

Matching Patterns of Activity in Primate Prefrontal Area 8a and Parietal Area 7ip Neurons During a Spatial Working Memory Task

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Chafee, Matthew V. and Patricia S. Goldman-Rakic. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *J. Neurophysiol.* 79: 2919–2940, 1998. Single-unit recording studies of posterior parietal neurons have indicated a similarity of neuronal activation to that observed in the dorsolateral prefrontal cortex in relation to performance of delayed saccade tasks. A key issue addressed in the present study is whether the different classes of neuronal activity observed in these tasks are encountered more frequently in one or the other area or otherwise exhibit region-specific properties. The present study is the first to directly compare these patterns of neuronal activity by alternately recording from parietal area 7ip and prefrontal area 8a, under the identical behavioral conditions, within the same hemisphere of two monkeys performing an oculomotor delayed response task. The firing rate of 222 posterior parietal and 235 prefrontal neurons significantly changed during the cue, delay, and/or saccade periods of the task. Neuronal responses in the two areas could be distinguished only by subtle differences in their incidence and timing. Thus neurons responding to the cue appeared earliest and were more frequent among the task-related neurons within parietal cortex, whereas neurons exhibiting delay-period activity accounted for a larger proportion of task-related neurons in prefrontal cortex. Otherwise, the task-related neuronal activities were remarkably similar. Cue period activity in prefrontal and parietal cortex exhibited comparable spatial tuning and temporal duration characteristics, taking the form of phasic, tonic, or combined phasic/tonic excitation in both cortical populations. Neurons in both cortical areas exhibited sustained activity during the delay period with nearly identical spatial tuning. The various patterns of delay-period activity—tonic, increasing or decreasing, alone or in combination with greater activation during cue and/or saccade periods—likewise were distributed to both cortical areas. Finally, similarities in the two populations extended to the proportion and spatial tuning of presaccadic and postsaccadic neuronal activity occurring in relation to the memory-guided saccade. The present findings support and extend evidence for a faithful duplication of receptive field properties and virtually every other dimension of task-related activity observed when parietal and prefrontal cortex are recruited to a common task. This striking similarity attests to the principal that information shared by a prefrontal region and a sensory association area with which it is connected is domain specific and not subject to hierarchical elaboration, as is evident at earlier stages of visuospatial processing.

INTRODUCTION

There now exists considerable evidence to support the hypothesis that prefrontal cortex is recruited in the formation of internal representations and their maintenance as “on-line” working memories (Goldman-Rakic 1987, 1995).

Thus the firing rates of neurons in various prefrontal regions increase tonically while monkeys retain particular spatial locations (Bruce and Goldberg 1985; Funahashi et al. 1989, 1993b; Kojima and Goldman-Rakic 1982, 1984; Niki 1974a–c; Niki and Watanabe 1976; Quintana and Fuster 1992; Rao et al. 1997), colors (Fuster et al. 1982; Quintana and Fuster 1992; Quintana et al. 1988; Watanabe 1981, 1986), visual patterns (Miller et al. 1996; Rao et al. 1997; Wilson et al. 1993), or faces (Ó Scalaidhe et al. 1997; Wilson et al. 1993) in working memory. Loss of these neurons provides an account for why monkeys with prefrontal lesions fail on delayed-response tasks, no longer able to correctly select their responses in the present moment on the basis of a visuospatial cue seen in the recent past (Bachevalier and Mishkin 1986; Butters and Pandya 1969; Butters et al. 1971; Funahashi et al. 1993a; Goldman and Rosvold 1970; Goldman et al. 1971; Jacobsen 1936; Mishkin 1957; Mishkin and Manning 1978; Passingham 1975). The working memory theory of prefrontal function has been supported also by functional imaging studies of human cortex, revealing prefrontal activation when working memory is recruited (Baker et al. 1996; Cohen et al. 1997; Courtney et al. 1996, 1997; Demb et al. 1995; Jonides et al. 1993; McCarthy et al. 1994; Owen et al. 1996; Paulesu et al. 1993; Petrides et al. 1993a,b; Roland and Friberg 1985; Smith et al. 1995, 1996; Swartz et al. 1995; Sweeney et al. 1996).

These data directly identify dorsolateral prefrontal cortex as a critical node in a neural system engaged by the various components of a working memory task (Goldman-Rakic 1987). However, it is widely appreciated that the neural system providing this capacity cannot reside wholly within prefrontal cortex but extends beyond it to involve and in fact require interactions with other cortical areas. Among these is the posterior parietal cortex, with which dorsolateral prefrontal cortex is anatomically directly connected (Andersen et al. 1985, 1990a; Barbas 1988; Barbas and Mesulam 1985; Cavada and Goldman-Rakic 1989b; Petrides and Pandya 1984; Schall et al. 1995; Schwartz and Goldman-Rakic 1984; Stanton et al. 1995; Tian and Lynch 1996). In addition to its role in spatial vision (for reviews, Andersen 1987, 1995), neuronal activity in posterior parietal area 7 (areas 7a and LIP) now has been shown to be elevated during the delay period of spatial working memory tasks, including delayed match-to-sample paradigms (Constantinidis and Steinmetz 1996), and also delayed saccade paradigms in which saccades are made toward the locations of remem-

bered visual (Andersen et al. 1990b; Barash et al. 1991a,b; Bracewell et al. 1996; Colby et al. 1996; Gnadt and Andersen 1988; Gnadt and Mays 1995; Mazzoni et al. 1996a; Snyder et al. 1997) or auditory (Mazzoni et al. 1996b; Stricanne et al. 1996) targets, much as do prefrontal neurons (Bruce and Goldberg 1985; Funahashi et al. 1989, 1993b; Russo and Bruce 1994). To our knowledge, however, only two previous studies (Batuev et al. 1985; Quintana and Fuster 1992), both involving manual responses, have compared posterior parietal and prefrontal neuronal activities during delayed-response performance directly, and only one of these concerned spatial memory (Batuev et al. 1985). As neither study required central ocular fixation, however, these studies could not fully discriminate whether the selective neuronal activity in the two areas might be differentially related to intended eye movements or other dimensions of the task. Nonetheless, they indicate that parietal cortex is integral to the prefrontal mechanisms underlying spatial working memory function, although the question of how this integration is achieved at the neuronal level is still not fully understood.

The present experiments assess patterns of neuronal activity occurring in prefrontal area 8a and posterior parietal area 7ip during memory-guided saccades to provide a direct, quantitative contrast between these patterns as they occur in reciprocally interconnected areas of the same brains. With the exception of two studies mentioned above, prefrontal and parietal cortex have been analyzed previously in separate studies of oculomotor function with different methodologies, different animals, different delay periods (sometimes <1 s) (e.g., Andersen et al. 1990b; Barash et al. 1991a), and different classifications of neuronal activity or measurements of spatial tuning (Prefrontal: Funahashi et al. 1989; Parietal: Barash et al. 1991b). By eliminating these differences through the use of one standard applied to two neuronal populations in the same cerebral hemispheres, the direct comparison afforded by the present approach more reliably addresses the central question of how corticocortical projections impact the function and physiology of the cortical areas they interconnect. The anatomy of their reciprocal projections and their common functional specialization in both visuospatial processing and oculomotor control qualifies parietal area 7ip and prefrontal area 8a as a suitable test case for examining one major link in a larger distributed system subserving spatial cognition (Selemon and Goldman-Rakic 1988). The data obtained in this manner may reveal principles of operation not limited to the cortical oculomotor system but that bear also on the general issue of neurotransmission in complex neural networks.

METHODS

Preparation of animals for recording

Two adult male rhesus macaques, 6 and 10 kg, were prepared for chronic single-unit recording using standard aseptic surgical technique. Antibiotics (cephalosporins, 25 mg/kg, b.i.d) were administered for 10–14 days beginning the day before surgery. Anesthesia was initiated with ketamine (5–10 mg/kg im) and atropine sulfate (0.03–0.05 mg/kg im), and maintained with pentobarbital sodium (≤ 25 mg/kg iv maximum dose). An eye-coil (Teflon-coated stainless steel biomed wire AS632, Cooner Wire, Chatsworth, CA), was implanted underneath the conjunctiva of one eye (Judge et al. 1980), and a recording chamber (20 mm OD)

positioned over a craniotomy made above posterior parietal cortex. Dental acrylic fixed the recording chamber, eye-coil connector, and a head-restraint device to stainless steel bolts implanted underneath the skull. In both animals, prefrontal cylinders were added to the implants during a later surgery. Postsurgical analgesic (talwin 2–5 mg/kg im b.i.d. or buprenex 0.01–0.03 mg/kg im t.i.d.) was administered ≤ 1 wk postoperatively as needed. Training on the oculomotor delayed-response (ODR) task began 2–3 wk after surgery. Animals earned their daily liquid intake 5 days/wk performing the ODR task (Funahashi et al. 1989). On weekends, water was provided ad libitum. Weights were monitored carefully to ensure adequate hydration.

Apparatus

The ODR task was administered in a dark, sound-attenuated chamber. Monkeys sat with their head restrained in a primate chair positioned within the field coils of an eye coil system (C-N-C Engineering, Seattle, WA). Visual stimuli were generated by a computer graphics card (Pacific Binary Systems, GRAPH-11) in a DEC PDP 11/73 computer and presented on a video monitor (RCA, TC1119 or NEC, DM3000P) 57 cm in front of the animals eyes, centered at eye level. There was no background illumination in the testing chamber. The ± 5 -V analog outputs of the eye-coil phase sensitive detector (C-N-C Engineering, Seattle, WA), proportional to horizontal and vertical gazing angle, were digitized with 0.1° resolution (12 bit A-to-D converter, ADAC, Woburn, MA), and sampled at 500 Hz. MONK, a program running on the PDP-11/73, developed by M. E. Goldberg and C. J. Bruce (and generously supplied by C. J. Bruce), controlled stimulus presentation and concurrently collected both single-unit and eye movement data. When an ODR trial was performed correctly (see further), a liquid reward was delivered to the monkey via a metering pump (Liquid Metronics, A741, Acton, MA).

ODR task

Each ODR trial was initiated as monkeys acquired fixation of a visual target (0.1° white square) presented at the center of the video monitor (Fig. 1, A and C, 1). Monkeys maintained fixation of this central target throughout several sequential task epochs; an initial 500-ms fixation period (Fig. 1, A and C, 2), an additional 500-ms cue period during which a second visual stimulus (the cue, a 0.5° white square) was presented in the periphery (Fig. 1, A and C, 3), followed by a 3-s fixed-duration delay period after cue offset during which only the central fixation stimulus remained visible (Fig. 1, A and C, 4). If monkeys broke fixation to foveate the peripheral cue during the cue period or at any time during the delay period, the trial was judged incorrect and terminated. The cue was presented in an unpredictable location each trial, selected pseudorandomly (modulo 5) from a set of eight possible locations, 13° in eccentricity from the fixation target, separated from each other by 45° polar angle (Fig. 1B). During the trial, the monkey was required to maintain its angle of gaze within an invisible circular window 4 or 6° in radius, centered on the fixation target. At the end of the delay period, the fixation stimulus extinguished, and the monkey was required to execute a memory-guided saccade in the dark bringing the eyes to rest in the approximate location where the peripheral cue was presented earlier that trial (Fig. 1, A and C, 5). If a saccade was made within 500 ms of the offset of the fixation target that ended within a 4–6° window centered on the location where the peripheral cue appeared, the trial was judged correct, and a 0.2-ml liquid reward was delivered. Both monkeys maintained central fixation with greater accuracy than required by the eye position window. Memory-guided saccades of *monkey AR* began on average within 1.5° of the fixation target (the mean start points of these saccades varying by $< 0.7^\circ$ as a function of saccade target location), and those of *monkey JK* began on average within

