

From Perception to Action: Temporal Integrative Functions of Prefrontal and Parietal Neurons

Javier Quintana and Joaquin M. Fuster

Department of Psychiatry and Biobehavioral Sciences and Brain Research Institute, School of Medicine, University of California at Los Angeles, Los Angeles, CA 90024-1759, USA

The dorsolateral prefrontal cortex (DPFC) and the posterior parietal cortex (PPC) are anatomically and functionally interconnected, and have been implicated in working memory and the preparation for behavioral action. To substantiate those functions at the neuronal level, we designed a visuomotor task that dissociated the perceptual and executive aspects of the perception–action cycle in both space and time. In that task, the trial-initiating cue (a color) indicated with different degrees of certainty the direction of the correct manual response 12 s later. We recorded extracellular activity from 258 prefrontal and 223 parietal units in two monkeys performing the task. In the DPFC, some units (memory cells) were attuned to the color of the cue, independent of the response-direction it connoted. Their discharge tended to diminish in the course of the delay between cue and response. In contrast, few color-related units were found in PPC, and these did not show decreasing patterns of delay activity. Other units in both cortices (set cells) were attuned to response-direction and tended to accelerate their firing in anticipation of the response and in proportion to the predictability of its direction. A third group of units was related to the determinacy of the act; their firing was attuned to the certainty with which the animal could predict the correct response, whatever its direction. Cells of the three types were found closely intermingled histologically. These findings further support and define the role of DPFC in executive functions and in the temporal closure of the perception–action cycle. The findings also agree with the involvement of PPC in spatial aspects of visuomotor behavior, and add a temporal integrative dimension to that involvement. Together, the results provide physiological evidence for the role of a prefrontal–parietal network in the integration of perception with action across time.

Introduction

The dorsolateral prefrontal cortex (DPFC) in primates (areas 9 and 10 of Brodmann, 46 of Walker) appears essential for integrating sensory information with subsequent – and consequent – action in goal-directed behavior (Fuster, 1997). Single-unit recording shows sustained activation of DPFC cells in the intra-trial interval (delay) of delay tasks (Fuster, 1973; Kubota *et al.*, 1974; Niki, 1974a,b,c; Niki and Watanabe, 1976; Fuster *et al.*, 1982; Quintana *et al.*, 1988; Rao *et al.*, 1997). These tasks epitomize the mediation of cross-temporal contingencies between perception and action. It has been postulated (Fuster, 1984) that the mediation of such contingencies is accomplished by the coordination of two complementary cognitive operations under the control of the DPFC. The first is the temporary storage of sensory information in active memory for prospective motor acts (working memory). The second is the preparatory set of the motor apparatus for such acts. Short-term memory and short-term set would thus constitute the two basic temporal integrative functions of the DPFC.

Electrophysiological studies of frontal field potentials (Walter *et al.*, 1964; Walter, 1967; Järvillehto and Fruhstorfer, 1970; Brunia *et al.*, 1985), as well as single-unit potentials (Fuster,

1973; Kubota *et al.*, 1974; Niki and Watanabe, 1976; Fuster *et al.*, 1982; Quintana *et al.*, 1988; Funahashi *et al.*, 1989), indicate that, in the delay interval of a delay task, DPFC cell activity is rarely in a steady state. As time passes between a sensory cue and the consequent action, surface potentials and the spike rates of some cells tend to increase or decrease, without a clear cortical topography to these changes. For lack of a better explanation, two trends of neural delay activity, one gradually waning and the other waxing, have been hypothetically ascribed respectively to the short-term memory of the cue and the short-term set for the response (Fuster, 1984). Those two neuroelectrical trends would thus somehow reflect the two temporally reciprocal frontal functions – memory and planning – inferred by human neuropsychology (Fuster, 1997). In the absence of reliable parametric evidence, however, these assumptions have remained unverified.

In order to carry out its temporally integrative functions, the DPFC probably works in close cooperation with areas of posterior cortex that specialize in particular modalities or aspects of sensory information. Unit studies in monkeys during performance of tasks with spatial information have shown that neurons in posterior parietal cortex (PPC) have both sensory and motor properties (Andersen *et al.*, 1987). In area 5, some cells appear involved in tactile discrimination as well as in haptic short-term memory (Koch and Fuster, 1989; Zhou and Fuster, 1997); others, in the anticipation of movement (Gnadt and Andersen, 1988; Andersen, 1995). Cells in a subregion of area 7 (LIP) seem to retain the memory of visual locations and to take part in preparation of ocular movements directed to them (Gnadt and Andersen, 1988; Andersen, 1995). Based on those findings, parietal-cell activations during an imposed interval between a stimulus and a motor response have been attributed both to short-term memory and to the intention to move (Duhamel *et al.*, 1992; Andersen, 1995).

Previously (Quintana and Fuster, 1993) we had observed that the cooling of prefrontal and parietal cortex (the same areas explored with microelectrodes in this study) resulted in impairments of visuomotor performance requiring short-term retention of color cues. Whereas prefrontal cooling impaired the retention of all cues, parietal cooling impaired performance almost exclusively when the cues indicated without ambiguity the direction of future manual response. We concluded that an active prefrontal–parietal network is essential for short-term visuospatial working memory, much as a prefrontal–inferotemporal network appears essential for non-spatial visual memory (Fuster *et al.*, 1985). There is anatomical support (Jones, 1969; Pandya and Kuypers, 1969; Pandya and Yeterian, 1985; Cavada and Goldman-Rakic, 1989a,b) as well as functional support (Quintana *et al.*, 1989) for interactions between the frontal and parietal components of that hypothetical network in spatial working memory. A single-unit study

