trials, K is the Gaussian kernel function, and h denotes the bandwidth. We use the "second generation" bandwidth selection rule of Sheather and Jones (1991)

$$h = \left[\frac{\int K^2}{n \int (f'')^2 \left\{ \int t^2 K \right\}^3} \right]^{1/5}$$

obtained by minimizing an asymptotic expansion of the mean integrated square error with respect to h . We use the estimated intensity to compute estimates of $\tau_{\max}^p - \tau_{\max}^s$, $\lambda_{\max}^p - \lambda_{\max}^s$, and $\lambda_{\text{end}}^p - \lambda_{\text{end}}^s$. We then obtain a bootstrap significance test by resampling (shuffling) the trials. For each neuron, we want to compare characteristics of the point processes in spatial and pattern tasks. We take the null hypothesis of no differences between tasks to mean that the point processes for pattern and spatial tasks have the same distribution. We combine the trials of the two tasks (because, under this null hypothesis, all trials are assumed to be realizations of the same process), then sample them at random with replacement, assign the n_1 first to the spatial task and the remaining to the pattern task, where n_1 is the original number of trials in the spatial task. This yields a nonparametric bootstrap sample, from which the value of each estimated difference may be computed, thereby yielding a bootstrap distribution for each estimated difference. Each observed difference, computed from the data, is then compared with the bootstrap distribution to produce a P value.

Population analysis

We consider each neuron to be drawn at random from a population of neurons. The differences $\tau_{\max}^p - \tau_{\max}^s$, $\lambda_{\max}^p - \lambda_{\max}^s$, and $\lambda_{\text{end}}^p -$

λ_{end}^s are assumed to follow a three-dimensional multivariate normal distribution across the ensemble of neurons: letting $\phi = (\tau_{\text{max}}^p - \tau_{\text{max}}^s, \lambda_{\text{max}}^p - \lambda_{\text{max}}^s, \lambda_{\text{end}}^p - \lambda_{\text{end}}^s)$, for the i th neuron we place a subscript on ϕ and assume

$$\phi_i \sim N(\mu, D) \quad (\text{A1})$$

where μ is the population mean and D is the population variance matrix. The estimated differences are also taken to be normally distributed

$$\hat{\phi}_i \sim N(\phi_i, \Sigma_i) \quad (\text{A2})$$

where the matrix Σ_i is obtained from the delta method (Agresti 1990, Chapter 12). Together, Eqs. A1 and A2 define a normal hierarchical model (e.g., Gilks et al. 1996) and Bayesian estimation of the population mean vector μ may be achieved using Markov chain Monte Carlo with the publicly available software BUGS (Spiegelhalter et al. 1996).

Q-Q plots to check the Poisson process assumption

Suppose that on the i th trial we have spikes at times $t_{i1}, t_{i2}, \dots, t_{in_i}$ in time interval $(0, T]$ with $i = 1, \dots, N$. The likelihood function in terms of the intensity $\lambda(t) = \lambda(t; \theta)$ is

$$\begin{aligned} L(\theta) &= \prod_{i=1}^N p(t_{i1}, \dots, t_{in_i}) \\ &= \prod_{i=1}^N \left\{ e^{-\int_0^T \lambda(u) du} \prod_{j=1}^{n_i} \lambda(t_{ij}) \right\}. \end{aligned}$$

If the spikes do conform to an inhomogeneous Poisson process, on the transformed time scale $\tau(t) = \int_0^t \lambda(u) du$, they will follow a *homogeneous* Poisson process with interspike intervals following an exponential distribution with mean 1. To check for departure from the Poisson process assumption we may therefore, as in Ogata (1988), plot the ordered interspike intervals on this transformed scale against the quantiles for an exponential distribution. Departures from the assumption are indicated by clear deviation from linearity in this plot. The standard statistical terminology ‘‘Q-Q plot’’ is short for ‘‘quantile-quantile plot.’’ The procedure may also be adapted effectively to the context of models for non-Poisson spike behavior (E. Brown, personal communication).

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