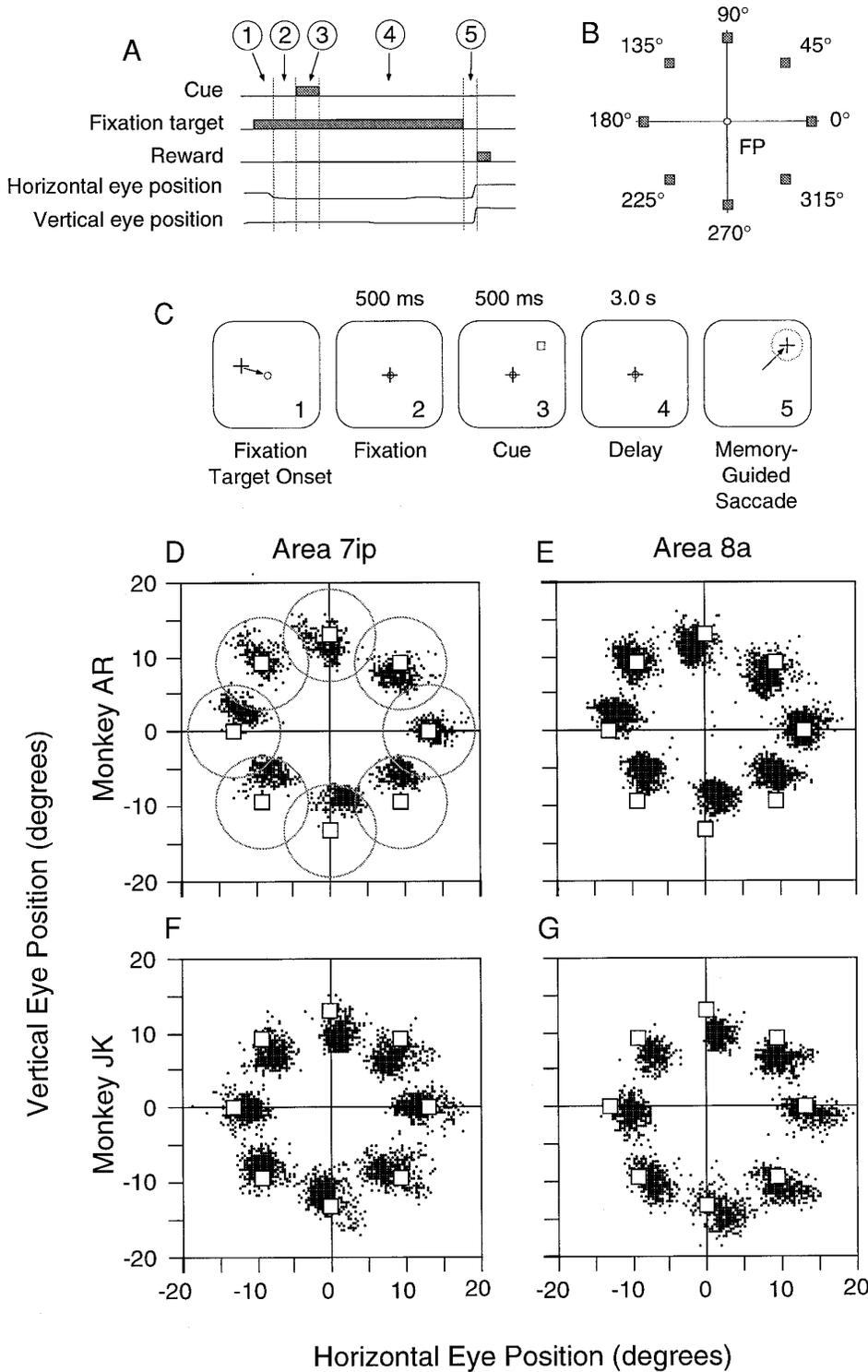


FIG. 1. Oculomotor delayed-response (ODR) task. **A:** relative timing of the fixation target, peripheral cue, and saccadic eye movement comprising an ODR trial. **B:** cue array. ODR cue was presented each trial in 1 location chosen pseudorandomly from the 8 locations indicated. **C:** diagrammatic representation of ODR trial events (monkey's gazing location indicated, +). Fixation of a central target was acquired (*panel 1*) and maintained (*panel 2*) while a cue stimulus appeared in the periphery (*panel 3*). Fixation of the central target continued after peripheral cue offset for an additional 3-s delay period (*panel 4*). On offset of the fixation target, monkeys completed the trial by making a saccade toward the location where the cue appeared in the periphery 3 s earlier. If the saccade ended within an invisible response window (dotted circle), the trial was judged correct (*panel 5*). **D–G:** endpoints of each saccade made while neural activity was recorded from parietal area 7ip (**D** and **F**) and prefrontal area 8a (**E** and **G**) in the present analysis. Saccades made by *monkeys AR* (**D** and **E**) and *JK* (**F** and **G**) are plotted separately. Relative size of the largest of the saccade windows (6°) used indicated by dotted circles in **D**.

0.8° of the fixation target (mean start points varying by <0.2° as a function of saccade target location).

Single-unit recording

Each day, unit recordings were conducted in the right cerebral hemisphere of both monkeys, either in prefrontal or posterior parietal cortex. In *monkey JK*, a prolonged period of parietal recording (>1 yr) was followed by several shorter alternating periods of prefrontal and parietal recording each of 1- to 2-mo duration (a

total of 3 parietal and 2 prefrontal recording periods were conducted in this monkey). In *monkey AR*, recordings were in prefrontal cortex initially then alternated with parietal recording for a total of two recording periods (of several months duration) in each cortical area. Single-unit activity was recorded using either glass-coated Elgiloy metal microelectrodes (0.6–1.5 MΩ at 1 kHz) or varnish-coated tungsten microelectrodes (FHC, part 120-110-1, Brunswick, ME), lowered into the brain by a hydraulic microdrive (Narhishige MO-95C). The microelectrode signal was amplified (BAK, MDA-4), filtered <0.5 and >10 kHz (Khrone-Hite, 3700,

Avon, MA), and displayed on digital storage (Nicolet 310) and analog (Tektronix 5110) oscilloscopes. Simultaneous isolation of up to two units was via waveform discrimination (Signal Processing Systems, 8701 waveform discriminator, Prospect, South Australia). The computer data acquisition system registered the occurrence of spikes with a resolution of 2 ms, recording the spiking activity of one or two units within the event buffer. If units did not perceptibly alter firing rate in relation to the ODR task, the isolations were abandoned without saving the data and the electrode advanced further to examine other units. As complete data were not obtained for all isolated units, our sample represents a bias toward those units with task-related activity.

Histological localization of recorded units

Iron deposits were placed in the brain at the end of these experiments and visualized by the Prussian blue (potassium ferrocyanide) reaction to facilitate the histological reconstruction of recording sites. Deposits were made by passing 15–20 μ A of DC current (tip positive) through Elgiloy electrodes for 2–3 min at sites marking the major (anterior-posterior, medial-lateral) axes of the recording grid. Animals were injected with a lethal dose of pentobarbital sodium and perfused through the heart, first with heparinized saline and then with buffered 4% paraformaldehyde. The brain, after being infused with ascending buffered sucrose solutions (5–20%), was sectioned on a freezing stage microtome at 20 or 40 μ m. Every third section was saved, counterstained for Nissl substance, and stained for the iron deposits. Sites, representing known microdrive coordinates, at which iron deposits were found, then were used to locate and orient the recording grid on reconstructions of the sulcal pattern of the cortical surface. The location of each unit in section was then estimated from the coordinates of the penetration, its angle (estimated from marked tracts), and the depth at which the unit was encountered.

Data analysis

MEASUREMENT OF FIRING RATES. Firing rates were measured in seven consecutive time windows spanning the ODR trial; one window in the intertrial interval (serving as a measure of the baseline firing rate of each neuron), and two windows within each of the cue, delay, and saccade periods. Early (50–150 ms after cue onset) and late (150–450 ms) windows within the cue period approximated the average timing of phasic and tonic neuronal activities observed during this period (Fig. 4). Similarly, early (0–1,500 ms after cue offset) and late (1,500–3,000 ms) delay-period windows more closely matched neuronal activation concentrated during the first of second half of the delay period (Fig. 9). Finally, early (125–325 ms after fixation offset) and late (325–675 ms) saccade period windows encompassed pre- and postsaccadic changes in activity (Fig. 4). The location of these windows within the cue and saccade periods was determined from an examination of the timing of 25 phasic and tonic visual responses and 25 presaccadic and postsaccadic responses, and it was found that this one set of standard windows well fit the timing and duration of the task-related changes in activity that were observed. Larger windows used in an initial analysis of variance (ANOVA), which encompassed all of the cue, delay, and saccade periods, proved less sensitive, failing to detect (at the $P = 0.001$ level) a number of brief but obvious task-related changes in activity.

ANALYSIS OF VARIANCE. Significant changes in firing rate during the various windows of the ODR task were detected in a repeated measures two-way ANOVA in which the two factors were cue/saccade direction (8 levels), and trial period (7 levels). Trial period was treated as a repeated measure. The significance level adopted for this analysis was $P \leq 0.001$. Huynh-Feldt corrected P values were employed. If the analysis for a given neuron yielded

a F statistic significant at this level either for the main effect of trial epoch, the trial epoch by cue direction interaction, or both, the neuron was classified as task-responsive (units for which only the factor of direction yielded significance, i.e., which did not exhibit any significant change in activity across trial epoch, were excluded from further analyses). Task-responsive neurons defined in this manner then were subjected to a set of single degree-of-freedom contrasts between the marginal means of trial period collapsed across cue/saccade direction. Thus firing rates during early and late cue, delay, and saccade periods (all cue/saccade directions taken together) were each contrasted to the baseline rate measured in the intertrial interval. If any of the mean firing rates during one of the task periods was significantly greater than the baseline firing rate ($P \leq 0.001$), the neuron was given either a C, D, or S (cue, delay, or saccade) designation, depending on the period(s) containing modulated activity. To receive C, D, or S designations, changes in activity in either the early or late window in each corresponding task period qualified. In cases where units exhibited a mixture of inhibitory and excitatory changes, classification was based on excitatory changes alone (this was a simplifying measure, as the number of combinations of excitatory and inhibitory changes across the 7 windows was large).

LATENCY DETECTION. Latencies of unit responses were determined by the technique of MacPherson and Aldridge (1979). Histograms of unit activity were smoothed by convolution with a Gaussian function (with a standard deviation of 10–20 ms) to produce continuous spike density functions (SDF), and the mean and standard deviation of the resulting SDF at 2-ms intervals were determined during a control period and used to establish a 99% (in cases of weaker activity, 95%) confidence interval. For changes in activity during the cue period, the control period was the 500-ms period of central fixation before cue onset. For saccade period responses, the control period was the middle 1 s within the 3-s delay period (this to permit detection of the timing of saccade-related activation superimposed on tonic delay-period activity, Fig. 8, A, B, E, and F). These control periods improved the detection of changes in activity during cue and saccade periods by establishing a baseline immediately preceding them (and therefore differed from the intertrial period employed as a baseline measure in the ANOVA). The time of onset of neuronal activation was based on the activity during preferred direction trials and was defined as the point midway between the intersection of the corresponding SDF with the upper limit of the confidence interval and the first peak in the function immediately thereafter (MacPherson and Aldridge 1979). The method provided latency measures that were in close agreement with the timing of neuronal activation in rasters and histograms. The activity of some neurons analyzed with this method provided indeterminate latencies. In these cases, the ANOVA detected a task-dependent change in activity in spite of the fact that the corresponding SDF did not reach the upper confidence interval in the latency analysis. These neurons were excluded from the analysis of latency.

SPATIAL TUNING OF UNIT RESPONSES. The spatial selectivity of each neuron was assessed using mean firing rates measured within a window manually adjusted off-line to span task related changes in activity. Windows initially were determined using trials in each neurons preferred direction and then subsequently applied to trials in which the cue was presented in the remaining seven locations, producing eight measurements of firing rate as a function of cue direction for each cue, delay, or saccade response detected by the ANOVA. Nonlinear regression then determined the parameters R , D , and Td of the Gaussian function (see further) that best fit these eight firing rate measurements (Bruce and Goldberg 1985).

$$f(d) = B + Re^{-1/2[(d-D)/Td]^2}$$

In this equation, B equals the background firing rate; R , the maximal increase in firing rate; d , the direction of the cue; D , the

preferred direction of the neuron; and Td , a width parameter given in degrees visual angle. The maximum of the function is given when $d = D$ (the cue is presented in the preferred direction), and the equation reduces to $f(d) = B + R$. At $1 Td$ unit on either side of a neuron's preferred direction, the value of the function has declined to $f(d) = B + R e^{-1/2}$, $\sim 60\%$ of its peak. To be considered spatially tuned, it was required that the fit for the given neuron be significant by an ANOVA ($P \leq 0.05$). A number of task-related neuronal activities in both prefrontal and posterior parietal cortex in our database failed to meet this criterion and were excluded from subsequent analysis of spatial tuning. These neurons generally evidenced crude spatial tuning, but the Gaussian fits were not significant.

ANALYSIS OF LINEAR TREND IN FIRING RATE DURING THE DELAY PERIOD. In some units, firing rates were found to either increase or decrease throughout the delay period. To quantify this trend, linear regression was applied to trial by trial firing rates measured within six consecutive 500-ms bins spanning the 3-s delay period, on those trials in which the cue was presented in each neuron's preferred direction.

RESULTS

ODR task performance

Memory-guided saccades are less accurate than saccades made to visible targets (White et al. 1994). In the present experiments, endpoints of memory-guided saccades made by *monkeys JK* and *AR* fell into eight distinct clusters close to each of the eight targets; however, these clusters were frequently offset from the actual target location (Fig. 1, *D–G*). The direction and distance of this offset was stereotypic for each monkey and varied with target location. *Monkey AR* was typically hypometric to lower targets (Fig. 1, *D* and *E*), whereas *monkey JK* was hypometric to upper targets (Fig. 1, *F* and *G*). Consequently, the windows centered on each target location where saccade endpoints were judged correct were necessarily large (the larger 6° windows that were used are shown, Fig. 1*D*). Each animal maintained a consistent pattern of saccadic performance across parietal and prefrontal neuronal recordings (compare Fig. 1, *D* and *E*, with *F* and *G*). For *monkey AR*, the average error between saccade endpoints and targets was 2.8° and 2.9° for parietal (area 7ip) and prefrontal (area 8a) datasets, respectively (errors ranged from 1.4 to 4.9° per target location but at each location varied by $<0.5^\circ$ between parietal and prefrontal recordings). The average amplitude of these saccades was 11.6° . For *monkey JK*, average saccadic errors were 2.3° and 3.2° during parietal and prefrontal recordings (errors ranged from 1.6° to 3.8° , but at each target location varied by $<1.5^\circ$ between parietal and prefrontal recordings). The average amplitude of saccades made by *monkey JK* was 11.4° . Average levels of correct performance for both monkeys were typically 80–90% of the trials in which they maintained central fixation.

Neuronal database

The extracellularly recorded action potentials of 343 neurons in the posterior parietal cortex and 340 neurons in the prefrontal cortex were recorded as monkeys performed a complete set of ODR trials (8–12 trials in each of the 8 cue locations). This sample is biased toward units that were task related, as isolations of neurons that did not appear to exhibit

any task-related change in activity were in many cases abandoned without saving the data. Of the 683 neurons for which complete data were obtained, 457 units ($2/3$) were confirmed to significantly alter their firing rate during one or more periods of the ODR task as assessed by a two-way repeated measures ANOVA (METHODS). Of these 457 neurons, 222 were located in posterior parietal cortex and 235 were located in prefrontal cortex.