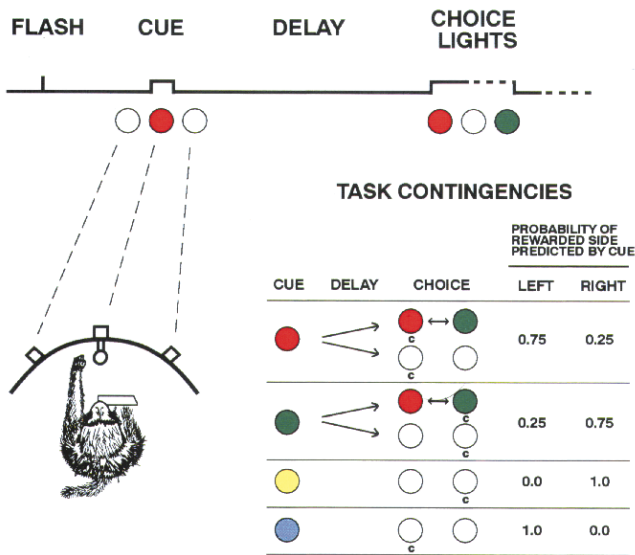


Figure 1. (A) Monkey in the testing situation, viewed from above. Temporal sequence of trial events, left to right in arbitrary time scale (see text for real scale). (B) Diagram of task contingencies. Circles represent initial cue and choice lights. Small 'c', correct choice.

of eye-movement regions of prefrontal and parietal cortex (Chafee and Goldman-Rakic, 1998), in monkeys performing a visuomotor memory task (3 s delay), provides further support to those interactions; cells in the two regions exhibit remarkable similarities of discharge patterns during the task.

The present study was designed to substantiate the role of DPFC and PPC cells in visual working memory and motor set, using a behavioral paradigm with stimulus-response contingencies intended to sharpen the evidence of cellular commitment to those cognitive functions. Our task had a stimulus-to-response delay presumed to be long enough (12 s) to clearly separate the temporal correlates of cellular activity with the stimulus, with the movement and with the cognitive processes between them. A variable of the task intended to define cognitive correlations was the probabilistic strength of the contingency between stimulus (color) and response direction. We postulated that parietal units would show patterns of delay-period activity similar to those of prefrontal cells, at least inasmuch as those patterns predict the direction and probability of a motor act. We further postulated that parietal cells would be more attuned to the spatial aspects of the task than to its visual (color) aspects. Preliminary results of this study were presented in a short report (Quintana and Fuster, 1992).

Materials and Methods

Subjects

Two adult, experimentally naive, male rhesus monkeys (*Macaca mulatta*) weighing approximately 9 and 8 kg were used for the studies reported here as well as for a previous study on behavioral effects of cortical cooling (Quintana and Fuster, 1993). They were caged individually, fed standard monkey chow diet, and had access to water *ad libitum* except for a period of 24 h before each recording session. Correct performance during the experiments was rewarded by fruit juice, of which the animals received on average 250–400 ml during each session. Throughout the investigation, the animals were cared for in accord with the guidelines of the Division of Animal Medicine (UCLA).

Apparatus

For an experimental session, the monkey was placed in a primate chair,

Table 1
Location of the units investigated

Location	Left hemisphere	Right hemisphere	Total units
Prefrontal			
AS	4	17	21
CG	0	5	5
UDLC	31	94	125
SPD	5	22	27
SPL	17	8	25
SPU	48	7	55
Total units	105	153	258
Parietal			
5	28	77	105
7	33	50	83
IPS	15	19	34
STS	0	1	1
Total units	76	147	223

Location and hemisphere precedence of the units investigated. AS, arcuate sulcus; CG, cingulate gyrus; UDLC, upper dorsolateral convexity; SP, sulcus principalis (D = depth, L = lower bank, U = upper bank); IPS, intraparietal sulcus; STS, superior temporal sulcus.

where it could use one hand for task performance and receive fruit juice directly in the mouth through a metal spigot connected to a dispenser. The chair had a rigid plastic collar with attached metal bars which, through articulated metal brackets, allowed head fixation during recording sessions (see surgery, below). The animal sat in front of the test panel in a sound-attenuated chamber with dim illumination and continuous mask noise. The animal (Fig. 1) faced a curved black panel with three small (2.8 cm) round recesses, situated on the same horizontal plane as the monkey's eyes. In the depth of the recesses a translucent stimulus-response circular disk (0.64 cm diameter, 2° visual angle) allowed the display of colored lights by rear projection through Kodak Wratten filters. Those recesses were situated at intervals of 11.45 cm, subtended a 60° overall visual angle and contained electronic sensors in their perimeter to detect the animal's responses (manual touch of the central disk in a recess). When the monkey sat in the performance position, its eyes were ~23 cm away from the panel. Under the panel was a centrally located, spherically shaped, rigid pedal, situated 16 cm below the level of the disks, on which the animal was trained to rest its performing hand (left) at all times except during a response. A strobe light reflector was placed above and behind the animal to illuminate the panel diffusely.

Behavioral paradigm

A task trial consisted of the following sequence of events (Fig. 1, top). The trial began with an alerting stroboscopic flash on the panel. Three seconds later, a colored light was presented on the central disk for 1 s as the initial cue. A delay period of 12 s ensued, at the end of which the choice/response lights were presented on the two lateral disks for up to 7 s, prompting the animal to choose one of them by touching it with its left hand. If the response was correct according to the learned task contingencies (below), a squirt of fruit juice (0.5 ml) was immediately delivered to the animal through the spigot. The response lights were turned off right after the animal's response, which was monitored by electronic sensors in the recesses of the panel, or after 7 s if no response occurred. The paradigm sequence was aborted if the animal released the resting pedal at any time other than the response time.

Stimulus-Response Contingencies

Four trial-initiating cue colors were used – red, green, yellow or blue – presented by rear projection on the central disk; and three choice-response cue colors – red, green or white – presented on the lateral disks. Dominant wavelengths (μm) were 606 for red, 581 for yellow, 527 for green and 489 for blue. All cues were of the same – circular – shape, and brightness (40 cd/m²), differing only in wavelength.

