Task-Specific Neural Activity in the Primate Prefrontal Cortex

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Asaad, Wael F., Gregor Rainer, and Earl K. Miller. Task-specific neural activity in the primate prefrontal cortex. *J Neurophysiol* 84: 451–459, 2000. Real-world behavior is typically more complicated than a one-to-one mapping between a stimulus and response; the same stimulus can lead to different behaviors depending on the situation, or the same behavior may be cued by different stimuli. In such cases, knowledge of the formal demands of the task at hand is required. We found that in monkeys trained to alternate between three tasks, the activity of many neurons in the prefrontal cortex was task dependent. This included changes in overall firing rate, in firing-rate profiles (shape of responses over time), and in stimulus and response selectivity. These findings support the hypothesis that a major prefrontal function is the acquisition and implementation of task context and the "rules" used to guide behavior.

INTRODUCTION

The flexibility of primate behavior depends on the ability to choose actions appropriate not only to the sensory information at hand but also according to the situation in which it is encountered. The prefrontal (PF) cortex is a neocortical region that has long been thought to be central to this ability. In fact, recent studies have indicated that the specific sensory, motor, and cognitive demands of the task the animal is performing (the behavioral context) can be an important factor in determining PF neural responses. For example, neural activity to an identical visual stimulus can vary as a function of which portion of that stimulus must be attended (Rainer et al. 1998b; Sakagami and Niki 1994) or with the particular motor response associated with it (Asaad et al. 1998). In fact, White and Wise have shown that, on a more abstract level, the "rule" by which an animal maps a given visual input to the correct motor output can have a significant impact on the observed neural responses (White and Wise 1999).

Indeed, damage to the PF cortex of humans and monkeys tends to produce impairments when available sensory information does not clearly dictate what response is required. For example, PF lesions impair spatial delayed response tasks in which a cue is briefly flashed at one of two or more possible locations and the monkey must direct an eye movement to its remembered location (Funahashi et al. 1993). However, no impairment is observed if there is no delay and monkeys can immediately orient to the cue. Thus the PF cortex seems critical when the correct action must be selected using recent memory and knowledge of task demands. Another example is the Wisconsin Card Sorting Task, a test of the ability of human subjects to flexibly alter their responses to the same stimuli. The sorting rule varies surreptitiously every few minutes and thus any given card can be associated with several possible actions; the correct response is dictated by whichever rule is currently in effect. Impairment on this task is a classic sign of PF damage in humans (Milner 1963), and monkeys with PF lesions are impaired on analogous tasks (Dias et al. 1997). Knowledge of the formal requirements of the task is critical in such cases. Indeed, several investigators have argued that the representation of rules and other task information is a cardinal PF function and that many of the deficits following PF damage are explicable within this framework (Cohen and Servan-Schreiber 1992; Grafman 1994; Miller 1999; Passingham 1993; Wise et al. 1996).

To further explore this issue, we recorded neural activity from the prefrontal cortices of two monkeys while they each alternated between three tasks, an "object task," an "associative task," and a "spatial task." The first two tasks shared common cue stimuli but differed in how these cues were used to guide behavior, whereas the latter two used different cues to instruct the same behavior (Fig. 1). All three required the same motor responses. The associative task required the animals to associate a foveally presented cue stimulus with a saccade either to the right or left (Asaad et al. 1998). The cue-response pairings were reversed within each session in order not to confound the influence of cue stimulus and response direction on neural activity. The object task used the same cue stimuli as the associative task; however, in this case, they needed only to remember the identity of the cue and then saccade to the test object that matched it. Conversely, the spatial task used small spots of light to explicitly cue a saccade to the right or left and required the monkeys to remember simply the response direction.

METHODS

Subjects

The subjects were two rhesus monkeys, *Macaca mulatta,* weighing 10 and 6 kg. Using previously described methods (Miller et al. 1993), they were implanted with head bolts to immobilize their heads and with recording chambers. One animal was implanted with an eye-coil to monitor eye movements (Robinson 1963), while an infrared monitoring system (ISCAN, Burlington, MA) was used for the second animal. The infrared system was slightly less accurate than the eye-coil (the standard deviation for the noise of the eye-coil was 0.06°
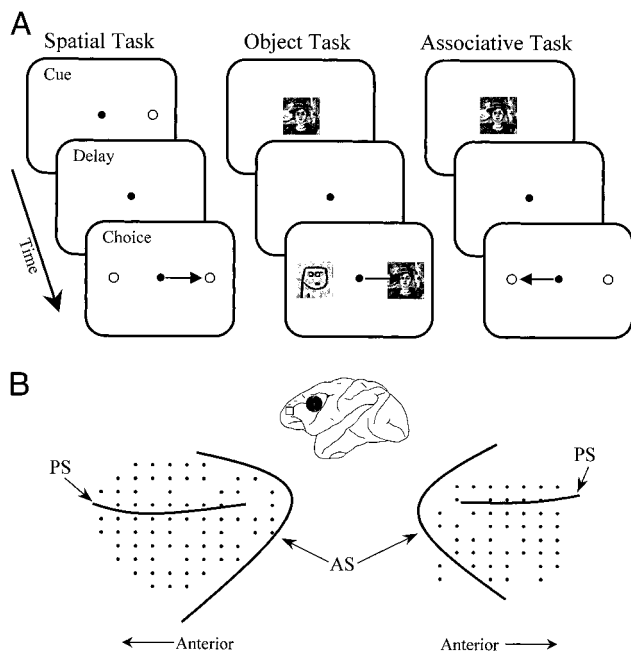
FIG. 1. Schematic depiction of the tasks and recording locations. *A*: the tasks. The spatial task (*left*) required the monkeys to saccade to the former location of the cue (a flashed dot). The object task (*middle*) required them to remember the identity of the cue stimulus and then saccade to the matching choice stimulus. The associative task (*right*) required the animals to learn to associate each of the cue stimuli with either a rightward or leftward response. Monkeys fixated a small spot of light for about 800 ms. They were required to maintain central gaze until the choice at the end of the trial. Fixation was followed by 500 ms of cue presentation and then a 1,000-ms memory delay during which the cue was absent. Simultaneous with offset of the fixation point, 2 choices were presented, one 4° to the right and the other 4° to the left. The animals selected their responses by a direct saccade to the appropriate target. The actual stimuli were multicolored. *B*: recording locations. The locations of recorded neurons in both monkeys are depicted for each animal. Often more than 1 neuron was recorded at each penetration site (on the same or across different sessions). The gray circle in the small *inset brain* shows the approximate location of the recording chambers.