LOCATION OF UNITS. One hundred twenty-nine units were located within the lateral bank of the intraparietal sulcus (area 7ip of Cavada and Goldman-Rakic 1989a or LIP of Blatt et al. 1990) (Fig. 2, *A–D* and *I–L*). Seventy-six units were located in area 7a, on the gyrus of the inferior parietal lobule, and also in the cortex superficial to the 7ip/7a border in the lateral bank of the intraparietal sulcus (Fig. 2, *B–D* and *I–L*). Units in area 7ip and 7a made up the bulk of the parietal sample. An additional 17 task-responsive units (Fig. 2, *A* and *B*) were recorded from *monkey JK* in area DP of Andersen and colleagues (1990a) adjacent to the intraparietal sulcus but at levels posterior to the superior temporal sulcus. As the majority of task-related parietal unit responses were recorded from neurons in the lateral bank of the intraparietal sulcus, our recordings in prefrontal cortex were focused on area 8a, the prefrontal area most strongly connected with area 7ip (Andersen et al. 1985; Cavada and Goldman-Rakic 1989b). Thus 195 of the ODR task-responsive units in prefrontal cortex were located in the anterior bank of the arcuate sulcus, at the level of the genu of this sulcus, as well as the gyral cortex immediately anterior to this sulcus (area 8a, Fig. 2, *E* and *F* and *M–P*), where the frontal eye fields (FEF) have been mapped by intracortical microstimulation (Bruce et al. 1985). In addition, 40 task-responsive units were recorded in *monkey JK* within the banks of the principal sulcus, in Walker's area 46 (Fig. 2, *G* and *H*). The analyses that follow focus on the two task-responsive neuronal populations located within area 7ip (129 units) and area 8a (195 units).

INCIDENCE OF TASK-RELATED ACTIVITIES. Neurons were classified according to the ODR task periods (cue, delay, saccade; designated C, D, S) during which their activity significantly increased (or decreased) relative to the baseline level. Approximately one-half of the task related neuronal population in area 7ip and in area 8a exhibited significantly modulated (increased or decreased) activity during only a single ODR task period (C, D, or S neurons, Fig. 3A). The remaining half of the sample of task-related neurons in each area exhibited altered activity during combinations of two task periods (CD, CS, DS neurons) or during all three task periods (CDS neurons, Fig. 3A). In the majority of these cases (85% in parietal cortex, 75% in prefrontal cortex), neurons exhibited excitatory changes during at least one ODR task period (and may have also exhibited inhibitory changes during other task periods). In the remaining minority of units, changes in activity were entirely inhibitory (Fig. 3A, *right*). Comparing the incidence of these various combinations of activation across the populations of task-responsive neurons in either cortical area, the only comparison to achieve significance was that of neurons exhibiting increased activity only during the delay period (D neurons), which were significantly more common ($\chi^2 = 7.73$, $df = 1$, $P = 0.005$) among task-related neurons in prefrontal area 8a

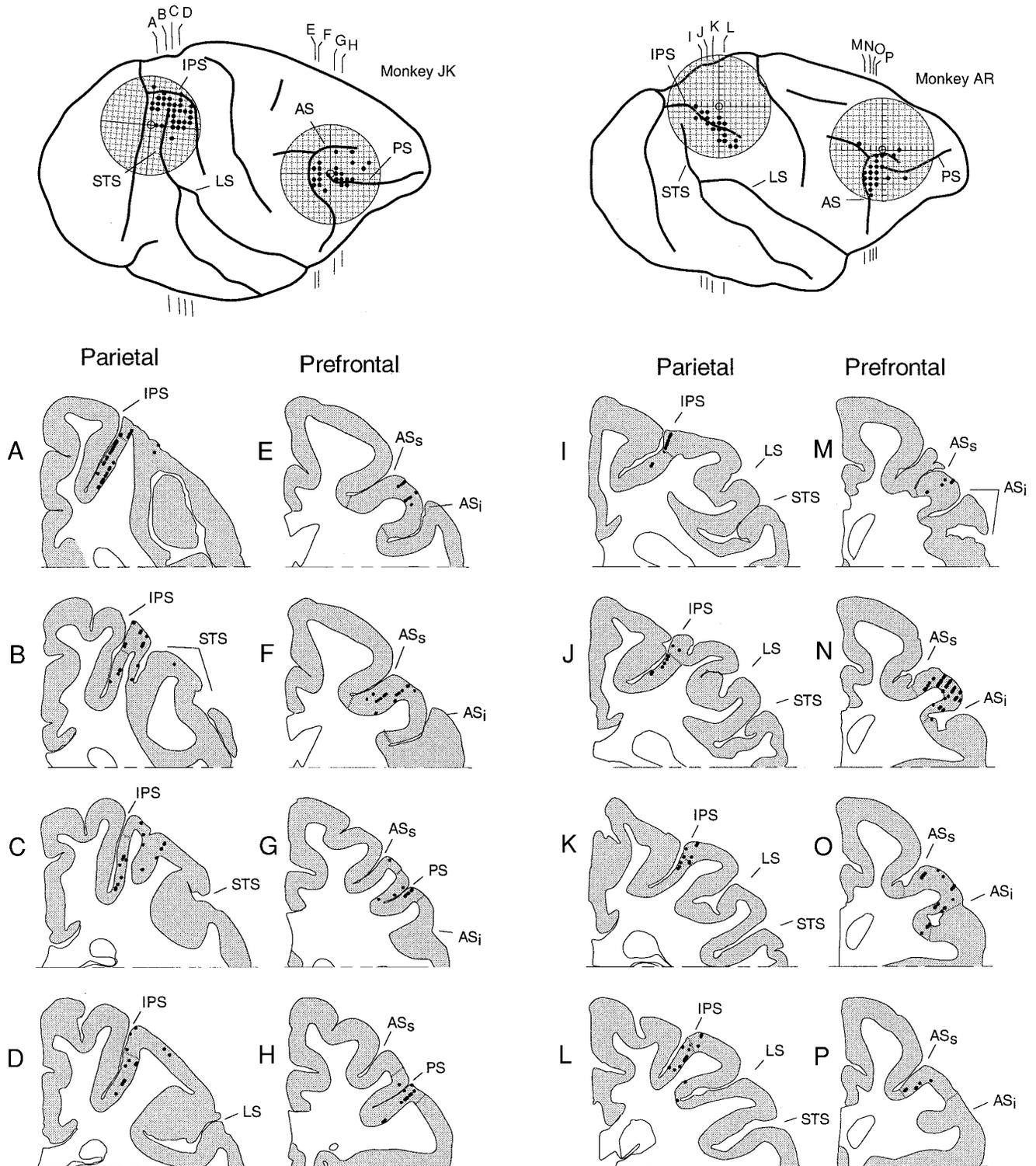


FIG. 2. Location of recording grids and coordinates of penetrations in which neurons with task-related activity were recorded, superimposed on the cortical surface of *monkeys JK* (top left) and *AR* (top right). A–P: locations of task-related neurons (dots) in depth, represented in histological sections taken through the regions of posterior parietal (A–D and I–L) and prefrontal cortex (E–H and M–P) sampled by single-unit recording. A representative subset of unit recording sites in each animal is shown. Parietal recordings are concentrated in area 7ip in the lateral bank of the intraparietal sulcus (IPS, A–D and I–L) but also extend in area 7a within the cortex of the laterally adjacent inferior parietal lobule. Prefrontal recordings are concentrated in area 8a within the anterior bank of the arcuate sulcus (AS, Figs. E, F, and M–P), but also extend anteriorly into area 46 in the banks of the principal sulcus (PS, G and H). Level of each section is indicated by the corresponding letter in the *top diagram* of the cerebral hemisphere. Cytoarchitectonic boundary separating areas 7ip and 7a in the intraparietal sulcus, and the limits of areas 8a and 46 are indicated by shaded lines in the section drawings. IPS, intraparietal sulcus; STS, superior temporal sulcus; LS, lateral sulcus; AS, arcuate sulcus (AS_s, superior limb; AS_i, inferior limb); PS, principal sulcus.

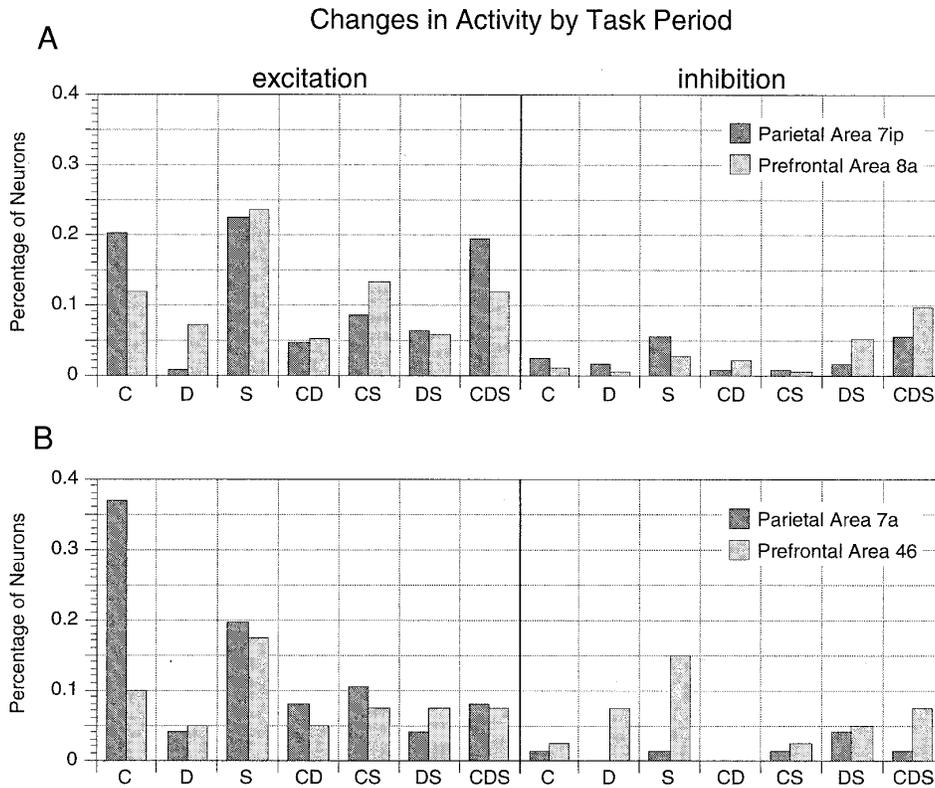


FIG. 3. Frequency distribution of neurons with various patterns of activation during the ODR task. Height of each bar indicates the proportion of the total number of task-related neurons in each area represented by the members of each neuronal class, exhibiting modulated activity during cue, delay, or saccade periods (C, D, or S class units) or during combinations of these task periods (CD, DS, CS, and CDS classes). *A*: distribution of excitatory (*left*) and inhibitory (*right*) task-related changes in activity in area 7ip (dark bars) and 8a (light bars). *B*: distribution of excitatory (*left*) and inhibitory (*right*) task-related changes in activity in parietal area 7a (dark bars) and prefrontal area 46 (light bars).

(7%) than in parietal area 7ip (1%). Neurons exhibiting increased activity only during the cue period (C neurons) were more frequent among task related neurons in parietal area 7ip (20%) than in prefrontal area 8a (12%), although this trend just missed significance ($\chi^2 = 3.68$, $df = 1$, $P = 0.055$). Thus neurons activated during all possible permutations of task period were distributed to both cortical populations but in somewhat different proportion.

Cue period activity

PHASIC AND TONIC ACTIVITY. In both prefrontal area 8a and posterior parietal area 7ip, activation during the cue period was one of three qualitatively different types. Phasic activity consisted of a short burst of action potentials tightly aligned to stimulus onset, that in most cases lasted on the order of 100–150 ms (Fig. 4, *A* and *B*) but that in extreme cases could consist of a single spike neatly aligned from trial to trial. Tonic activity, in contrast, consisted of a more sustained increase in firing rate that continued for most of the 500-ms period during which the cue was visible, and frequently lasted for several hundred milliseconds beyond it (Fig. 4, *C* and *D*). In addition to occurring separately in different populations of parietal and prefrontal neurons, phasic and tonic activity could both be distinctly present in the activity of single neurons in both parietal area 7ip (Fig. 4*E*) and prefrontal area 8a (Fig. 4*F*). This form of cue period activity was particularly strong in prefrontal cortex (Fig. 4*F*).

The distinction between phasic and tonic visual responses observed in our study has been recognized previously in the frontal eye fields by Bruce and Goldberg (1985), in the periprincipal and periarculate cortex by Suzuki and Azuma

(1983) and Mikami and colleagues (1982), and in parietal area 7a by Motter and Mountcastle (1981).

ONSET LATENCY. Distributions of onset latencies of the cue period activity of 57 area 7ip units (Fig. 5*A*, *upright histogram*) and 71 area 8a units (Fig. 5*A*, *inverted histogram*) had similar ranges (from 60 to 340 ms). However, the mode of the parietal distribution was shifted to the left (earlier) with respect to the prefrontal distribution (\Rightarrow), and the mean cue response latency in area 7ip (130 ms), preceded that in area 8a (141 ms). This trend, however, was not significant. Considering latencies <150 ms, the mean onset latency of cue period activity in parietal area 7ip (96 ms) was significantly earlier than that in prefrontal area 8a (107 ms; Student's $t = -2.507$, $df = 71.1$, $P = 0.014$). Recruitment curves (Fig. 5*B*), plotting the percentage of the population of 7ip and 8a neurons with cue period activity active as a function of time after stimulus onset, reflect the early lead of this activity in parietal cortex. The onset latency of cue period activity did not vary significantly between C, CD, CS, or CDS neuronal classes, either in prefrontal area 8a [$F_{(3,67)} = 2.015$, $P = 0.120$] or parietal area 7ip [$F_{(3,53)} = 1.286$, $P = 0.289$].