The color of the initial cue on the central disk varied in random order from trial to trial. The colors of the two response disks varied in accord with predetermined contingencies as illustrated in Figure 1. Thus, a red

Table 2Prefrontal and posterior parietal unit firing changes during trial periods^a

	Cue		Cue-delay		Delay		Delay-choice		Choice		Post-choice	
	PF	PP	PF	PP	PF	PP	PF	PP	PF	PP	PF	PP
Non-differential												
Activated	48	38	7	5	68	57	0	0	70	66	29	36
Inhibited	32	20	4	3	48	34	0	0	37	40	33	33
Differential ^b												
Sensory-coupled (R>, G>, Y>, B>, RY>, GB>)	36	11	3	7	17	12	0	0	2	4	6	3
Direction-coupled (GY>, RB>, Right> or Left> at choice)	11	7	1	2	19	16	0	7	51	64	27	48
Certainty-coupled (YB>)	2	0	0	1	10	5	0	0	2	0	2	1

^aAll changes represent differences of firing frequency from intertrial baseline firing. Since many units, especially those non-differentially activated, displayed such differences in more than one trial period (Table 3), the numbers for non-differential categories in this table represent unit reactions rather than units. The numbers for differential activations, however, coincide with unit numbers. PF, prefrontal cortex; PP, posterior parietal cortex.

^bColor symbols: R, red; G, green; Y, yellow; B, blue. Sensory-coupling indicates preferential (>) response to one color or to two wavelength-related colors (R and Y, or G and B), regardless of color-direction contingency. Direction-coupling indicates preferential (>) response to two colors (R and B, or G and Y) linked to one response direction over the other two colors indicating opposite direction.

'Certainty'-coupling indicates preferential response to the two colors (B and Y) that connote 'certain' response direction over the other two colors (R and G), which are 'ambiguous' — although 'weighted' to one response direction or the other.

or a green central cue would determine, after the delay, the appearance of either two white lights or two colored lights, red and green (relative position changing also at random between trials). In half of the trials, the choice lights were white, and in the other half colored. If the choice lights were white (delayed conditional position discrimination, DCPD) and the initial cue had been red, the animal had to touch the left white disk, the right if the initial cue had been green. If the choice lights were colored (red and green), the animal had to choose the one with the color of the initial cue (delayed matching to sample, DMS). An initial yellow central cue was always followed by two white response lights (DCPD), and the animal had to choose the right. Finally, a blue central light always preceded two white response lights (DCPD), the left being the correct choice.

Because of this design, a red initial cue predicted correct response on the left side with 75% probability, and on the right 25%. Conversely, a green initial cue predicted response on the right side with 75% probability, and on the left 25%. Responses after yellow or blue initial cue were 100% predictably correct on the right or left side respectively. Thus, red and green were 'ambiguous' cues, but 'weighted' to one side or the other. Yellow and blue, on the other hand, connoted 'certain' direction. Furthermore, it is important to note that colors close in the wavelength spectrum, such as red and yellow in the upper range, or green and blue in the low range, to some degree predicted opposite directions of correct response.

Training Procedures

Successive approximation techniques were used for training the animals. They were taught first to maintain their left hand on the pedal, then to press any light when displayed, then to press only the lateral lights, and finally to respond by touching the correct choice-disk according to the trial contingencies. In early training, the three colored lights were presented simultaneously, and the animal was allowed unlimited time to respond. Then, the response time was limited to 7 s. The color-matching contingencies were taught first, the color-position contingencies later. The last stage of training involved the progressive temporal separation between initial cue and response lights up to 12 s. Each step of the training was considered complete when the animal reached 85% correct performance level or better in two consecutive days. The training of each animal was completed in 8–10 months.

Surgical Procedures

After attaining full training, each animal underwent surgery. This was performed in one step under general Nembutal anesthesia (20 mg/kg, slow i.v. infusion) with continuous physiological monitoring and stereotaxic guidance. Four hollow stainless steel wells, 1.66 cm internal diameter, were implanted through trephine holes above the dura: two on DPFC bilaterally, covering parts of areas 9 and 10 of Brodmann; and two on PPC bilaterally (parts of areas 5a, 5b, 7a and 7b). Microthermistors were introduced through small holes in the dura and placed between

Table 3

Temporal distribution of non-differential firing changes

Number of Units		FLASH	SAMPLE	DELAY	CHOICE
PFC	PPC				
10	2				
6	7				
8	10				
12	9				
3	3				
9	3				
13	6				
11	2				
7	8				
5	5				
18	17				

cortex and dura. Wells and thermistors were anchored with acrylic cement and the ensemble reinforced with small stainless steel screws in the skull surrounding the wells. Four threaded metal sockets were embedded in the cement for head fixation with external brackets. In one of the monkeys, two eye movement (EOG) electrodes, each consisting of a Delrin screw filled with a Ag/AgCl mixture (Quintana *et al.*, 1989), were implanted on the external border of the orbital bone. The wires from the EOG electrodes and thermistors were soldered to a miniature multipin connector anchored to the cement implant. After surgery, the animals were treated with decreasing doses of corticosteroids and with antibiotics. The wells could be filled with solid stainless steel cylindrical probes or microelectrode positioners for cooling or recording purposes respectively. The cooling probes allowed the attachment of external cooling devices for a separate experiment on the effects of cortical cooling (Quintana and Fuster, 1993). After recovery from surgery, the animals were retrained in the performance of the task until they reached again an 85% correct response criterion (random order of contingencies, full 12 s delays) with head fixed.

Recording Procedures

Data collection procedures were initiated ~2 weeks after surgery. A series of sessions were first dedicated to collect data for cooling experiments