while for the infrared system it was 0.12°). Except during the inter-trial interval and until their saccade response at the end of each trial, the monkeys were required to fixate within a small box, 2.5° in width and height. However, monkeys were trained such that their eye positions only very rarely varied more than 1° during any given trial (less than 1% of trials). Breaking fixation immediately aborted the trial without the delivery of juice.

Recording sites were localized using magnetic resonance imaging (MRI). The recording chambers were positioned stereotaxically over the left or right lateral prefrontal cortices of each animal. They were positioned such that the principal sulcus and surrounding cortex, especially the ventrolateral PF cortex, was readily accessible. All surgeries were performed under aseptic conditions while the animals were anesthetized with isoflurane. The animals received postoperative antibiotics and analgesics and were handled in accord with National Institutes of Health guidelines and the recommendations of the MIT Animal Care and Use Committee.

Behavioral tasks

Monkeys performed an object memory task (delayed match-to-sample), a spatial memory task (spatial delayed response), and an associative task (conditional visuomotor task, Fig. 1*A*) (Funahashi et al. 1989; Fuster 1973; Glick et al. 1969; Passingham 1975; Petrides 1982). In two of these tasks, the same stimuli were used to cue different behaviors (object vs. associative tasks), while in another two

the same behavioral responses were cued by different stimuli (spatial vs. associative tasks).

The tasks were administered and behavior monitored by a computer running the "CORTEX" real-time control system (http://cog.nimh. nih.gov/CORTEX/). The three tasks were interleaved block-wise. Blocks lasted 100–200 trials depending on the animals' level of performance. Each task was repeated at least twice during any single session (the time during which the same set of neurons were isolated), and one recording session was run each day. No explicit cues were used to signal to the animals which task they were performing. Each animal performed the spatial and object tasks at a high level (more than 90% correct for each, on average). Their performance on the associative task was somewhat lower (77–90% correct overall) because it required monkeys to learn new cue-response pairings each day and reverse them twice during any single session. For all analyses, however, only neural data from correct trials were used, and for the associative task, only correct trials after the pairings were well learned. These were selected by requiring the animals' performance to be at least 80% correct across a moving window of ten trials. By pairing each object with each saccade direction during the associative task, we were able to disambiguate a neuron's response as cue-related (object selective) or response-related (spatially selective). Neural activity during learning in the associative task has been described previously (Asaad et al. 1998).

For each recording session, two novel cue stimuli, never before seen by the animal, were chosen at random. The same two stimuli and two behavioral responses were used across the object and associative tasks. The stimuli were small, complex objects about $2 \times 2°$ in size. The objects were presented on a computer screen positioned directly in front of the animal. We made no attempt to determine which features of particular objects were responsible for the cells' responses; for this study, it was necessary only that different cue stimuli elicited selective activity from a number of PF neurons. Complex objects were used because they have been shown to elicit robust activity from lateral prefrontal neurons (Miller et al. 1996).

Recording technique

Monkeys were seated in primate chairs within sound-attenuating enclosures (Crist Instruments, Damascus, MD). Their heads were restrained, and a juice spout was placed at their mouths for automated reward delivery. Recordings were made using arrays of eight dura-puncturing, tungsten microelectrodes (FHC Instruments, Bowdoin, ME) mounted on custom-made, independently adjustable miniature microdrives. These were introduced into the brain using a grid (Crist Instruments) with 1-mm spacing between adjacent locations. We did not prescreen neurons for task-related responses. Rather we advanced each electrode until the activity of one or more neurons was well isolated, and then data collection began. This procedure was used to ensure an unbiased estimate of prefrontal activity. In any given session, we were able to simultaneously record the activity of up to 18 individual neurons. Recording locations are pictured in Fig. 1*B*.

Electrical events crossing a chosen threshold were digitized and stored (DataWave, Longmont, CO). Off-line, we sorted these events into single-neuron records using parameters derived from individual components of these collected waveforms (such as peak-height, peak time, valley depths and times, etc.). The data were discarded if these parameters were unstable across the recording session, or if we were unable to cleanly separate neural waveforms from noise or multiple neural waveforms from each other.

Analysis of neural data

Data were analyzed using custom-written routines in MATLAB (Mathworks, Natick, MA) and SPSS (Chicago, IL). Trials were divided into four epochs for the analysis of neural activity. The "fixation" period consisted of the 500 ms immediately preceding stimulus

onset. The "cue" period started 100 ms after stimulus onset and had a duration of 600 ms. The first 100 ms were excluded to compensate for the minimum latency of visual responses in PF cortex, and the length of this time window was selected to include any activity related to the offset of the stimulus. The "delay" epoch consisted of the subsequent 800 ms. The "presaccadic" epoch was the 250 ms immediately preceding the animals' responses (which usually occurred 150–300 ms after the end of the delay and choice onset, depending on the task and the animal). These epochs were chosen for simplicity. The results reported here were insensitive to the exact time windows used.