SPATIAL TUNING OF CUE PERIOD ACTIVITY. The area 7ip (left) and 8a (right) neurons illustrated in Fig. 6 exhibit a feature common to cue period activity in parietal and prefrontal cortex in general—the magnitude of the increase in activity is a function of the location of the cue. For the parietal neuron, increased activity was observed when the cue appeared in each of three contralateral locations (at 135, 180, and 225°, Fig. 6*E*); for the prefrontal neuron, increased activity accompanied presentation of the cue in two locations (90 and 135°, Fig. 6*F*). In both instances, this spatially selective increment in activity during

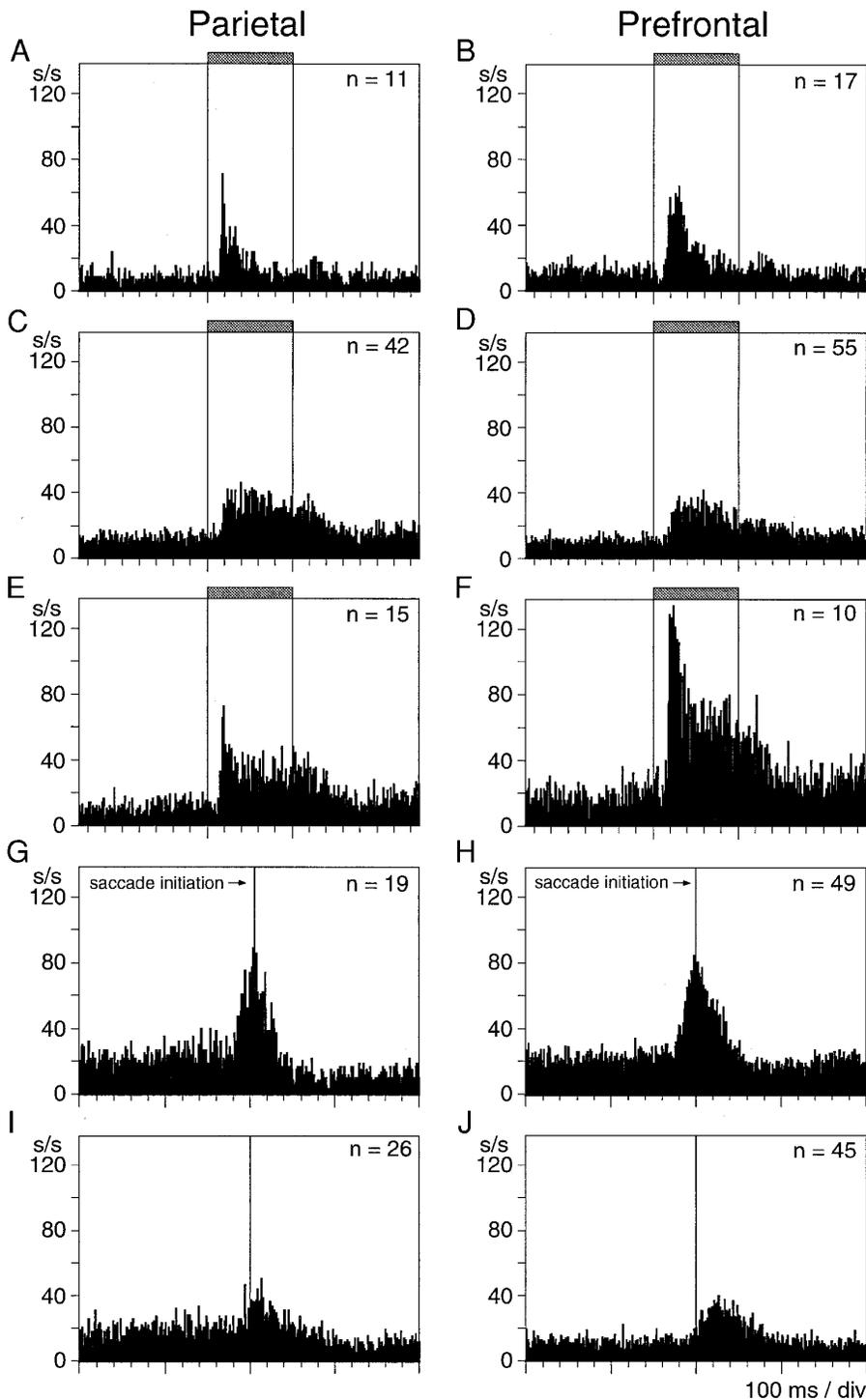


FIG. 4. Population responses of various classes of neuron active during the cue (A–F) and saccade (G–J) periods of the ODR task. Histograms are formed from the pool of preferred direction trials recorded from each neuron in the group (numbers of neurons contributing to each histogram in the *top right*). A and B: phasic cue period activity (the 500-ms span of the cue period indicated by the 2 vertical lines within each histogram). C and D: tonic cue period activity. E and F: combined phasic/tonic cue period activity. G and H: presaccadic activity (saccade initiation indicated by vertical line). I and J: postsaccadic activity.

the cue period was the most conspicuous feature of each neuron's activation during the various epochs of the ODR task (Fig. 6, C and D), and in both cases, the spatial tuning of this activation was closely approximated by the accompanying Gaussian functions (Fig. 6, E and F). Significant Gaussian fits were obtained in 37 (of 68) area 7ip units, 48 (of 82) area 8a units, and 15 (of 48) area 7a units responding to the visual cue.

The distributions of Td values associated with cue responses were very similar between parietal and prefrontal cortex—most Td values in each cortical area were found

between 10 and 40° (Fig. 7A). The mean Td value of 38 cue-responsive units in parietal area 7ip was 27.4°, and of 48 cue-responsive prefrontal area 8a units, the mean Td value was 31.8°. These population means did not significantly differ (Student's $t = 0.267$, $df = 84$, $P = 0.267$).

Delay-period activity

SIMILARITY IN PATTERNS OF DELAY-PERIOD ACTIVATION. As reported previously (e.g., Boussaoud and Wise 1993b; Funahashi et al. 1989, 1990), the tonic activation of prefrontal

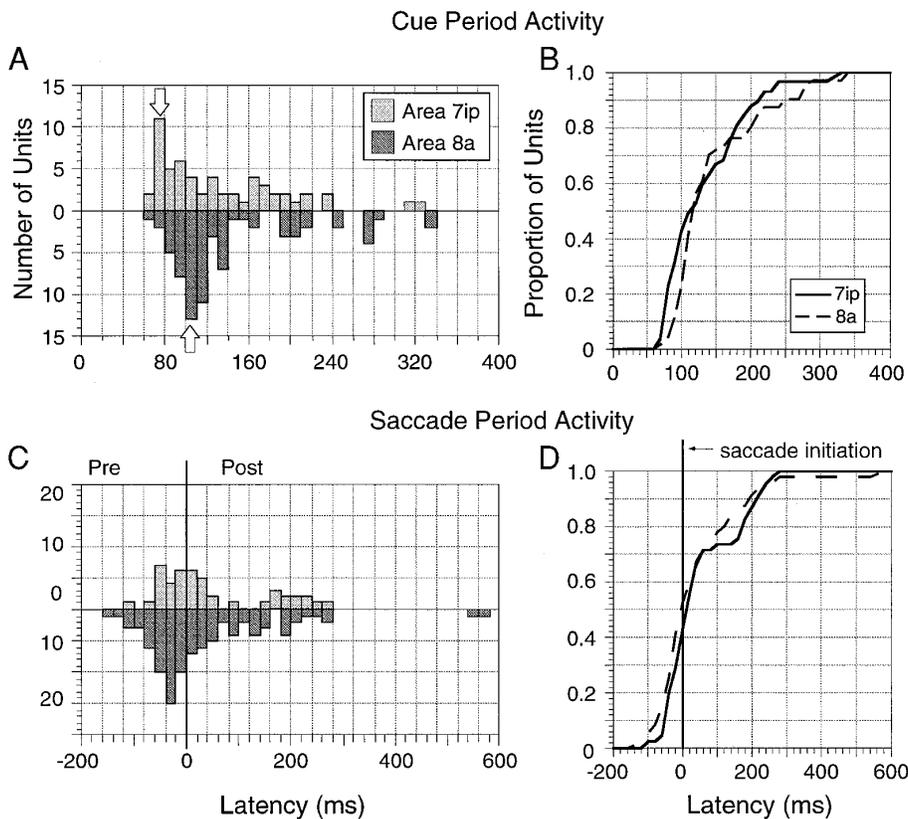


FIG. 5. Timing of the onset of neuronal activity during cue and saccade periods, relative to cue onset and saccade initiation, respectively. *A*: distribution of onset latencies of cue period activity in parietal area 7ip (light bars) and prefrontal area 8a (dark bars). Mode of the area 7ip distribution is shifted to the left relative to the area 8a distribution. *B*: cue period activity recruitment curves. Each curve represents the percentage of the total number of neurons with cue period activity in areas 7ip and 8a active at successive time points after cue onset. *C*: distribution of onset latencies of saccade period activity in parietal area 7ip (light bars) and prefrontal area 8a (dark bars). Initiation of the saccade occurs at 0 ms. *D*: saccade period activity recruitment curves showing percentage of neurons with saccade period activity in each area active at successive time points spanning the initiation of the saccade.

neurons during the delay period can occur in combination with more robust activation during the periods of visual stimulation or movement. We found all combinations to be present in both prefrontal and parietal populations: neurons with tonic delay-period activity and more robust activation during both cue and saccade periods (Fig. 8, *A* and *B*), during the cue period (Fig. 8, *C* and *D*), the saccade period (Fig. 8, *E* and *F*), or neither (Fig. 8, *G* and *H*). Further, about half of the area 7ip delay units (22 of 40) and area 8a delay units (25 of 58) exhibited significant linear trends in firing rate during the delay period (Fig. 9, *A–D*). Of these neurons, most exhibited increasing delay-period activity (Fig. 9*E*), in both parietal area 7ip (16 of 22) and prefrontal area 8a (17 of 25).

Barash and colleagues (1991a) found that 50% of LIP neurons with excitatory responses were active during the delay period of a delayed saccade task. We obtained a similar percentage (40%). In parietal studies, relatively short delay periods occasionally have been used (400 ms for many neurons) (Barash et al. 1991a; Mazzoni et al. 1996a). The present data strengthen the evidence for the involvement of parietal cortex in mnemonic processing by showing that neuronal activity in parietal cortex can be consistently sustained across the 3-s delay period commonly used in prefrontal unit recording (Funahashi et al. 1989).

SPATIAL TUNING OF DELAY-PERIOD ACTIVITY. Directionally selective delay-period activity was observed in both cortical areas. The area 7ip unit shown in Fig. 10 showed increased activity beginning during the cue period and continuing throughout the delay period for more than three seconds after cue offset but only on trials in which the cue appeared in the 90° location. The Gaussian tuning function fit to this

activity was correspondingly narrow ($Td = 15.6^\circ$, Fig. 10*B*). Similar neuronal activity was observed in prefrontal area 8a (Figs. 11 and 12). Like their parietal counterparts, increased activity in prefrontal neurons was spatially selective, whether accompanied by activation during the cue period (Fig. 11, *A* and *B*, $Td = 15.9^\circ$) or exhibiting enhanced activity exclusively during the delay period, beginning several hundred milliseconds after cue offset and returning to baseline just before saccade initiation (Fig. 12, *A* and *B*, $Td = 19.6^\circ$). Both parietal and prefrontal delay neurons similarly emitted bursts of action potentials after saccades in the direction opposite that associated with the delay response (Figs. 10–12), as has been reported previously (Funahashi et al. 1989; Gnadt and Andersen 1988). This may be due to programming the next, centering saccade during the intertrial interval. Neurons such as the one illustrated in Fig. 12, in which increased activity occurred only during the delay period, were more common in prefrontal area 8a (7% of task-related neurons) than parietal area 7ip (1% of task-related neurons, Fig. 3*A*).

As was the case for cue period activity, approximately half of the neurons with delay-period activity in parietal area 7ip (23 of 40 units), and prefrontal area 8a (25 of 58) provided significant Gaussian fits. Those not fit by Gaussian functions in most cases still exhibited crude spatial tuning. Best directions of the Gaussian functions fit to delay-period activity were typically contralateral in both populations, and the widths of these functions were similar. The distributions of Td values obtained in areas 7ip and 8a overlap considerably (Fig. 7*B*), and the means of the area 7ip (26.3°) and 8a (26.8°) distributions did not significantly differ (Student's $t = -0.063$, $df = 46$, $P = 0.95$).