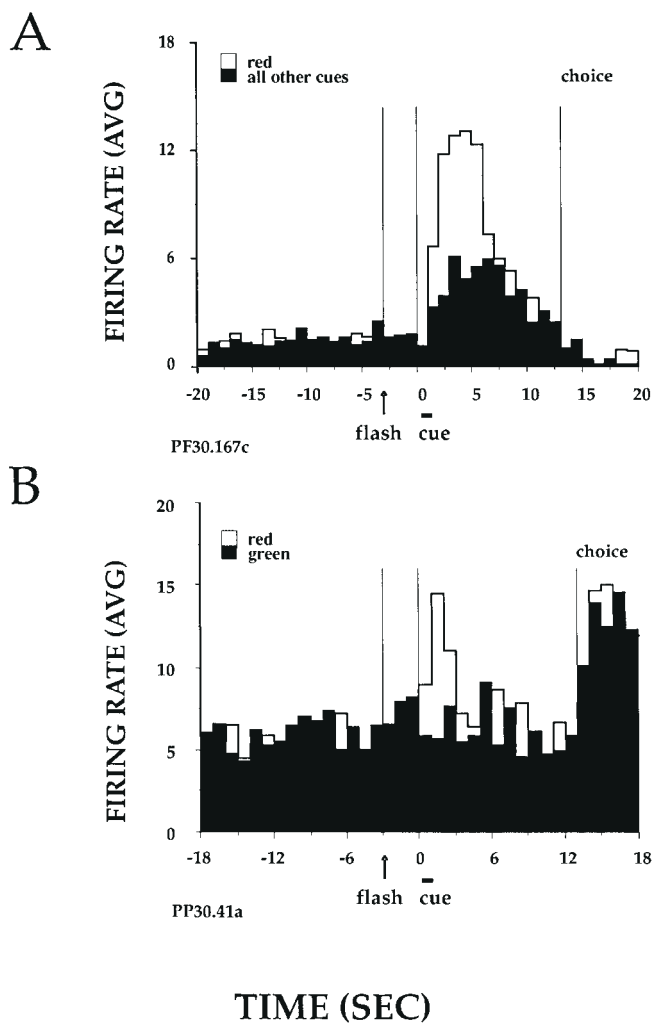


Figure 2. Average firing frequency histograms of a prefrontal (A; 37 trials for 'red', 54 for 'all others') and a parietal (B; 14 trials per condition) sensory-coupled cell. In these and subsequent histograms, vertical lines mark the alerting flash, the onset of the cue and the onset of the choice lights. Both units respond preferentially ($P < 0.01$) to the red cue; their activity is maximal in the early part of the delay.

(Quintana and Fuster, 1993). For the unit recording experiments, a hydraulically operated microelectrode positioner with a glass-coated Elgiloy microelectrode of an impedance between 0.7 and 1.7 m Ω at 1 kHz was mounted on one of the recording pedestals. The microelectrode was slowly lowered while the animal performed the task. The descent was halted as well-isolated unit activity was observed that merited recording (stable and well-isolated spike potentials). Spike potentials were amplified, digitized and recorded on computer disk. The characteristics of those potentials were monitored acoustically (earphones) and visually (oscilloscope). Each record contained the unit's identifying information as well as data on the location of the electrode's tip, trial events and contingencies, and response performance. Resting activity was obtained between trials to serve as baseline control activity for statistical analysis. EOG activity was also recorded for control purposes in one of the animals. During task performance, the animals were monitored by an infrared video camera to control for movements and possible strategies they might use for performance. No positional strategy was observed in either animal for mnemonic bridging of the delay period.

Histology, Unit Localization

Two to three weeks before the animals were killed, small electrolytic lesions were made in the cortical areas investigated by passage of a 100 μ A current, for 30 s, through a glass-coated Elgiloy microelectrode

Table 4
Location of differential posterior parietal units

	Area 5	Area 7	IPS
Delay-differential			
Sensory-coupled	5	4	3
Certainty-coupled	4	0	1
Direction-coupled			
Right-direction	1	4	2
Left-direction	4	4	1
Choice-differential			
Right-direction	20	15	1
Left-direction	15	8	5

(impedance \sim 30 k Ω). After completion of the experiments, the animals were killed and their brains extracted, fixed in formaline and coronally cut in 80 μ m thick sections, which were then stained with thionin to expose iron deposits from the electrolytic lesions. The estimated position of all units sampled was reconstructed on the histological sections using those lesions as points of reference.

Data Analysis

Statistical analyses and graphic displays were obtained using a Digital PDP11-53 computer. For each unit, frequency histograms (spikes/s) were constructed for each type of trial contingency. Using the average firing frequency in the 15 s preceding each trial as baseline, the differential activity with respect to baseline was calculated for each bin and averaged across all trials of the same type (i.e. color cue and contingency type). Differential unit reactions related to cue color, task event, direction of response, etc., were studied with *t*-tests for correlated means, using trial variance in the error term. Trials with different initial color cues were grouped and compared in similar manner to analyze differential unit reactions related to sensory features of the cue (i.e. cues grouped by range of wavelength: red-yellow and blue-green), response direction (i.e. cues grouped by direction of the response they indicated: red-blue and green-yellow) or degree of prediction (i.e. cues grouped by probability with which they predicted a direction: blue-yellow and red-green).

In a separate analysis, once units were classified according to their predominant differential activities, the units showing delay activity differentially related to the *sensory* aspects of the cues (i.e. one color 'preferred' to others or two wavelength-related colors 'preferred' to the other two colors) were identified. The delay activity on the trials with preferred differential activity was averaged and graphically displayed as a per-bin ratio versus the average baseline activity. Similarly, all those units were identified whose differential activity during the delay was related to the *directional* aspects of the cues (i.e. the units 'preferred' the two colors linked to one response direction over the other two indicating the opposite direction). Delay activity related to response direction was thus analyzed and graphically displayed.

Results

Prefrontal Units

A total of 258 units were recorded from four hemispheres. Table 1 shows the location of those units within the prefrontal areas explored, as well as their distribution per hemisphere. The majority of the units were located in the superior aspect of the dorsolateral prefrontal convexity (UDLC). Lower numbers of them were located in the banks and depth of the sulcus principalis (SP) and the arcuate sulcus (AS). Because of the depth and angle of the electrode's penetration, some units were also isolated in the depth of the cingulate gyrus (CG).