To assess the effects of the cues, saccade directions, and tasks on neural activity, a set of two-way ANOVAs was performed for each cell and on activity from each epoch. To compare cue-related object-selective activity across behaviors, we used two-way ANOVAs with cue stimulus (either "A" or "B") and task (either object or associative) as factors. To compare activity related to the animals' behavioral responses across tasks, we used two-way ANOVAs with direction (right or left) and task (spatial or associative) as factors. A significant effect of stimulus, direction, or task means that activity varied significantly with the cue stimuli, saccade direction, or task being performed. If stimulus or direction had different effects on neural activity depending on the task, this would produce a significant interaction between this factor and the task factor. All ANOVAs were evaluated at $P < 0.01$. This alpha level was adjusted for multiple comparisons where appropriate. All neural activity histograms were calculated with a resolution of 1 ms, then smoothed with a rounded-shoulder boxcar (50-ms boxcar convoluted with a 5-ms Gaussian).

Neurophysiological experiments that compare activity across different blocks of trials must make efforts to be confident that any neural effects are not the result of artifacts of that design, such as slow-wave changes in neural activity over time. We made certain such artifacts did not influence our data in several ways. First, we required animals to perform at least two repetitions of each task within any single session, and any cells showing gross instability across the recording session were never included in our studied population. In addition, to be certain that nonspecific changes in neuronal activity over time were not mistaken for true task-specific effects, analyses were repeated using only the subpopulation of neurons which showed no difference in activity across task repetitions (1-way ANOVA using block as a factor, $P > 0.1$). All results reported here have been replicated in this manner. Furthermore we confirmed the task effects by controlling for possible drift in two ways: we subtracted the average baseline activity on each block from the within-trial activity to express neural responses as a difference from baseline, and we divided within-trial activity by baseline activity so that within-trial activity would be expressed as a proportional change over baseline. Across the population, both techniques yielded identical results to the analyses based on raw data reported here.

Analysis of eye movements

Eye position was monitored at 100 Hz in both animals. In seven of nine sessions in the second animal, these data were stored for off-line analysis. Microsaccades and saccades were detected using a simple velocity threshold set at four times the standard deviation of the signal derived from the fixation period. The start and end of each saccadic movement was determined by finding, respectively, the last point before and first point after this threshold crossing in which eye-velocity fell below 1 SD. This method reliably selected the smallest "microsaccadic" movements that could be confidently confirmed by eye given the signal-to-noise of the infrared monitoring system used in this animal.

Reaction times were available for all sessions, even when continuous eye position was not, as they were determined by simply time-stamping the moment when eye position first left the fixation box.

Where a particular neural or behavioral effect was significant in both animals, the data across them were pooled for simplicity of presentation. All major effects were observed in both animals. The few results that differed between the monkeys are so noted in RESULTS.

RESULTS

We recorded 210 neurons from the left lateral PF cortex of one monkey and 95 neurons from the right lateral PF cortex of the other. Across all tasks, nearly all cells were responsive (within-trial activity differed significantly from inter-trial activity) in at least one epoch (294/305 or 96.4%, t-test, $P < 0.01$). Similarly in any single epoch, most cells were responsive (243/305 or 79.7% during the cue period; 233/305 or 76.4% during the delay; 255/305 or 83.6% in the presaccadic period).

Task-selective baseline activity

Most of the 305 neurons displayed a task-dependent change in overall activity, particularly in the fixation interval preceding cue presentation. Because the task remained constant for a block of 100–200 trials, the monkeys could usually predict which task they would perform on an upcoming trial. Indeed their behavior suggests that they did: when they switched to a new task, reaction times initially increased ($P < 0.01$ by t-test comparing 20 trials before a task-switch to the 20 trials just after) then decreased again over the course of a few trials ($P = 0.03$ t-test comparing 20 trials just after a task-switch to the next 20 trials).

During the precue fixation interval, about half of the cells showed small but significant differences in activity depending on which task was being performed (114/210 cells, or 54.3%, in one animal, and 53/95 cells, or 55.8%, in the other, by ANOVA, $P < 0.01$). Figure 2 shows two such cells. Here, activity during the inter-trial interval was similar for all tasks. However, shortly after the monkey began the trial by directing gaze to the fixation point, each showed an increase in activity whose level was significantly dependent on the current task. During this fixation interval, sensory stimulation was identical across all three tasks; all that differed was which task the monkey was about to perform. Note that although the absolute difference in spike rate is low (on the order of just a few spikes per second), this might nevertheless comprise a meaningful proportion of a neuron's activity during the fixation period, when activity is generally low (less than 10 spikes/s on average, across our population). In fact, the percent change in fixation activity between the best and worst tasks for the cells showing a significant difference was 32.0% (best minus worst divided by best; SD: 18.9%).

While in one animal there was a slight tendency for cells to prefer the associative over the object and spatial tasks during the fixation period (26, 11, and 16 cells, respectively: χ^2, $P = 0.037$), no significant tendency was observed in the other monkey (44, 30, and 40 cells preferring each task, respectively: χ^2, $P = 0.254$). That a sizeable proportion of neurons was found to prefer each of the three tasks suggests that different neurons are selective for different tasks much as they are selective for different objects or saccade directions.