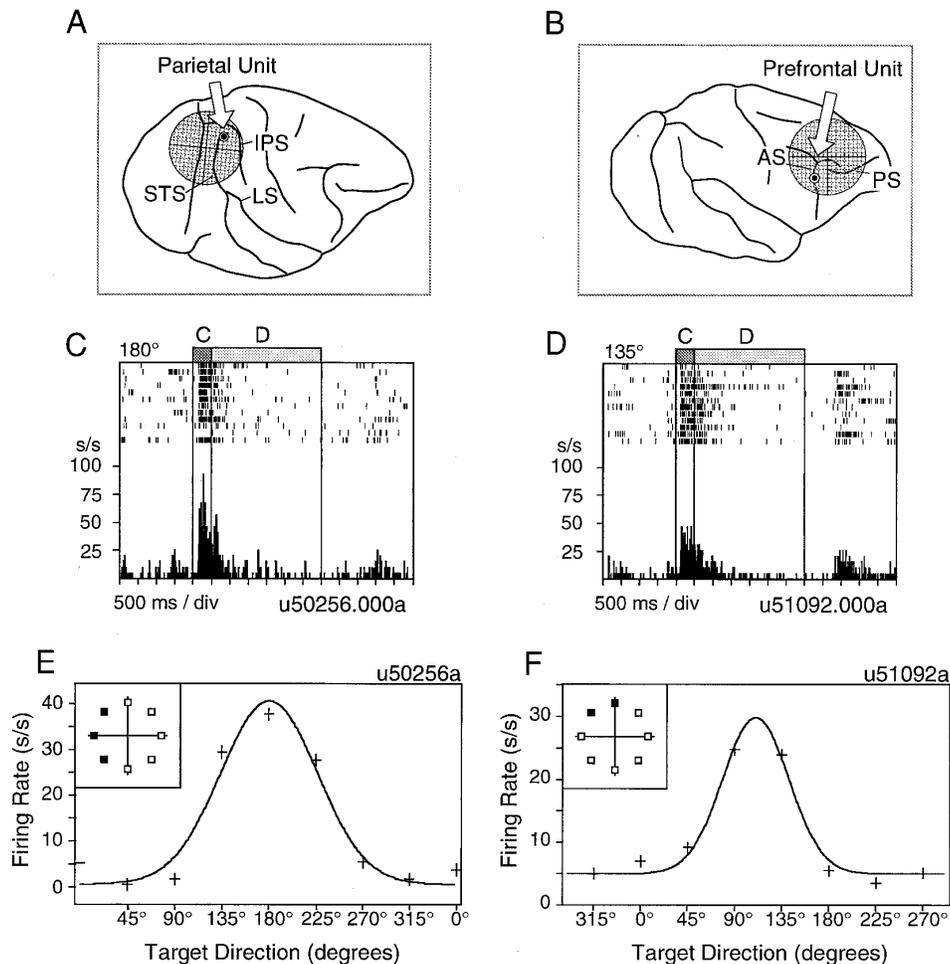


FIG. 6. Similarity of the cue period activity of single neurons in parietal and prefrontal cortex. *A* and *B*: locations of neurons. Dots (arrows) indicate coordinates of the penetrations encountering neurons in parietal area 7ip (*A*) and prefrontal area 8a (*B*). Parietal penetration entered area 7a but passed into the lateral bank of the intraparietal sulcus at depth. *C* and *D*: activity of each neuron on preferred direction trials, aligned to cue onset. Cue onset, offset and fixation target offset are indicated by the 3 vertical lines across each raster and histogram. Tick marks indicate timing of action potentials, histograms indicate average firing rate in 25 ms bins. *C*: activation of a parietal area 7ip neuron during the cue period. *D*: similar cue period activation of a prefrontal area 8a neuron. In both cases, activation outlasts the stimulus, and in the case of the area 8a neuron, a second burst of activity is evident after the saccade. *E* and *F*: Gaussian tuning functions fit to mean firing rates (crosses) measured during the cue period, on trials in which the cue appeared in each of the 8 locations (the location of each cue expressed in degrees polar angle in the counterclockwise direction from the 0° location, to the right of the fixation target). Cue locations for which elevated neuronal activity was observed are darkened in the diagram of the cue array (*inset*). *E*: tuning function fit to the cue period activity of the area 7ip neuron. Elevated cue period activity was observed as cues were presented in each of 3 adjacent, contralateral (135, 180, and 225°) locations. Width parameter of the Gaussian function, T_d , was 46.3°. *F*: narrower tuning function fit to the activity of the area 8a unit. Elevated cue period activity in this case was observed as cues were presented in either of two adjacent (90 and 135°) cue locations. The width parameter of this function, T_d , was 31.6°.

Saccade period activity

Of the neurons in area 7ip and area 8a that exhibited increased activity during the ODR task, approximately one-half exhibited excitatory saccade period activity. Saccade period activity also was observed in neurons within area 7a and area 46.

ONSET LATENCY. Saccade response latencies could be determined in 45 area 7ip units and 94 area 8a units. Of these units, the responses of approximately half in area 7ip (19 units, 42%) or in area 8a (49 units, 52%) were presaccadic. In the remaining 26 area 7ip units and 45 area 8a units, responses were postsaccadic. Distributions of the onset latencies of saccade period activity in area 8a and 7ip spanned

similar ranges (Fig. 5C). However, the mean latency of presaccadic activity in area 8a (−49 ms) preceded that in area 7ip (−37 ms), and the area 8a recruitment curve over the presaccadic range is shifted to the left relative to the area 7ip curve (Fig. 5D), though this difference was not significant (Student's $t = 1.422$, $df = 66$, $P = 0.160$). The mean latencies of postsaccadic activity in areas 8a (120 ms) and 7ip (108 ms) also did not differ significantly ($t = -0.417$, $df = 69$, $P = 0.678$). In both prefrontal area 8a and parietal area 7ip, presaccadic activity peaked close to the initiation of the saccade (Fig. 4, *G* and *H*), while postsaccadic activity peaked ~100 ms after saccade initiation (Fig. 4, *I* and *J*).

Neuronal activity preceding memory-guided saccades has

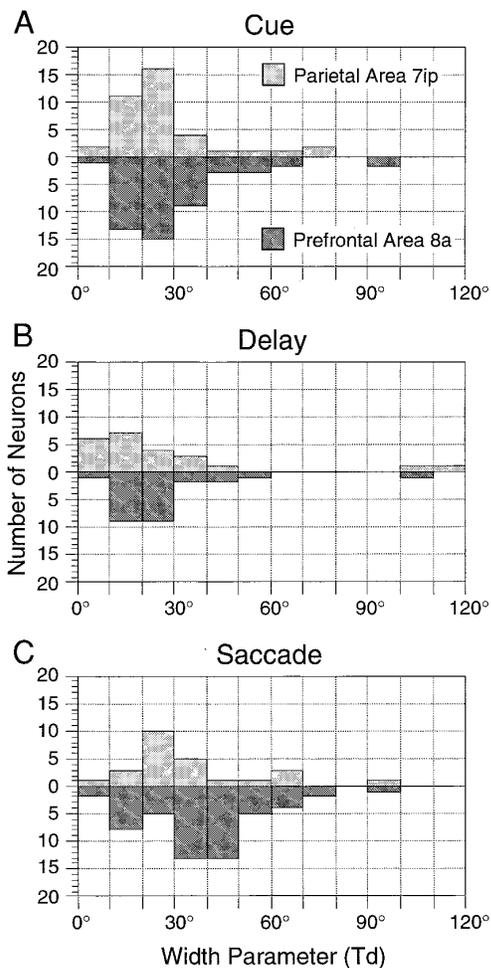


FIG. 7. Distributions of widths (Td parameters) of Gaussian spatial tuning functions representing significant fits to mean cue (A), delay (B), and saccade (C) period firing rates of neurons in parietal area 7ip (light bars) and prefrontal area 8a (dark bars). Td distributions for cue period activity are nearly identical in area 7ip and 8a. There is a trend (although not significant), for tuning of delay and saccade period activities to become progressively broader in area 8a relative to the 7ip distribution.

been described both in prefrontal area 46 (Funahashi et al. 1991), the frontal eye fields (Bruce and Goldberg 1985), as well as in area LIP (Andersen et al. 1990b; Barash et al. 1991a,b). Barash and colleagues (1991a) report presaccadic latencies in roughly 3/4 (72%) of the LIP neurons responding during the saccade, a larger proportion than presently encountered.

SACCADIC RESPONSE SPATIAL TUNING. Neurons in both cortical areas increased their activity briefly around the time at which saccades were made in preferred directions. The area 7ip (left) and 8a (right) neurons illustrated in Fig. 13 both exhibited an abrupt increase in activity immediately preceding the initiation of the memory-guided saccade. In the case of the parietal neuron, the burst preceded the initiation of saccades made toward 90 and 135° cue locations (Fig. 13, C and E). On these trials, a slight increase in firing rate during the preceding delay period was also evident (Fig. 13C). In the case of the area 8a neuron, the burst preceded the initiation of saccades made toward 135–225° cue locations (Fig. 13, D and F).

Significant Gaussian fits were obtained for the saccade

period activity of 25 of 45 area 7ip neurons and 52 of 94 area 8a neurons (Fig. 7C). The peak of the area 8a distribution is shifted to the right relative to the corresponding 7ip distribution, however, the means of these distributions in area 8a (39.8°) and area 7ip (35.2°) were not significantly different ($t = -0.974$, $df = 76$, $P = 0.333$).

Areas 7a and 46

AREA 7A COMPARED WITH 7IP. The third largest population of neurons studied was located in area 7a. A significantly larger proportion of these neurons exhibited elevated activity that was confined to the cue period in area 7a (37%) than in area 7ip (20%; $\chi^2 = 5.047$, $df = 1$, $P = 0.025$, see Fig. 3B), and considering all neurons with cue period activity in the two populations, the mean onset latency was later in area 7a (180 ms) than in 7ip (130 ms; $t = 3.591$, $df = 92$, $P = 0.001$) as well. No significant difference in the width of spatial tuning in area 7a (mean $Td = 36.8^\circ$) and in area 7ip (mean $Td = 27.4^\circ$; $t = 1.58$, $df = 48$, $P = 0.120$) was obtained. Thus differences in the timing and incidence of cue period activities of two areas in posterior parietal cortex, area 7a and 7ip, were more pronounced than differences between areas in parietal and prefrontal cortex (7ip and 8a).

In addition to cue period activation, neurons in area 7a were also active during the delay and saccade periods. Although modulated delay-period activity was more common among task-related neurons in area 7ip (37%) than in area 7a (26%), this difference was not significant ($\chi^2 = 2.55$, $df = 1$, $P = 0.110$). Modulated saccade period activity, in contrast, was significantly more common among task-related neurons in area 7ip (69%) than 7a (49%; $\chi^2 = 8.80$, $df = 1$, $P = 0.003$). Otherwise, the mean latency of saccade period activation in area 7a (50 ms) and 7ip (47 ms) did not differ significantly ($t = 0.109$, $df = 70$, $P = 0.913$). No significant differences between area 7a and 7ip were found in the spatial tuning of either delay-period activities (26° vs. 18°; $t = 1.229$, $df = 23$, $P = 0.231$) or saccade period activities (46° vs. 35°; $t = 1.726$, $df = 34$, $P = 0.114$). The region of area 7a where the majority of these neurons were recorded was immediately adjacent to the border with area 7ip in the lateral bank of the intraparietal sulcus. Interestingly, this part of area 7a, like area LIP, receives a direct projection from prefrontal area 8a (Stanton et al. 1995).

AREA 46. The sample within prefrontal area 46 comprised only 40 task-related neurons. However, all combinations of task-related activation during cue, delay and saccade periods were found within it (Fig. 3B). The mean latency of cue period activation in area 46 (206 ms) was significantly later than that in area 8a (141 ms; $t = 2.48$, $df = 77$, $P = 0.015$), however, the mean latencies of saccade period activation, although earlier in area 8a (32 ms) than in area 46 (72 ms), were not significantly so ($t = 1.097$, $df = 104$, $P = 0.275$).

Similarity in patterning of task-related activities

Figure 14 summarizes the results of the comparison of single unit activities observed in areas 7ip and 8a during memory-guided saccade performance. The firing rates of corresponding subpopulations of neurons in parietal (left) and prefrontal (right) cortex increase and decrease in unison over time, producing a single set of diverse activity patterns

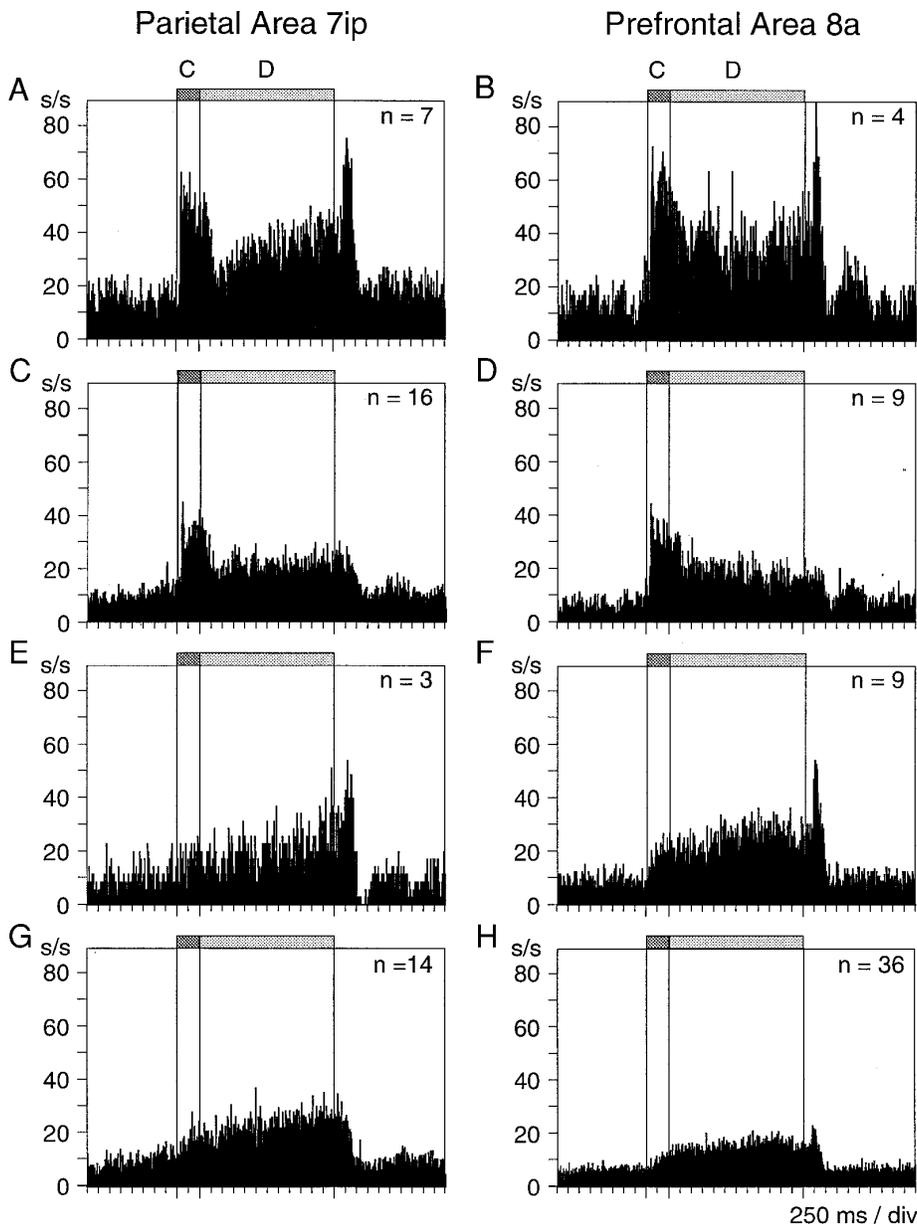


FIG. 8. Population responses of various classes of neuron active during the delay period in parietal area 7ip (left) and prefrontal area 8a (right). Conventions as in Fig. 4. Each neuronal class is distinguished by the additional presence or absence of larger bursts in activity during cue and saccade periods. Cue onset, offset, and fixation target offset are indicated by the 3 vertical lines across each histogram. A–H: neurons in which tonic delay-period activity was accompanied by 2 larger bursts in activity during the cue and saccade periods (A and B), a larger burst during the cue period (C and D), a larger burst during the saccade period (E and F), or in the absence of notable bursts in activity during either cue or saccade periods (G and H).

common to both cortical areas. This set of distributed activity patterns included tonic (Fig. 14, A and B), phasic (Fig. 14, C and D), and phasic/tonic (Fig. 14, E and F) cue period activities; delay-period activity with larger bursts in activity during cue and saccade periods (Fig. 14, G and H) or only during the cue period (Fig. 14, I and J) or only the saccade period (Fig. 14, K and L); tonic delay-period activity without these bursts, beginning during the cue period (Fig. 14, M and N) or after it (Fig. 14, O and P); and finally, both pre- (Fig. 14, Q and R) and postsaccadic (Fig. 14, S and T) saccade period activities.