Thirty-two of the units, to judge by firing frequency, were not related to task performance in any way. All others showed consistent deviations from average baseline discharge during

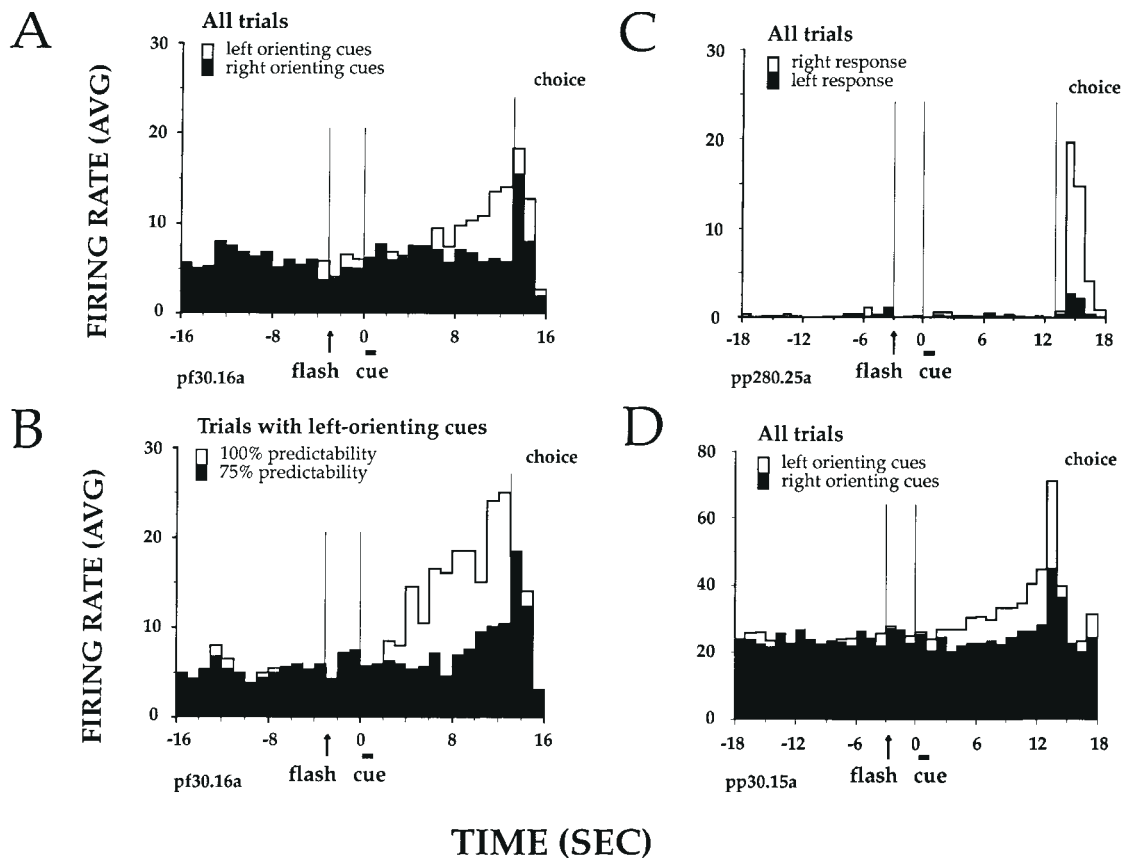


Figure 3. Direction-coupled cells. (A) Histograms from a prefrontal cell in trials with left-orienting (red and blue; eight trials) and right-orienting (green and yellow; nine trials) cues. (B) Histograms from the same cell in trials with a 100% predicting (blue; four trials) and 75% predicting (red; four trials) cue. The unit accelerates its firing, especially in the delay after a left-orienting cue (red or blue) ($P < 0.05$). The acceleration is greater ($P < 0.05$) after blue (100% predictability) than after red (75% predictability). (C) Histograms from a parietal cell (area 5) in trials with right responses and left responses (23 trials each). This unit responds preferentially ($P < 0.01$) during the choice when the response direction is to the right. (D) Histograms from a parietal unit (area 7) in trials with left (22) and right (23) orienting cues. During the delay, this cell responds preferentially ($P < 0.01$) to left-orienting cues (red and blue). The unit accelerates its firing, especially after a left-orienting cue.

one or more periods of the trial (Table 2). A significant number of those deviations (Table 2, non-differential changes) were non-specific, appeared on all trials, and were thus considered not related specifically to the sensory cues or the motor response of the task. A large proportion of units displayed non-differential reactions that spanned or occurred in more than one trial period (Table 3). Some units showed transient, mostly excitatory, responses to the alerting flash preceding each trial.

A total of 189 units (differential) were found coupled to sensory (color) features of the cues, to the response direction that those cues indicated, or to the degree of predictability of response direction, in one or more trial periods (Table 2). Most of the differential – i.e. coupled – units showed their preferential firing during one single trial period. Sensory coupling was defined as preferential excitatory response to one color or two wavelength-related colors regardless of directional connotation: red, green, yellow, green, blue, red/yellow or green/blue. It was observed during the presentation of the trial-initiating cue color and/or during the ensuing delay (Fig. 2A). Direction coupling was defined as preferential response to the two colors indicating response to the right (yellow and green) or to the left (red and blue) (Fig. 3A). It was observed during the delay and, more commonly, at the time of right or left choice. Certainty coupling was defined as greater response to the colors indicating fully predictable response direction (yellow and blue) than to the other two colors (red and green). It was most prominent during

the delay period. Figure 4 illustrates a ‘certainty-coupled’ unit. It shows preferential delay firing in those trials in which the initial cue predicts with 100% probability the direction of the correct response (i.e. yellow and blue), regardless of its direction. No relationship was found between delay firing and eye movements, as monitored by EOG in one of the animals.

Figure 5 shows the location of units showing differential delay activity of the three types described above. The figure also shows the *relative* cortical depth of units that were recorded along the same electrode track. Color- and direction-coupled units were rarely found in the same track and, in general, did not conform to an organized pattern of cortical distribution. However, several color-coupled units and ‘certainty-coupled’ units were noted to be clustered and recorded along the same electrode penetrations.