Effects of task on neural activity related to cues and saccades

Across the object and associative tasks, the cue stimuli seen at the start of the trial were identical. The tasks differed in what
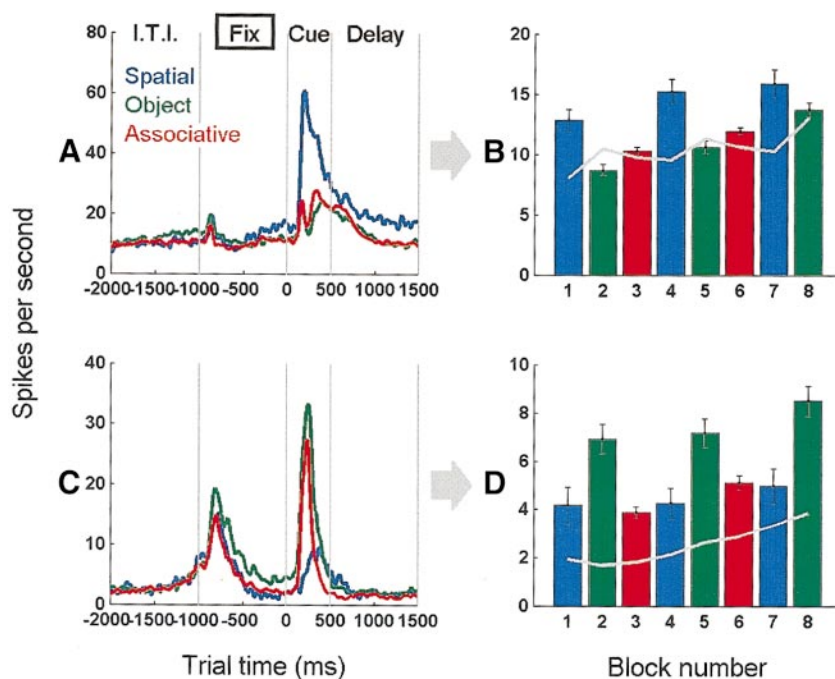
FIG. 2. Task-related changes in baseline neural activity. *A* and *C*: shown are spike rate vs. time histograms for 2 neurons, each sorted by task. The final second of the 3-s inter-trial interval (ITI) is represented by the first 1,000 ms ($-2,000$ to $-1,000$ ms). Fixation occurs soon after (around $-1,000$ to -800 ms). Cue presentation occurs at the time point marked 0 ms. All trials were aligned on this event. The cue was extinguished after 500 ms and was followed by a 1,000-ms delay. Task-related differences in baseline firing rate were generally observed to begin in the fixation period. While the activity of some neurons diverged almost coincident with initial fixation (*B*), the activity of others diverged progressively as the appearance of the cue became more imminent (*A* and see also Fig. 7*A*). *B* and *D*: the bar graphs at the *right* demonstrate the reproducibility of these small task-specific changes in activity across multiple repetitions of the same task. Shown is the mean fixation-period firing rate (with SEs) for each block of trials for the 2 cells presented to the *left* (activity during the last 400 ms before the cue is shown in *B*, whereas activity during the 800 ms preceding the cue is shown in *D*). The bars are color-coded to reflect the task being performed in each block, and the colors match those in the histograms to the left. The light gray line superimposed over these bars shows the activity of these neurons during the immediately preceding 1 s of the ITI.

needed to be done with the cues, either find its match (object task) or perform the saccade currently associated with it (associative task). Many neurons (163/305 or 53.4% see Fig. 3*A* and Table 1) showed sensory-related activity; they reflected the identity of the objects irrespective of the task (stimulus $P <$ 0.01, stimulus $\times$ task interaction $P > 0.01$ in at least 1 epoch). However, over a quarter of the neurons showed stimulus selectivity that was modulated by the task (84/305 or 27.5%), i.e., selectivity that was significantly stronger in one of the tasks (Fig. 3, *B* and *C*, stimulus $\times$ task interaction $P < 0.01$). Indeed,
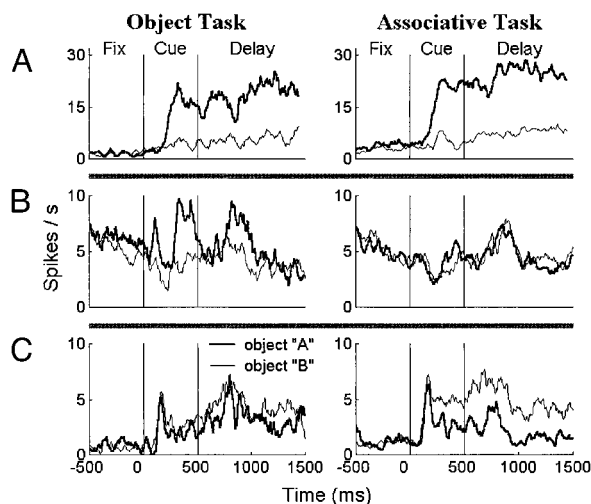

FIG. 3. Task-specific stimulus selectivity in single neurons. The average spike rates over time are presented for 3 neurons, sorted by the identity of the cue stimulus. The histograms begin 500 ms before cue onset (which occurs at 0 ms, indicated by the 1st vertical line), and last until 1,000 ms after cue offset (the 2nd vertical line). Each neuron is represented by 2 panels. *Left*: stimulus-specific activity in the object task; *right*: stimulus-specific activity in the associative task. Activity during the associative task was averaged across response directions. *A*: a cell with stimulus selectivity maintained across both tasks. *B*: this cell was stimulus selective in only the object task but not the associative task despite the use of identical stimuli across both. *C*: stimulus selectivity in this cell was restricted to the associative task.

for some cells the task influence could be so powerful as to make a neuron unresponsive in one task while clearly responsive to the same stimulus in the context of the other task (Fig. 4).

A similar pattern of results was found when we compared activity between the spatial and associative tasks (Table 2). They required the same saccadic responses, but differed in whether they were explicitly cued (spatial task) or inferred from an association with a cue stimulus (associative task). Many neurons (125/305 or 41.0%, Table 2) showed saccade-direction selectivity whose magnitude was about equal across both tasks (Fig. 5*A*; direction, $P < 0.01$, no interaction with task, $P > 0.01$, in at least 1 epoch). This activity presumably reflects a mechanism common to both tasks, perhaps a "premotor" signal and/or a shift in attention preceding the saccade. Other neurons (139/305 or 45.6%) showed direction selective activity whose magnitude depended on which task the animal was performing (direction $\times$ task, $P < 0.01$, in at least 1 trial epoch). For some neurons, direction selectivity was stronger in the spatial than the associative task (103/305 or 34%, Fig. 5*B*). This could reflect a neuron's response to the peripheral cues used in the former but not the latter. There is no such simple explanation for the neurons that showed stronger direction selectivity in the associative than the spatial task (49/305, or 16%). For example, the neuron depicted in Fig. 5*C* showed delay activity during the associative task that reflected the forthcoming saccade and not the cue stimuli (effect of stimulus, $P > 0.01$; direction, $P < 0.01$; interaction, $P > 0.01$). However, during the spatial task, when the identical saccades were cued, it was not selective. Thus its ability to convey information about the saccade is task dependent. We also noted that, across our population of neurons, spatial selectivity took longer to appear in the associative than in the spatial task (Table 3). This latency difference is visible in the cell in Fig. 5*A*. It presumably reflects the additional time needed to recall the saccade direction associated with the cue object.