DISCUSSION

Although a common objective of cortical research is the elucidation of anatomic, physiological, and ultimately functional differences between cortical areas, a central feature of the present results was the physiological similarity between

neurons in posterior parietal cortex (area 7ip) and in prefrontal cortex (area 8a) as monkeys performed a memory-guided saccade task. In both neuronal populations, neurons were found to exhibit all permutations of cue, delay, and saccade period activities (Fig. 3A), which had similar spatial tuning (Fig. 7, A–C), and although there was some suggestion that cue period activity lead in parietal cortex and saccade period activity lead in prefrontal cortex, to a large degree neurons became simultaneously active in the two regions (Fig. 5, A–D). The variety of neuronal activity patterns within each task epoch was remarkably constant across the two cortical areas (Fig. 14), so that neurons within them could not be unambiguously distinguished on the basis of their activity alone; prior knowledge of the location of recording was required. The detailed congruence of neuronal activity patterns found in parietal and prefrontal cortex during this task may be the direct result of the reciprocal projection linking these cortical areas. The present data in conjunction with

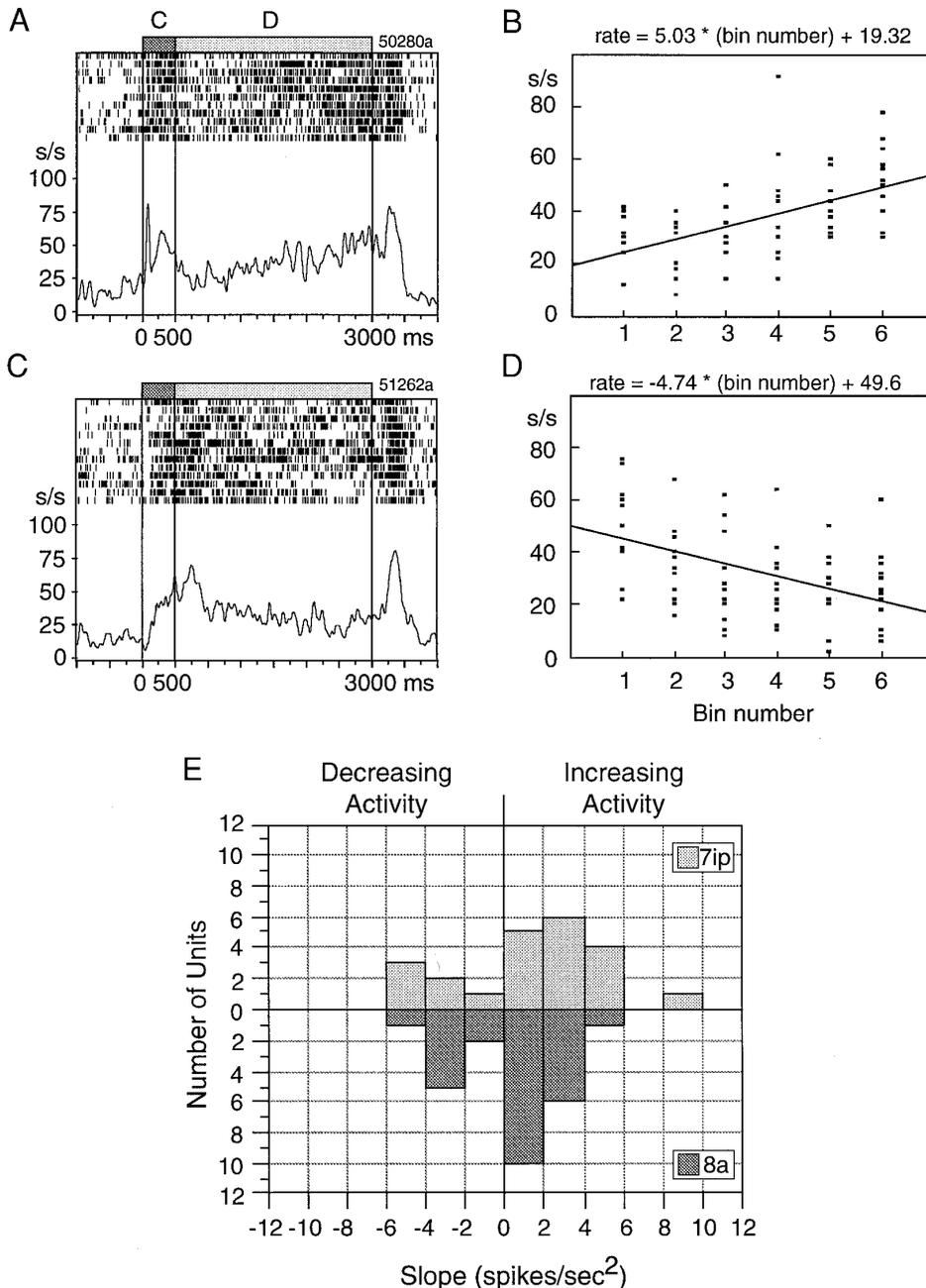


FIG. 9. Linear trends in delay-period firing rate. *A*: increasing delay-period activity in an area 7ip neuron. Spike density function accompanying raster represents a smoothed peristimulus time histogram formed by convolution of the histogram with a Gaussian function. *B*: trial-by-trial firing rates of the same neuron measured within successive 500-ms bins throughout the 3-s delay period (dots), and the regression line fit to these data (see earlier). *C*: decreasing delay-period activity of an area 8a neuron. *D*: regression line fit to the corresponding firing rates. *E*: distribution of the slopes of regression lines representing significant fits to the delay-period activity of neurons in areas 7ip (light bars) and 8a (dark bars).

the results of other studies discussed further support a view of cortical function in which neuronal activity patterns are shared and cooperatively generated by interacting cortical areas.

Other comparative recording studies

The comparative approach has documented parallel neuronal activity patterns in parietal, premotor and prefrontal cortex during a variety of manual reaching tasks. The results of Batuev and colleagues (1985) and Quintana and Fuster (1992) parallel our own in that the full complement of activity patterns occurring during working memory tasks were found distributed to both neuronal populations. That this distribution of activity occurred when working memory-guided arm movements, and not eye movements, suggests

that the present results are not peculiar to the cortical oculomotor system. Likewise, subsets of prefrontal and premotor neurons exhibit sustained activation during delayed reaching related to motor set, i.e., the direction of the planned movement (Boussaoud and Wise 1993a,b; di Pellegrino and Wise 1991), while other prefrontal and premotor neurons respond in concert to the location of a remembered visual stimulus (Boussaoud and Wise 1993a,b). A number of different parameters relating to arm movements, including the direction of a forthcoming movement are similarly encoded by neuronal activity in posterior parietal area 5, motor cortex, and premotor cortex (Ashe and Georgopoulos 1994; Ferraina and Bianchi 1994; Georgopoulos et al. 1984; Kalaska and Crammond 1995; Kalaska et al. 1983; Smyrnis et al. 1992). Experiments combining tract tracing and single-unit recording in this system (Caminiti et al. 1996; Johnson et al.

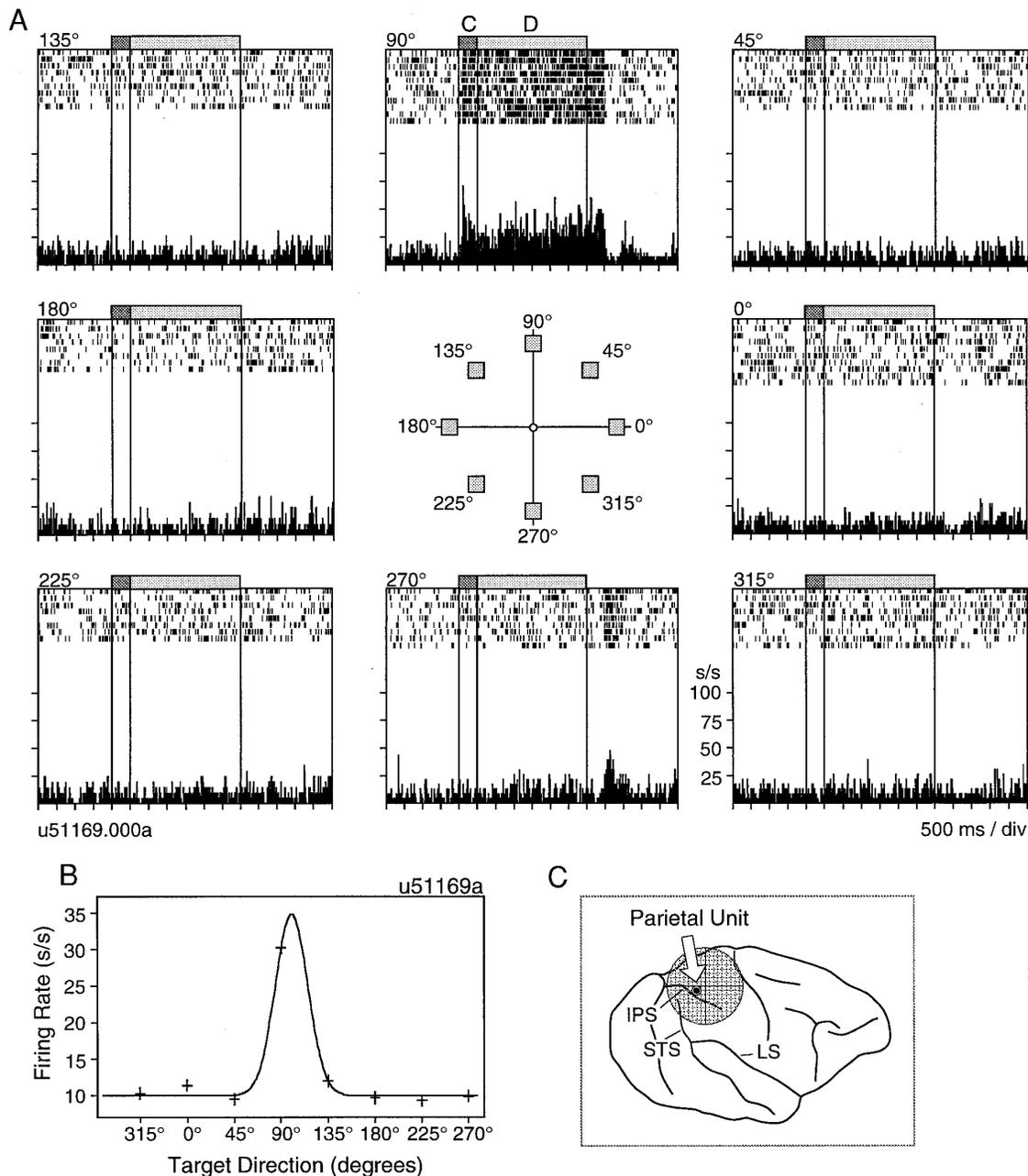


FIG. 10. Delay-period activity recorded from a neuron in parietal area 7ip. Each raster and histogram illustrates neuronal activity on the collection of trials in which the cue appeared in a single location, the 8 rasters/histograms corresponding to each of the 8 cue locations represented in the center panel. Other conventions as in Fig. 6. *A*: spatially selective delay-period activity. Elevated activity is evident through cue and delay periods on trials when the cue appeared in a single, preferred location (90°) until the memory-guided saccade to this location was completed. *B*: Gaussian tuning function fit to the mean delay-period firing rate (crosses) after presentation of the cue in each of the eight locations. Width parameter, T_d , of this function is 15.6° . *C*: location of the penetration (arrow) from which this neuron was recorded in the lateral bank of the intraparietal sulcus (entered at depth).

1993, 1996) have revealed that subregions of parietal, motor, and premotor cortex, which share direct reciprocal projections, contain individual neurons with similar reach-related activity. Alexander and Crutcher (Alexander and Crutcher 1990a,b; Crutcher and Alexander 1990) reported remarkably similar patterns of activity in the supplementary motor cortex, motor cortex, and caudate putamen during memory-guided arm movement tasks. Similarly, in the cortical oculomotor system, distributed activity patterns have been described within the frontal eye fields and the supplementary

eye fields, during both visually guided (Schall 1991a,b) and memory-guided (Chen and Wise 1995a,b) saccades. It appears, therefore, that in both the skeletal and oculomotor systems, neuronal activity patterns are distributed along "labeled" lines of cortical and subcortical projections.