Among the units classified as color-coupled or direction-coupled, those that showed their differential firing during the delay period were grouped for separate analysis, focusing on their firing trend during that period. In the course of the delay, sensory-coupled units tended to decrease their firing (Fig. 2). Conversely, direction-coupled units exhibited progressively increasing delay firing (Fig. 3). In addition, when the differential delay firing of direction-coupled units was analyzed as a function of the direction-predictive values of cues (i.e. red versus blue, or green versus yellow, for units coupled to left or right response respectively), the increase in firing was found to be significantly

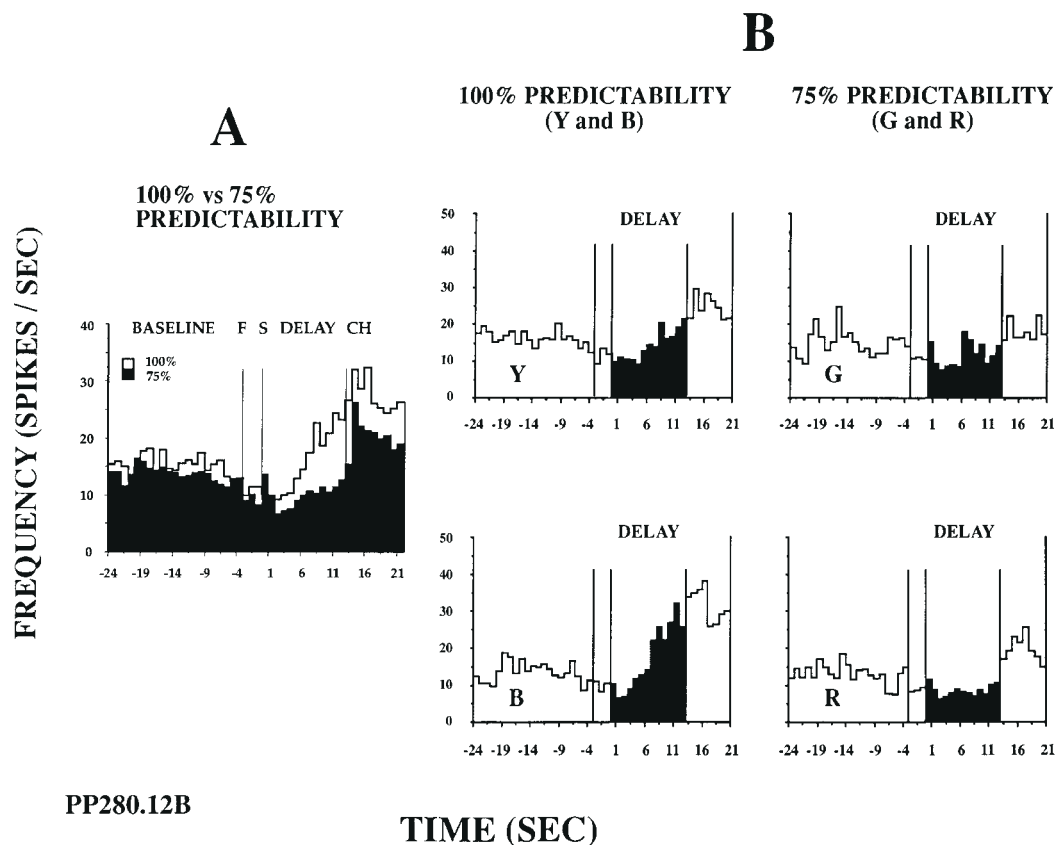


Figure 4. A prefrontal ‘certainty-coupled’ cell: (A) Delay activity was higher ($P < 0.05$) after yellow (Y; 12 trials) and blue (B; 8 trials) than after red (R; 14 trials) and green (G; 14 trials). (B) Note pronounced increasing pattern of delay firing activity only in Y and B trials (100% predictability). Note also differences in delay firing pattern between Y and R trials, or between B and G trials (colors contiguous in wavelength spectrum), as well as between Y and G trials, or between B and R trials (pairs indicating predominantly responses to right or left respectively). The unit is thus attuned to the predictability of the prospective response as conveyed by the cues, and its differential activity is independent from the contiguity in wavelength spectrum of those cues or from the direction of response they indicate.

steeper during trials with unambiguous cue colors, i.e. when the correct response could be predicted with 100% probability, than after ambiguous cues (Fig. 3). Figure 6 illustrates the results of delay-trend analysis for sensory- and direction-coupled units.

Posterior Parietal Units

A total of 223 parietal units were recorded from the two animals (four hemispheres). Their location is shown in Table 1. A significant number of the units were located in the banks and depth of the intraparietal sulcus (IPS), most of them within its anterior aspect. The range of baseline frequency in the units investigated was similar for all architectonic locations. Ten of the units investigated showed no consistent task-related firing changes. The rest showed statistically significant changes from baseline activity during one or more trial periods. Some of those changes were independent of cue-color or response direction (Table 2, non-differential changes). Most non-differential reactions occurred in more than one trial event (Table 3).

A total of 188 units showed significant firing changes from baseline that could be statistically characterized as sensory, direction or certainty coupling (Table 2, differential changes). Most units showed differential firing reactions in only one trial period. Sensory coupling, i.e. differential reaction to the sensory aspects of the cue regardless of directional meaning (e.g. to yellow and red, or to green and blue, or to one single color), was less common than in DPFC, and equally common during the cue and delay periods (Fig. 2B). However, posterior parietal units

with direction coupling – i.e. differential firing to the two colors indicating right response (green and yellow) or the two indicating left response (red and blue) – were more common than their prefrontal counterparts. Direction coupling was especially pronounced during the choice (Fig. 3C) and less so during the delay period (Fig. 3D). Differential reactions coupled to the degree of prediction of response direction indicated by the cue (i.e. greater response in trials with yellow or blue cues, which fully predicted response direction, than in those with red or green cues, which did it only partially) were especially prominent during the delay period and less common than among dorsolateral prefrontal units. As in the case of prefrontal units, no relationship was observed between delay firing changes and eye movements in parietal cells, regardless of their type.

Sensory- and direction-coupled delay units were found in approximately similar numbers in area 5, area 7 and the IPS (Table 4). No delay units related to certainty were found in area 7. The delay firing of direction- and sensory-coupled units was analyzed for temporal trend as in prefrontal units. Posterior parietal units, like prefrontal ones, increased progressively their differential direction-coupled firing (Fig. 6). Also, as with prefrontal cells, the progressive firing increase of parietal cells was found to be steeper if the correct response direction could be predicted by the animal with 100% probability. However, contrary to what we observed in DPFC, the majority of parietal sensory-coupled units exhibited a relatively flat profile of frequency change during the delay (Fig. 6).