To determine the extent to which neural activity was mod-

TABLE 1. *Incidence of stimulus and task selectivity in the object and associative tasks*

	Cue Epoch	Delay Epoch	Presaccadic Epoch	Any Epoch
Task-independent stimulus selectivity				
Neurons showing effect	106 (135)	102 (124)	47 (65)	162 (187)
Percentage of 305	34.8	33.4	15.4	53.1
Stimulus-independent task selectivity				
Neurons showing effect	105* (136)	111* (133)	137* (166)	211 (234)
Percentage of 305	34.4	36.4	44.9	69.2
Task-dependent stimulus selectivity				
Neurons showing effect	45†	35†	39†	84
Percentage of 305	14.8	11.5	12.8	27.5
Any stimulus selectivity				
Neurons showing effect	151	137	86	210
Percentage of 305	49.5	47.9	28.2	68.9
Any task selectivity				
Neurons showing effect	150	146	176	244
Percentage of 305	49.2	47.9	57.7	80.0
Any type of task or stimulus selectivity				
Neurons showing effect	207	207	194	271
Percentage of 305	67.9	67.9	63.6	88.9

Neuronal selectivity compared across tasks. The number of neurons showing the indicated type of selectivity in each task was determined by ANOVA evaluated at $P < .01$. The different task epochs were defined as described in METHODS. Cue stimulus selectivity compared across the object and associative tasks. Stimulus-independent task selectivity refers to a main effect of task on the ANOVA (without an interaction with stimulus), i.e., an overall change in activity that depended on the task. The task preferences of the neurons are noted in the appropriate boxes. The total numbers of neurons showing a main effect, including those with a significant interaction, are noted in parentheses. * Number of neurons preferring the object task were 41 in cue epoch, 45 in delay epoch, and 98 in presaccadic epoch. † Number of neurons more selective in object task were 25 in cue epoch, 22 in delay epoch, and 24 in presaccadic epoch.

ulated by task—particularly in relation to its modulation by "external" factors such as the cues or responses—we calculated a selectivity index (see Fig. 6 legend) for each epoch of each neuron found to display significant modulation by stimulus identity, response direction, or task (according to the ANOVAs, see the preceding text). These were computed separately for each task, and the resulting indices are plotted in Fig. 6. Points lying along the diagonal represent instances of equal selectivity across tasks; the further from the diagonal, the more modulated was the neuron by task. In both the cases, of cue stimulus selectivity by task (*6A*) and direction selectivity by task (*6B*), the general pattern of points is elongated along the diagonal, suggesting that the stimulus and the response were the dominating influences (the divergence of cue period selectivities in *6B* is a trivial consequence of the different stimuli used across these tasks). The influence of task on neural
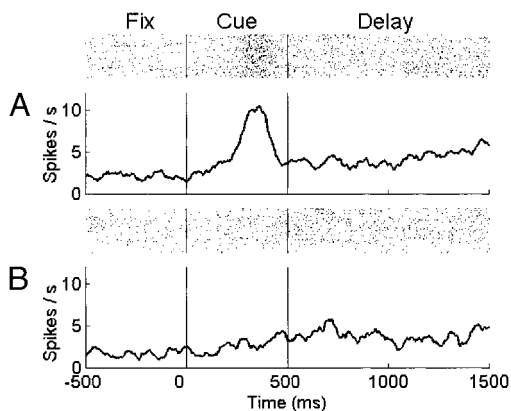

FIG. 4. Cue-period activity across tasks. Shown is the activity of a single neuron in response to a single cue stimulus as it is presented in each task. *A*: the response of this cell during performance of the associative task. *B*: response of the same neuron during execution of the object task. Note the good response during the cue period of the associative task that is absent from the neuron's activity during the object task, even though the identical stimulus was presented in both cases.

activity, therefore seems to be a biasing of responses away from the "external" sensory- or motor-driven levels. It is perhaps possible that the use of tasks which again shared the same cues or responses, but differed more radically in the rules to be applied, could result in even stronger biases.

Consistent with previous reports (Fuster et al. 1982; Rainer et al. 1998a; Rao et al. 1997; White and Wise 1999), neurons selective for object and/or spatial information (saccade direction) were intermixed throughout the recording locations (areas 46, 45, 12, 9) as were neurons modulated or not modulated by task.

To make certain that sensory and motor conditions across the object and associative tasks were truly equivalent, we considered the possible influence of eye position and microsaccades. For these analyses, we examined 60 neurons recorded during the seven sessions in which we acquired continuous eye-position data (sampled at 100 Hz) from the second monkey. Microsaccades were not found to differ significantly across the object and associative tasks in number, velocity, or amplitude in any of the seven sessions ($P > 0.1$). Eye position, however, was found to differ significantly across the object and associative tasks in five of these seven sessions. However, the average magnitude of this difference in these five cases was only 0.16°. Such a difference is quite small when considered in the context of the reported size of prefrontal receptive fields, which are on average about 10° across (Rainer et al. 1998). Equivalent differences in eye position across tasks were found during the inter-trial-interval in six of seven sessions, suggesting that these differences may result from slow drift, perhaps due to mechanical variations (e.g., head position) or animal fatigue.