Delay-period neuronal activity and working memory function

Working memories as cognitive operations and delay-period neuronal activity, such as presently observed, share sev-

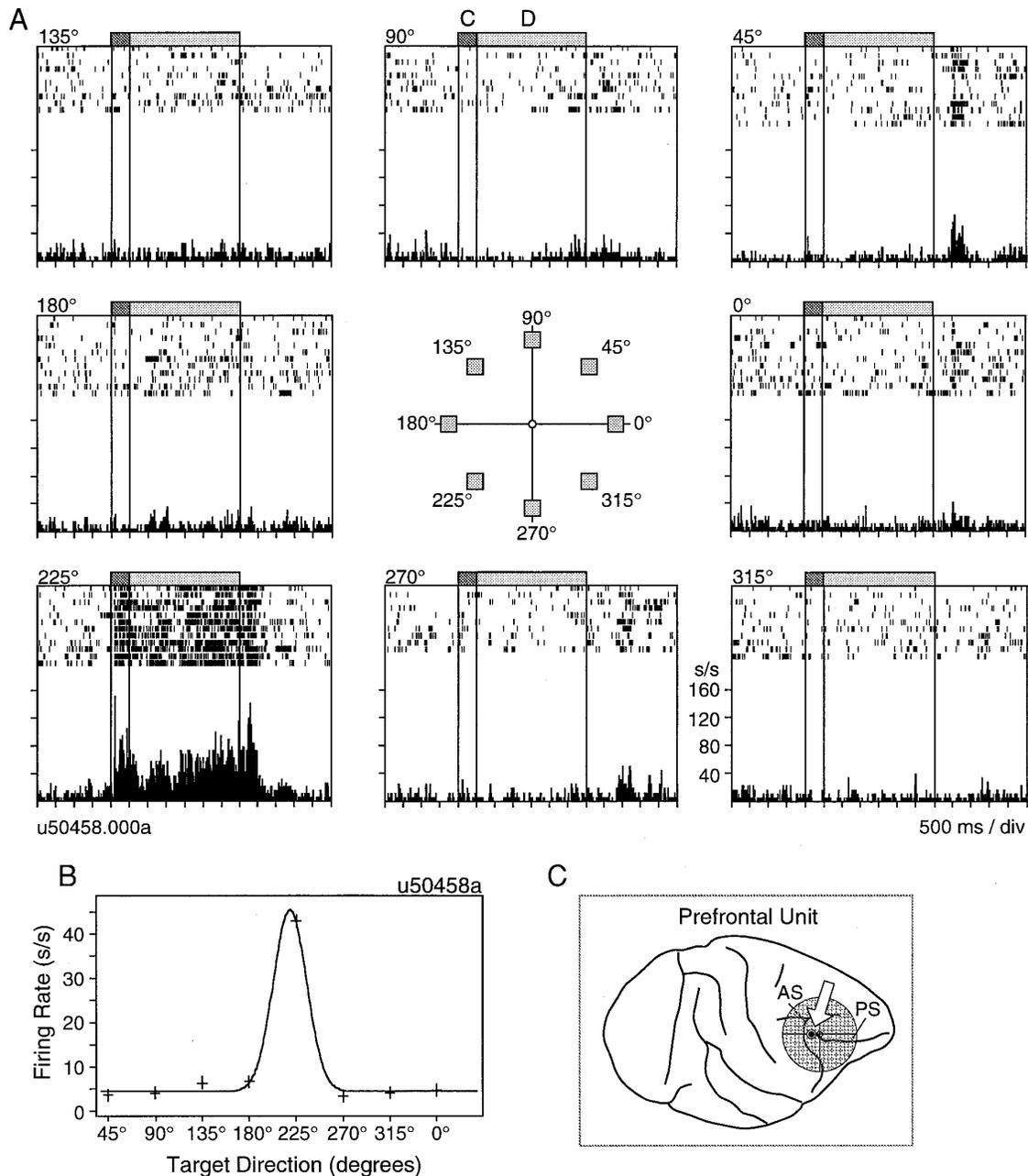


FIG. 11. Delay-period activity recorded from a neuron in prefrontal area 8a (conventions as in Fig. 10). *A*: like the previous example in parietal cortex, increased activity in this prefrontal neuron is evident through cue and delay periods after the cue appears in a single preferred location (225°). *B*: Gaussian tuning function fit to the mean delay-period firing rates (crosses) after presentation of the cue in each of the 8 locations. Width parameter, T_d , of this function is 15.9°. *C*: location of the penetration (arrow) from which this neuron was recorded within the anterior bank of the arcuate sulcus.

eral features—both encode specific attributes of past or future events, both exist independently in time from the external events they encode, and both are relinquished when the information is no longer useful. Although delay-period activity is to date one of the best candidates for a critical neural correlate of working memory (for additional physiological correlates, see Miller et al. 1993, 1996), delay-period activity is not limited to prefrontal neurons. Nevertheless, robust deficits in working memory performance as measured by classical delayed response tasks administered in a Wisconsin General Testing Apparatus are reliably produced by lesions limited to prefrontal cortex and remain an organizing princi-

ple in theories of prefrontal function (for reviews, see Fuster 1995; Goldman-Rakic 1987). In the oculomotor domain, dependence of memory-guided saccade performance on prefrontal cortex has been demonstrated both by cortical resections (Deng et al. 1986; Funahashi et al. 1993a) and pharmacological manipulation (Dias et al. 1995; Sawaguchi and Goldman-Rakic 1991). In contrast, although much less investigated, the effect of parietal lesions on delayed-response performance tested in the classical manner, i.e., in a Wisconsin General Testing Apparatus, have been largely negative (Butters and Pandya 1969; Jacobsen 1936; Pu et al. 1993). However, Li and colleagues (1995) recently have reported

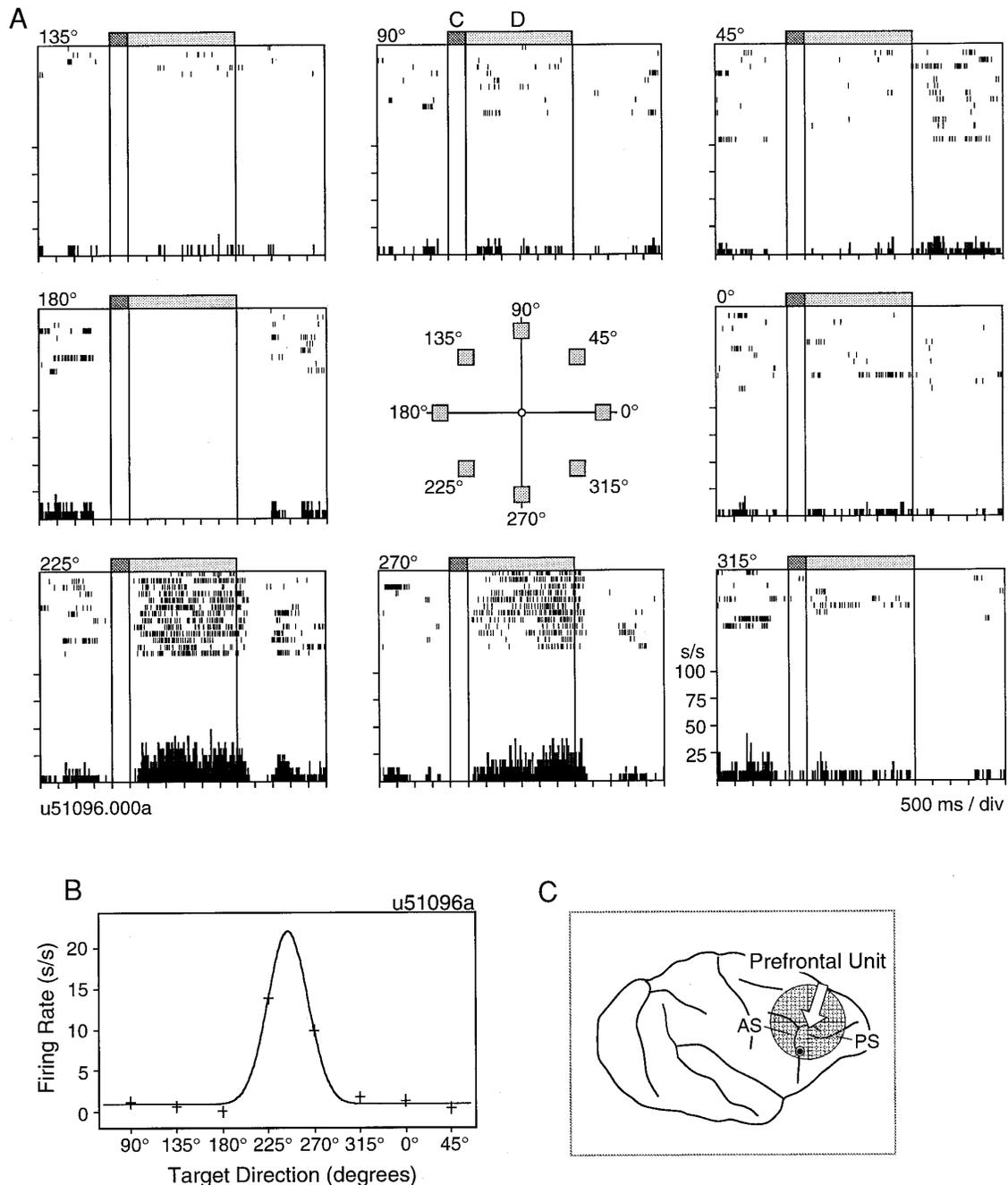


FIG. 12. Delay-period activity recorded from a neuron in prefrontal area 8a (conventions as in Fig. 10). *A*: delay-period activity of this neuron, unlike that of the neurons illustrated in Figs. 10 and 11, did not increase until after the cue had disappeared and was evident following the presentation of the cue in 2 locations (225 and 270°). *B*: Gaussian tuning function fit to the mean delay-period firing rate (crosses) after presentation of the cue in each of the 8 locations. Width parameter, Td , of this function is 19.6°. *C*: location of the penetration (arrow) from which this neuron was recorded within the anterior bank of the arcuate sulcus.

that injections of lidocaine in area LIP induce deficits in memory but not visually guided saccades. Reversible cooling experiments have shown mixed results. A delayed response deficit from transient inactivation of parietal cortex also has been reported (Quintana and Fuster 1993), but we have not observed this in our ODR task (Chafee and Goldman-Rakic 1994). Interestingly, visually guided saccade function appears to be more widely distributed in the brain than memory-guided saccade function in that insults to multiple corti-

cal and subcortical areas usually are required to seriously impair visually guided saccades (Keating and Gooley 1988; Lynch 1992; Schiller et al. 1979, 1980), whereas lesions limited to prefrontal cortex are sufficient by themselves to profoundly disrupt memory-guided saccades. If parietal cortex were as competent in memory-guided saccade function as prefrontal cortex, milder deficits would be predicted from lesions limited to prefrontal cortex, and that is clearly not the case. Therefore, a similarity of physiological properties

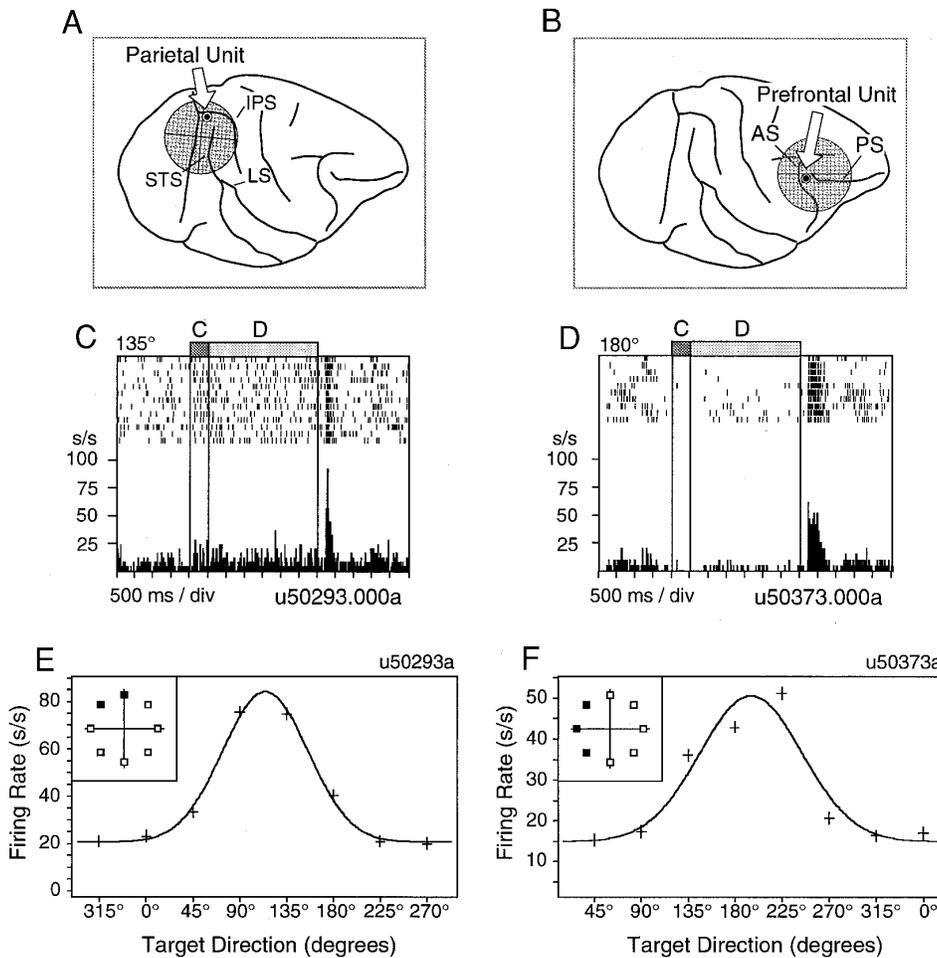


FIG. 13. Similarity of the saccade period activity of single neurons in parietal and prefrontal cortex (conventions as in Fig. 6). *A* and *B*: penetrations (arrows) encountering neurons in parietal area 7ip (*A*) and prefrontal area 8a (*B*). *C* and *D*: activity of each neuron on preferred direction trials (trials aligned to cue onset). Burst of activity in both cases preceded the initiation of the saccade (trials aligned to saccade initiation not shown) by 16 ms in the case of the parietal neuron, and 120 ms in the case of the prefrontal neuron. *E* and *F*: Gaussian tuning functions fit to mean firing rates (crosses) measured during the saccade period on trials in which the cue appeared in each of the 8 locations. Cue locations associated with elevated saccade period activity are darkened in the diagram of the cue array (*inset*). Widths (T_d parameters) of the Gaussian functions were 41.0 and 56.9° for parietal and prefrontal neurons, respectively.

between neurons located in different cortical areas may not indicate that the areas themselves have equivalent functions, reflecting instead a unity of coding and mutual connectivity.