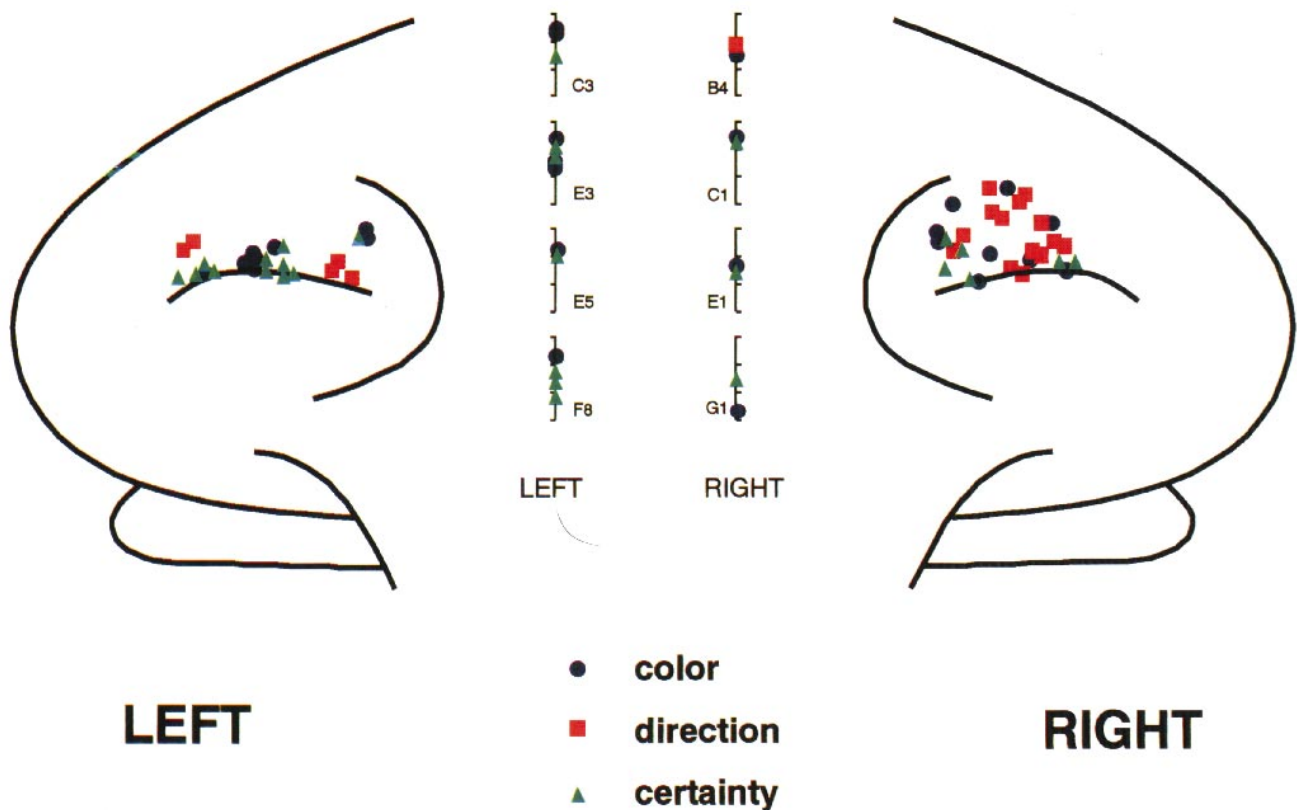


Figure 5. Topographic distribution of prefrontal units coupled to color, direction, or certainty. In the center of the figure, the relative depth is indicated of some cells recorded during the same electrode penetrations (eight penetrations, each arbitrarily labelled); 3 mm is the depth span represented for each penetration.

Discussion

In general terms, these results are evidence of a role of both prefrontal and parietal neurons in sensory-motor integration across time. Thus they provide further support to the postulated involvement of DPFC and PPC in the temporal closure of the perception-action cycle at the cortical level. Because of the behavioral paradigm utilized, these results go beyond those of the relevant studies to date, in that they point to a division of labor among cells within discrete functional domains. The sensory-coupled neurons seem to engage in active perceptual memory, commonly designated working memory. Neighboring neurons, direction-coupled, seem to engage in the less widely accepted role of motor set, also called motor attention (Fuster, 1997). Still other neurons nearby, previously unrecognized, seem attuned to the certainty, i.e. the determinacy with which a sensory stimulus will lead to a specific motor act in the near future.

The color-coupled DPFC units that are protractedly active during the delay are implicated in the retention of visual information for impending response. Their presence and our inference from it agree not only with other single unit studies but with lesion studies (Mishkin and Pribram, 1956; Fuster and Alexander, 1970; Goldman and Rosvold, 1970; Goldman *et al.*, 1971; Passingham, 1975; Bauer and Fuster, 1976; Quintana and Fuster, 1993) and imaging studies (Jonides *et al.*, 1993; Paulesu *et al.*, 1993; Petrides *et al.*, 1993; Cohen *et al.*, 1994; Swartz *et al.*, 1995; McCarthy *et al.*, 1996; Courtney *et al.*, 1997, 1998). Nonetheless, those units were here recorded from the upper dorsolateral convexity, which is not the area of preferred termination of direct fibers from inferotemporal cortex (Pandya

and Yeterian, 1985), where color memory cells are also found (Fuster and Jervey, 1982). In any case, the DPFC as a whole receives profuse inputs from several areas of associative and polymodal posterior cortex (for review, see Fuster, 1997).

We also found sensory-coupled units in PPC, although their number and proportion were smaller than in prefrontal areas. Parietal units have been found to be active in haptic short-term memory (cells in area 5 – Koch and Fuster, 1989; Zhou and Fuster, 1997) and in spatial short-term memory (cells in area 7, LIP – Gnadt and Andersen, 1988; Andersen, 1995). In contrast to prefrontal cells (Quintana *et al.*, 1988) and inferotemporal cells (Fuster and Jervey, 1982), few parietal units seem involved solely in the mnemonic retention of color. However, the present results provide considerable evidence of parietal cell involvement in prospective aspects of spatial working memory. Indeed, in PPC, direction-coupled cells were found in this study to predominate over sensory-coupled ones. Furthermore, whereas prefrontal color-coupled cells showed decreasing firing during the delay, the few color-coupled parietal cells we found generally showed temporally invariant delay discharge. On the other hand, the anticipatory, direction-coupled, parietal cells seem to mirror those with similar characteristics in the prefrontal cortex.