Nevertheless to be confident that these differences in eye position did not influence our neural data, we examined directly the effect of eye position on neural activity within a single task. To do this, we divided trials into those in which the average fixation position was less than the mean fixation po-

TABLE 2. *Incidence of direction and task selectivity in the spatial and associative tasks*

	Cue Epoch	Delay Epoch	Presaccadic Epoch	Any Epoch
Task-independent direction selectivity				
Neurons showing effect	48 (100)	52 (99)	59 (101)	122 (179)
Percentage of 305	15.7	17.1	19.3	40.0
Direction-independent task selectivity				
Neurons showing effect	146* (203)	121* (164)	106* (142)	215 (255)
Percentage of 305	47.9	49.7	34.8	70.5
Task-dependent direction selectivity				
Neurons showing effect	87	70	59	139
Percentage of 305	28.5	23.0	19.3	45.6
Any direction selectivity				
Neurons showing effect	135	122	118	204
Percentage of 305	44.2	40.0	38.7	66.9
Any task selectivity				
Neurons showing effect	233	191	165	275
Percentage of 305	76.4	62.6	54.1	90.2
Any type of task or direction selectivity				
Neurons showing effect	245	218	194	283
Percentage of 305	80.3	71.5	63.6	92.8

Spatial selectivity compared across the spatial and associative tasks. Direction-independent task selectivity also refers to a main effect of task (without an interaction with direction), but in this case, it could be related to the different cues used in the spatial and associative tasks. The conventions are as for Table 1. * Number of neurons preferring the spatial task were 37 in cue epoch, 36 in delay epoch, and 35 in presaccadic epoch. † Number of neurons more selective in spatial task were 68 in cue epoch, 51 in delay epoch, and 37 in presaccadic epoch.

sition (in either the *x* or *y* dimension, in separate analyses) or greater than this mean. Between these two groups of trials, this induced an average distance of 0.33°—about twice the actual distance observed across tasks. However, in only 3 of 60 cases did this manipulation result in a significant difference in neural activity. This is not surprising, given the large size of prefrontal receptive fields. Differences in eye position, therefore were not contributing notably to the reported differences in neural activity across the object and associative tasks during the cue

FIG. 5. Task-specific response-direction selectivity. These histograms show the average spike rates over time for 3 cells beginning 500 ms before the cue presentation which occurs at 0 ms. As in Fig. 2, each cell is represented by 2 panels. *Left*: direction-specific activity in the spatial task in which the animals' saccade target was explicitly cued. *Right*: direction-specific activity in the associative task in which the animals had to associate cue stimuli with the same saccades. The required behavioral responses were identical in both tasks. Activity during the associative task was averaged across cue stimuli. *A*: a neuron which was spatially selective in both tasks. Note that spatial selectivity in the associative task appears later than in the spatial task. *B*: this neuron was spatially selective in only the spatial task. *C*: this neuron had the opposite pattern of response, showing spatial selectivity in only the associative task.

presentation (which were found in approximately half of all cells).

Similarly, to determine if differences in the animals' responses could be contributing to differences in neural activity across the spatial and associative tasks, we examined the metrics of the saccadic responses and reaction times. No difference in saccade velocity, amplitude, or accuracy was observed in any of the seven sessions in which continuous eye-position data were recorded. However, we found that reaction times did indeed differ across these tasks in 13 of the 31 total sessions (9/21 in the 1st monkey, and 4/10 in the 2nd). In these cases, the monkeys responded slightly more quickly (~14 ms, on average) in the associative than in the spatial task, possibly as a result of their greater experience with the associative task.

Although the magnitude of this reaction time difference was small, we nevertheless examined the 107 neurons recorded in these 13 sessions to be certain that differences in neural activity—particularly during the presaccadic epoch—were not related to differences in reaction time. In a manner analogous to that employed in the preceding text, we divided trials within a
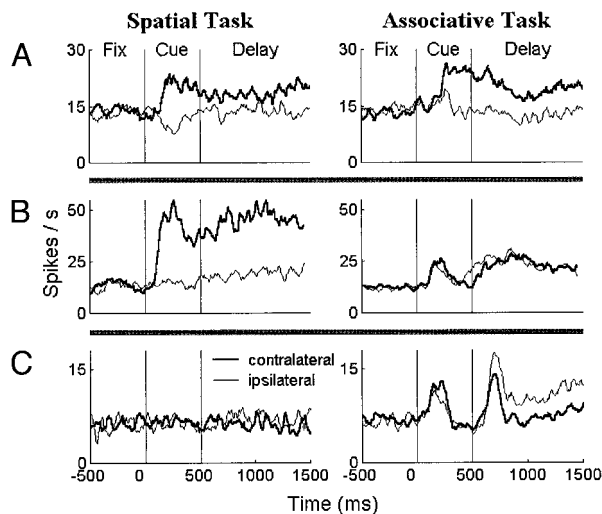
TABLE 3. *Latencies to the appearance of direction selectivity across tasks*

	Task	Mean Latency, ms	Significance
Monkey 1	Spatial	267 ± 160	$P < 0.001$
	Associative	477 ± 147	
Monkey 2	Spatial	296 ± 190	$P = 0.03$
	Associative	362 ± 188	