More complex behavioral paradigms may reveal differences between the types of information encoded by sustained neuronal activity in parietal and prefrontal cortex, for example, the degree to which spatial information stored in working memory is encoded in sensory or motor coordinates during the delay period. Using an antisaccade paradigm, we have shown that both iconic memories and motor plans are represented in the activity of single prefrontal neurons during delay periods (Funahashi et al. 1993b) as did Niki and Watanabe using manual paradigms (1976). These studies demonstrated that distinct sensory and motor processes are both fundamental to the cognitive operations carried out by the prefrontal cortex. In contrast, in parietal area LIP sustained activation during oculomotor paradigms was reported to encode almost exclusively the direction of the forthcoming saccade (Barash et al. 1991b; Gnadt and Andersen 1988), although more recent evidence suggests that like prefrontal neurons, parietal neurons under some circumstances also encode the location of past visual stimuli (Constantinidis and Steinmetz 1996; Mazzoni et al. 1996a).

Network activation in functional and metabolic imaging

The commonality of task-related neuronal activity between parietal and prefrontal populations provides a neural

basis for the concurrent activation of these areas consistently found in functional imaging studies of animals (Friedman and Goldman-Rakic 1994) and humans (Baker et al. 1996; Jonides et al. 1993; Roland and Friberg 1985; Smith et al. 1996; Sweeney et al. 1996) engaged in working memory tasks as well as nonspatial working memory paradigms (Courtney et al. 1996; Demb et al. 1995; Smith et al. 1996; Swartz et al. 1995). A major conclusion from these studies is that each of these different forms of working memory is associated with increased activity in broadly distributed cortical networks with obligatory prefrontal and parietal components. Recent studies of human cognition are supportive of distinct functional roles for the prefrontal and parietal cortices. Of particular interest in this context is the study of Sweeney and colleagues (1996), which employed both a sensory and memory-guided saccade paradigm modeled on the ODR task employed in the present study. This study showed coactivation of dorsolateral prefrontal and posterior parietal cortex only during the memory-guided version of the task, supporting metabolic mapping studies in the monkey that demonstrated increased glucose utilization in both prefrontal and posterior parietal cortex during tasks involving spatial working memory (Friedman and Goldman-Rakic 1994). Recent reports suggesting differences in the relative weighting in mnemonic and sensorimotor factors in determining activation of prefrontal and posterior cortical regions during nonspatial working memory tasks are also in accord with the preeminent importance of prefrontal cortex

for working memory function (Cohen et al. 1997; Courtney et al. 1997). In both of these studies, activation in prefrontal regions was either more sensitive to working memory load

(Cohen et al. 1997) or more clearly restricted to the time within the task over which working memory had to operate (Courtney et al. 1997), whereas in posterior regions, activation generally followed a time course more closely aligned with periods of sensory input and/or motor output (Cohen et al. 1997; Courtney et al. 1997). The effect of load and temporal parameters may explain the apparent paradox of comparable cellular activity profiles observed in this study but incomparable lesion effects in the literature. In our data, neurons in posterior parietal and prefrontal cortex each participated in sensorimotor and mnemonic processing, and only small differences in the relative weighting of these processes was obtained. However, when summed across the much larger number of neurons producing changes in activation imaged in functional MRI, these neuronal differences may account for differences in functional activation at the areal level.

Relationship to hierarchical models

Cortical networks have been described as hierarchical in that a general direction of the flow of neural activity could be discerned through a sequence from lower to higher levels, where neurons exhibit successively more complex receptive field properties, for example. The feed-forward and feedback model of Felleman and Van Essen (1991) posits that efferents from lower areas that project to hierarchically higher cortical areas terminate most densely in layer IV and constitute feed-forward "input" pathways; whereas the feedback efferents from higher to lower areas in the cortical hierarchy avoid layer IV, terminating most densely in layers I and VI. A third type, the lateral projection, is identified by terminals spanning all layers equally. According to this model, the projection from LIP to the FEF has been characterized as a feed-forward projection, and the projection from the FEF to LIP as a feedback projection (Felleman and Van Essen 1991). One might expect this hierarchical relationship to be reflected in different patterns of neuronal activity during behavior. Although a significantly larger proportion of delay responsive neurons were observed in prefrontal (7%) than in parietal (1%) cortex and the peak of the area 7ip latency distribution was shifted toward earlier latencies compared with the area 8a distribution, overall, the similarities in activation between prefrontal and posterior parietal neurons were more impressive than the differences. The concurrent physiological data are more consistent with the FEF and area LIP occupying the same hierarchical level, with projections

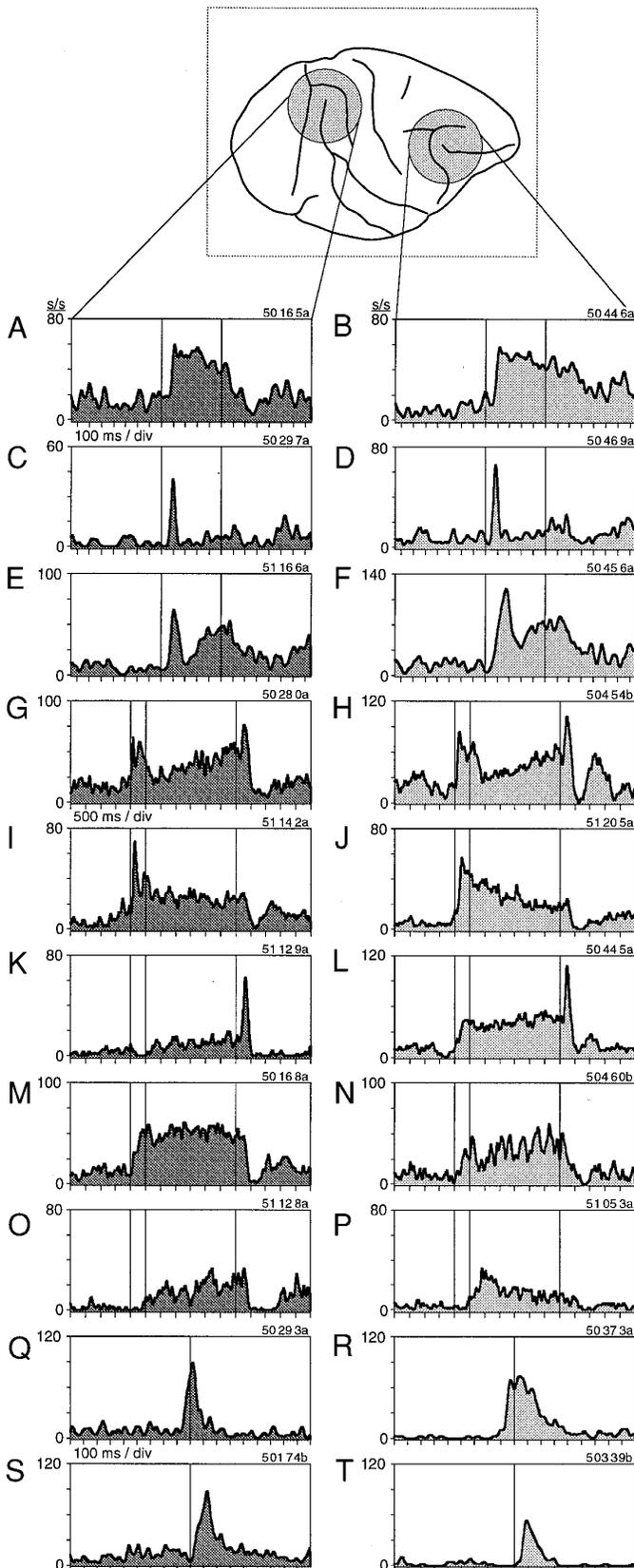


FIG. 14. Similarity between the full set of task-related activity patterns observed among single neurons in posterior parietal area 7ip (left) and prefrontal area 8a (right) during ODR performance. Spike density functions in each panel represent the activity of a single neuron, formed by convolution of a peristimulus time histogram of its activity with a Gaussian function. A–F: tonic (A and B), phasic (C and D), and phasic/tonic (E and F) cue period activity. Two vertical lines within each panel indicate cue onset and offset. G–P: delay-period activity in combination with greater bursts of activity during cue and saccade periods (G and H), during just the cue period (I and J), or the saccade period (K and L). Delay-period activity without conspicuous bursts in activity during cue and saccade periods, beginning during the cue period (M and N), or after cue offset (O and P). Three vertical lines in each panel indicate cue onset, cue offset, and fixation target offset, respectively. Q–T: saccade period activity beginning before saccade initiation (Q and R) or after saccade initiation (S and T). Vertical line indicates saccade initiation.

between them being the lateral type. In fact, it has been reported recently that projections from the FEF to area LIP do not target layers I and VI, as would be predicted for a feedback projection, and are instead distributed evenly to all cortical layers, indicative of a lateral projection (Stanton et al. 1995). Indeed, no evidence was found in the present study to indicate that neuronal activity evoked by a spot stimulus was further elaborated in its neurotransmission from parietal to prefrontal cortex. In both areas, receptive fields had the same size (as estimated by a standard stimulus array) and cue period activity exhibited similar temporal dynamics (exhibiting either phasic, tonic or combined activation). This stands in contrast to earlier stages in the visual hierarchy, where receptive fields become larger and selectivities for stimulus attributes more complex in moving from V1 through the various stages of dorsal and ventral extrastriate streams. It thus appears that this progressive elaboration of stimulus processing in the dorsal stream is completed at posterior parietal cortex, whereafter sensory evoked activity is passed forward to prefrontal cortex without further modification. Our data strongly support the principle that prefrontal neurons adopt the receptive field properties of neurons providing their direct input from posterior sensory association cortex. In keeping with this principle, face cells, one of a number of different feature-selective visual neuron found in inferotemporal cortex (for review, Gross 1992), now have been observed in the inferior prefrontal convexity (Ó Scailaidhe et al. 1997; Wilson et al. 1993), where inferotemporal cortex projections terminate (Barbas 1988; Bates et al. 1994; Ungerleider et al. 1989).

Neural codes and corticocortical projections

There has been an active debate as to whether cortical neurons represent information in a temporal code format, i.e., in the precise pattern of spikes, or in a rate code format, i.e., in changes in average firing rate over time. The present study may bear on the issue in the following manner. The overall similarity between prefrontal and posterior parietal neuronal activity patterns during the ODR task appears to represent a shared rate code as discussed by Shadlen and Newsome (1994). This does not exclude the possibility of a coexisting form of temporal coding embedded in the finer structure of spike trains, such as phase-synchronized oscillations in firing rate (Engel et al. 1991; Gray and Singer 1989; Gray et al. 1989) or repeating spike patterns (Abeles et al. 1993; Vaadia et al. 1995), as there is evidence to suggest these additional coding mechanisms exist in the temporal domain (for reviews of these and related issues, see Bressler 1995; Sakurai 1996; Shadlen and Newsome 1994; Singer 1994). At present, it can be stated that in one system, neurons within a pair of cortical areas sharing a particularly strong reciprocal projection (Andersen et al. 1985; Stanton et al. 1995) exhibit a rich and matching variety of activity patterns synchronized to the epochs of the ODR task. Thus it would appear likely that corticocortical interactions influence rate coding.

Although the present study in conjunction with many other reports establish the importance of long-tract connections in the generation of receptive field properties, whether these connections also participate in the mechanism for sustaining neuronal activation during delay periods is still unclear. In

the dorsolateral prefrontal cortex, for example, columns of pyramidal neurons in layers II/III and V issue regularly spaced recurrent axonal projections that extend horizontally over many millimeters in several directions (Kritzer and Goldman-Rakic 1995; Levitt et al. 1993; Lund et al. 1993). These radiating connections as well as intracolumnar projections (Kritzer and Goldman-Rakic 1995) provide a neural basis for positive feedback circuits in prefrontal cortex that may play a role in sustaining neural activity. Although comparable anatomic data are not available for parietal areas, a similar structural lattice could be predicted in these areas as well as they represent a canonical feature of local circuitry (Douglas et al. 1995; Lund et al. 1993). Such lattices are likely to provide a type of recurrent excitation similar to that which has been employed to generate sustained activation in an artificial neural network model trained to fulfill a working memory function (Zipser et al. 1993). In other models, sustained activation depends more heavily on events that are largely intrinsic to individual pyramidal neurons (Amit and Brunel 1997; Guignon et al. 1995; Lisman and Idiart 1995; Marder et al. 1996) as supported by evidence provided by a growing number of studies of single prefrontal neurons in slice preparations (Cepeda et al. 1992; Law-Tho et al. 1994; Yang and Seamans 1996). The variety of mechanisms these models employ are to varying degrees dependent on local circuits triggered by input from other cortical areas and the interplay of these two levels of processing may hold the key to the neural mechanisms subserving the correlated patterns of activity in neural networks subserving working memory.

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