Direction-coupled units appear to be functionally complementary to sensory-coupled units. They are distinguished by accelerating and response-specific discharge during the delay, in anticipation of the manual response. Further, the magnitude of their accelerating firing is related to the probability with which the animal can predict the particular direction of that response. These properties implicate direction-coupled cells in two closely related functions: (i) the representation of a movement, and (ii)

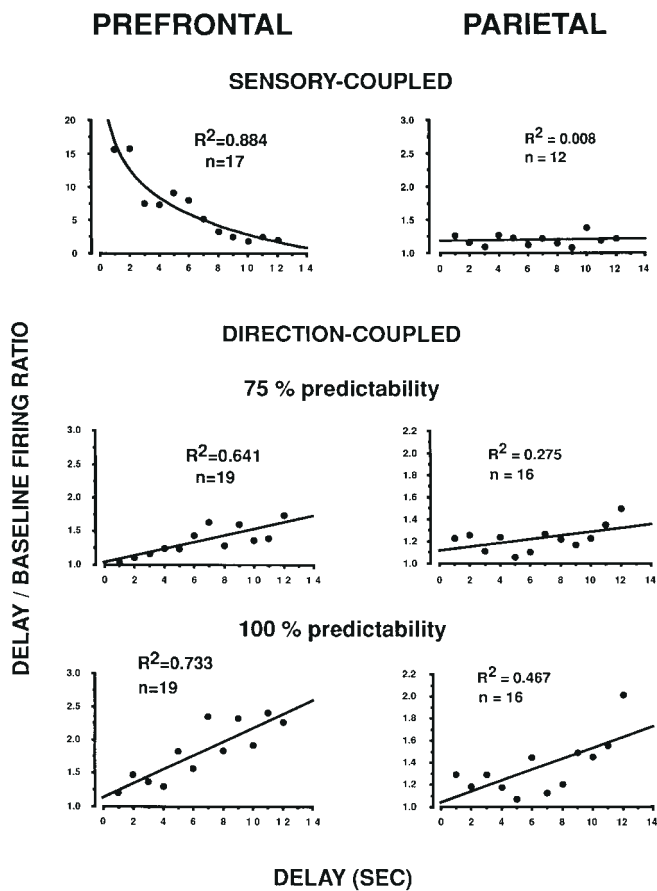


Figure 6. Average delay/baseline firing for sensory-coupled (17 prefrontal and 12 parietal) and direction-coupled (19 prefrontal and 16 parietal) cells. Note the descending firing of sensory-coupled prefrontal cells and the relatively unchanged firing of the parietal ones. Both prefrontal and parietal motor-coupled cells accelerate their firing during the delay. Note also that, in direction-coupled cells (both prefrontal and parietal), the acceleration of firing is greater when direction can be predicted with 100% probability than when direction prediction is only 75%.

the enactment of that movement. The direction-coupled cells of DPFC may be constituents of frontal networks of motor memory. As such, they would contribute to encode a particular skeletal movement within a broader scheme of action, i.e. within a larger network of frontal neurons representing the entire behavioral trial with its temporal dimension. As the cue activates it, that network would become operational. The prefrontal direction-coupled units would initiate a volley of activation, ahead of the motor action they represent, that would cascade through lower levels of the frontal hierarchy – and striatal loops – toward motor cortex. That descending process of activation, which might largely take place through parallel channels (Alexander *et al.*, 1992), would have the net effect of priming lower motor stages for the action to be ultimately released by the choice stimuli. As our results indicate, the degree of that priming may depend on the predictability of the anticipated action.

It is reasonable to relate the apparent representational and operant properties of prefrontal direction-coupled units to the well-substantiated importance of the human DPFC in the formulation and execution of plans (Blumer and Benson, 1975; Fuster, 1997). Plans are broad schemes of action with temporal order and dimensions, much as any of the trials of our task. Allowing for differences in complexity and timescale, it is a

plausible inference that action-coupled neurons, such as those found here, are the essential constituents of networks that represent and intervene in the execution of plans. Further in this line of reasoning with implications for the human, we can attempt an interpretation of ‘certainty-coupled’ cells, which are more common in DPFC than in PPC. These cells may also have a representational and an operant function. The first would be the representation of an act relatively high in the hierarchy of actions that define the temporal scheme of the trial. The operant function of ‘certainty-coupled’ cells is apparently more complex than that of direction-coupled neurons, however. In ‘certainty-coupled’ cells, the role of probability overshadows the specifics of the movement. These cells would seem to reflect not only the determinacy of the impending act but the ‘decidedness’ of the animal to act. At least in part, therefore, the ‘certainty-coupled’ neurons may constitute the neural substrate for decision-making, another of the executive functions of the human frontal cortex.

In both DPFC and PPC the close proximity of sensory-coupled and direction-coupled neurons indicates a local temporal transfer of information from a perceptual network to a motor network. Sensory-coupled cells with their ‘working memory’ and direction-coupled cells with their apparent motor-set attributes would cooperate to ensure the orderly and timely processing of information from one network to the other, and thus in the translation from perception into action.

In summary, at the level of analysis and interpretation that our behavioral paradigm permits, the results of this study provide evidence of the functional cooperation of prefrontal and posterior parietal neurons in the cross-temporal integration of behavior. The temporally bridging functions of short-term memory and preparatory set, which appear necessary for such integration, may be served by the dynamics of prefrontal-parietal networks representing spatial and motor information. The role of such networks in cognitive visuospatial behavior has been previously surmised on the basis of anatomical and other functional evidence (Goldman-Rakic, 1988; Fuster, 1995).

Notes

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Address correspondence to Dr Javier Quintana, UCLA Neuropsychiatric Institute, Room C8-846, 760 Westwood Plaza, Los Angeles, CA 90024-1759, USA.

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