Latency to the appearance of spatial selectivity compared across tasks. The latency to the appearance of spatial selectivity was determined using a sliding 50-ms window to find the earliest point at which the spatial selectivity index was consistently greater than twice the standard deviation of a dummy index calculated during the preceding 500 ms of fixation. This provided a cell-specific noise estimate and allowed consistent estimates of selectivity latency. Used in this analysis are 135 cells showing either a main effect of, or interaction with, response direction during the cue period on the direction by task two-way ANOVA.
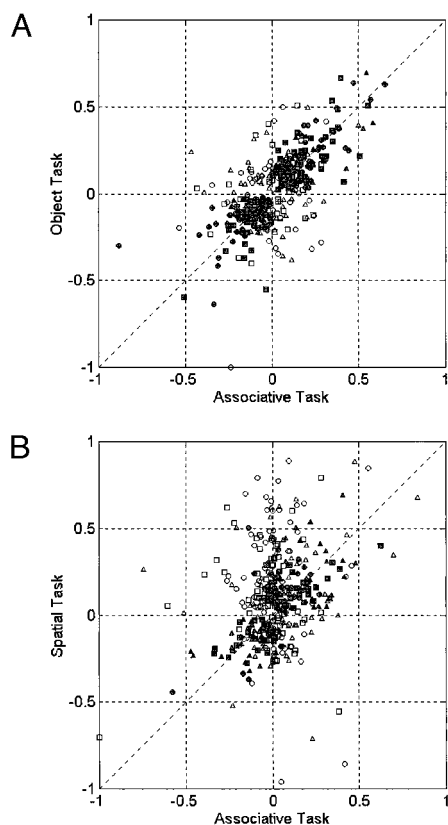
FIG. 6. Magnitude of stimulus- and response-selectivity compared across tasks. These scatter diagrams plot the stimulus (*A*) or response-direction (*B*) selectivity index of significant neurons in one task against the same index calculated for the other task. These indices are simply the difference in activity for stimuli or responses divided by their sum. Positive or negative values in *A* reflect simply a preference for the cue stimuli arbitrarily designated "A" or "B", respectively. Positive index values in *B* reflect a preference for the direction of response contralateral to the recorded hemisphere. Circles, squares, and triangles reflect selectivity during the cue, delay, or presaccadic epochs, respectively. Equal selectivity across tasks would be reflected in points lying near the diagonal. Filled symbols indicate only main effects on the ANOVA, whereas open symbols indicate an interaction with task factor.

task according to whether reaction time was faster or slower than the mean reaction time. This induced an average difference in reaction time of 63 ms, which is greater than the observed difference across tasks of only 14 ms. Despite this, only 12 of these 107 neurons were found to display significant differences in neural activity depending on reaction time. Furthermore only five of these also displayed task-specific activity that was of the same sign as the influence of reaction time on neural activity would predict, as determined for each. These considerations led us to conclude that the observed small differences in reaction time were not contributing significantly to the task-selective responses that were prevalent across our population of neurons.

Consistency of neural task preferences across trial epochs

Often task selectivity was maintained across the three main trial epochs (cue, delay, and presaccade). Across the object and associative tasks, 133 of 244 neurons (54.5%) had consistent task preferences in all three epochs. In comparison, consistent cue stimulus preferences were less common (68/210 neurons or 32.4%). Likewise, across the spatial and associative tasks,

consistent task preferences across these epochs were observed in 158 of 275 neurons (57.4%). This was similar to the proportion of neurons showing consistent direction preferences in these tasks (110/244 or 54.5%). These data suggest that the task-selective signal is at least as robust, over time within a trial, as stimulus or response selectivity.

Task-related "climbing" activity

Another frequently observed task difference occurred toward the end of the memory delay and into the presaccadic period: Neuronal activity "ramped-up" more often during the object task than during the spatial or associative tasks. An example of one such single neuron is shown in Fig. 7*A*. Note that beginning shortly before the saccadic response, activity in the object task (green line), but not in the spatial (blue) or associative (red) tasks, began to ramp up, apparently culminating in a response to the choice objects (which did not appear in the other tasks). To assess the prevalence of this type of activity across our population of neurons we fit a least-squares line to a 300-ms time period (divided into 1-ms bins) at the end of the delay and during the presaccadic period for each and every recorded neuron. This revealed that the slopes were more positive (i.e., there was more climbing activity) for the object task than for both the spatial and associative tasks (ANOVA with post hoc contrasts, $P < 0.001$ for 1 animal and $P = 0.06$ for the other). For every cell in our population, we plotted the slope obtained for the object task against the slopes from each of the other two tasks (Fig. 7*B*). That most of the points lie above the diagonal reflects the generally greater spike rate acceleration at the end of the delay of the object task.

Within the object task, a negative correlation was observed between the degree of ramping and the magnitude of cue stimulus selectivity during this epoch (correlation coefficient = -0.15, $R^2 = 0.36$, and $P < 0.01$ for the 1st animal, ml = -0.22, $R^2 = 0.51$, and $P < 0.01$ for the 2nd animal). This suggests that ramping activity serves not simply to augment a stimulus-selective signal to be used for the upcoming choice but rather has a still undetermined function.

DISCUSSION

These results show that for many PF neurons, activity was influenced by the task being performed. This influence included changes in their baseline firing rates, modulations of neuronal activity related to particular stimuli and behavioral responses, and differences in their firing rate profiles (shape of the responses over time). This suggests that the formal demands of behavior are represented within PF activity and thus supports the hypothesis that one PF function is the acquisition and implementation of task context and the "rules" used to guide behavior (Cohen and Servan-Schreiber 1992; Grafman 1994; Miller 1999; Passingham 1993; Wise et al. 1996).

To perform efficiently, the animals needed to keep track of which task was current. This was reflected in modulations in the baseline activity of many neurons. The spike rate differences were relatively small, but because this effect was evident in over half of the recorded cells and represented a sizeable fraction of their over-all level of activity (~30%), this may nevertheless provide a means through which PF cortical activity can bias processing in other brain regions. Previously,
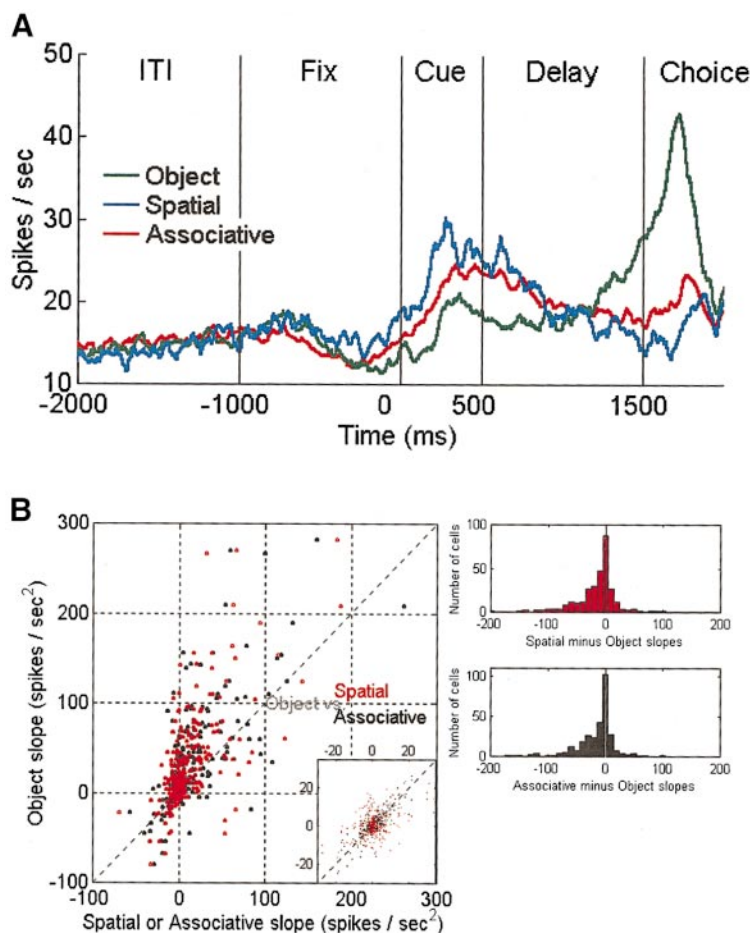
FIG. 7. Ramping activity. Toward the end of the delay, the activity of many cells ramped up in the object task but not in the spatial or associative tasks. *A*: a single-cell example; note the upward slope in activity toward the end of the delay for the object task (green line) but not the other tasks. *B*: we fit a least-squares line to a 300-ms epoch at the end of the delay for activity from each task and plotted the slopes in the object task against the spatial task (red) and the object task against the associative task (black). The mean slope in the object task was twice that of the spatial and associative tasks. The histograms show in spatial or associative slope values (in spikes/s^2) minus the object values for each cell. The leftward skew indicates that the slopes were more positive in the object task. In contrast, the slopes for the analogous period of time preceding the appearance of the cues did not differ significantly across tasks ($P = 0.92$ by ANOVA comparing effects of task). *Inset*: the scatter plot of these precue slopes. Note the much weaker ramping over-all and the lack of skew (most points lie near the diagonal).

modulations of PF baseline (precue) activity were observed when monkeys had to remember a particular stimulus between trials (Rainer et al. 1998). In this case, however, there was no sensory information to be remembered. Nor could this effect be explained by a "prospective code" of the anticipated cue stimuli; for many cells precue activity was significantly different between the object and associative tasks (which used the same cues). Thus the information conveyed was necessarily more abstract. More generally, when the same stimuli are involved in several possible behaviors, this sort of task-specific activity could provide a signal that allows ambiguous or conflicting sensory information to be mapped to the appropriate motor output (Cohen and Servan-Schreiber 1992; Fuster 1995). Conversely, task-specific activity in the PF cortex could function, via "top-down" signals, to bias the activity of sensory systems toward the representation of relevant information (Desimone and Duncan 1995). Along the same lines, the PF cortex is likely involved in the retrieval of information from long-term memory (Buckner et al. 1996; Hasegawa et al. 1998; Wagner et al. 1998). A task-related signal may therefore contribute to the phenomenon of context-dependent recall.

Stimulus or saccade-direction selectivity whose magnitude differs with the current task indicates that some PF neurons do not simply reflect single stimuli or forthcoming actions. Rather this suggests that behavioral context (i.e., information associated with the cue or saccade that is unique to a particular task or the manner in which it is used) modulates PF activity. For example, a neuron apparently selective during a "pure" object

memory task (the object task) does not necessarily exhibit selectivity for the same objects in other contexts (e.g., the associative task). That many neurons did reflect a given object or saccade regardless of task indicates that both sensory information and convergence toward motor output are indeed present in the PF cortex. But the existence of task-specific selectivity suggests that the PF cortex also has information about what is "in between," i.e., the mechanisms for mapping sensory input to motor output (Fuster 1990). Results from recent neurophysiological studies lead to the same conclusion. The responses of neurons in the lateral PF cortex and frontal eye fields to a visual target can differ dramatically depending on the rule used to acquire the target (Ferrera et al. 1999; Hoshi et al. 1998; White and Wise 1999). Similarly, we have previously shown that the activity of many PF neurons simultaneously reflects a visual cue and the particular action it instructs (Asaad et al. 1998). In addition, the existence of task-specific signals could provide an alternative explanation for the differences in neural activity previously observed across the spatial and associative tasks (Wilson et al. 1993). It had been suggested that these differences were due entirely to the use of patterned stimuli versus simple spatial cues, whereas now it is apparent that even identical cues could result in different patterns of PF activity if each is embedded within a different task context. Therefore one must consider the possibility that differences in the nature of the stimulus-response mapping—the rule—contributed to differences in neural activity.

A ramp-up of neural activity was observed near the end of

the delay and into the presaccadic period in predominantly the object task. This might anticipate the impending choice, perhaps serving in some manner to prepare for the stimulus comparison about to be performed (Rainer et al. 1999). Alternatively, this activity may function to inhibit the actions associated with the cues during the associative task because, unlike the object task, the associative task did not require the animals to withhold a response until a target (match) was located. This ramping is unlikely to reflect simply the expectation of a visual stimulus because the degree of ramping was much weaker preceding the appearance of the cue.

Together, these results support the notion that the information conveyed by PF neurons is not limited to discrete sensory events or motor plans. Rather the behavioral context in which the animals were engaged had a pervasive influence on PF activity. This abstracted representation of information within the PF cortex may provide the necessary foundation for the complex forms of behavior observed in primates in whom this structure is most elaborate.

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