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# Comparison of Effector-Specific Signals in Frontal and Parietal Cortices

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**Lawrence, Bonnie M. and Lawrence H. Snyder.** Comparison of effector-specific signals in frontal and parietal cortices. *J Neurophysiol* 96: 1393–1400, 2006. First published May 24, 2006; doi:10.1152/jn.01368.2005. We previously demonstrated that the activities of neurons in the lateral intraparietal area (LIP) and the parietal reach region (PRR) of the posterior parietal cortex (PPC) are modulated by nonspatial effector-specific information. We now report similar modulation in FEF, an area of frontal cortex that is reciprocally connected with LIP. Although it is possible that these effector-specific signals originate in LIP and are conveyed to FEF, it is also possible that these signals originate in FEF and are "fed back" to LIP. We found that signal magnitude was no larger, and onset time no earlier, in FEF compared with LIP. Moreover, effector-specific activity in FEF, but not in LIP, was largely driven by spatial prediction. These results suggest that the saccade-related effector-specific signals found in LIP do not originate in FEF. Conversely, LIP may contribute to the effector-specific signals found in FEF, but does not wholly account for them.

## INTRODUCTION

The execution of a goal-directed movement, such as a reach to a coffee cup, requires the selection of both a target (the cup) and an effector (the hand). Previously, it was thought that the posterior parietal cortex (PPC) operates in an effector-nonspecific manner (Bushnell et al. 1981), whereas the frontal cortex operates in an effector-specific manner (Goldberg and Bushnell 1981), raising the possibility that target selection is the domain of parietal cortex, whereas effector selection is the domain of the frontal cortex. More recently, however, Snyder and colleagues found evidence consistent with the role of PPC in effector selection (Calton et al. 2002; Dickinson et al. 2003). They developed a novel paradigm to isolate effector-selection signals from target-selection signals. A color cue signaling the type of movement (saccade or reach) was presented at fixation and, after a variable delay period, a spatial target signaling the goal of the movement was presented at a peripheral location. Neurons in the lateral intraparietal area (LIP) were more active when the effector cue signaled a saccade than when the effector cue signaled a reach (Dickinson et al. 2003). The reverse pattern of activity was found in neurons in the parietal reach region (PRR) (Calton et al. 2002).

It is important to emphasize that these effector-specific signals are *nonspatial*, occurring when the effector—but not the spatial target—for an upcoming movement has been specified. The presence of such nonspatial effector-specific signals in LIP and PRR is surprising not only because PPC is situated along the dorsal visual pathway, which is thought to be involved primarily in spatial processing (Ungerleider and Mishkin 1982), but also because PPC is generally thought to operate on the sensory side of the sensorimotor transformation, responding to sensory stimuli independent of the effector that is to be used to acquire those stimuli (Colby et al. 1996; Goldberg et al. 2002; Wardak et al. 2004; but see Snyder et al. 1997). It is possible, however, that the effector-specific activity found in PPC is simply the result of "top-down" influences from the frontal cortex (Fuster 1997). A potential source of the effector-specific signals found in LIP is the frontal eye field (FEF). Like LIP, FEF contains neurons that are activated when a salient visual stimulus appears in the receptive field and also when a saccade is directed to such a stimulus (Bruce and Goldberg 1985; Goldberg and Bushnell 1981; Schall 1991). Although the two areas are reciprocally connected (Andersen et al. 1985; Petrides and Pandya 1984; Schall et al. 1995; Stanton et al. 1995), FEF is generally thought to operate at a higher level in the cortical hierarchy (Felleman and Van Essen 1991) and on the motor side of the sensorimotor transformation (Goldberg and Bushnell 1981; but see, for example, Thompson and Bichot 2005).

In the present study, we examined whether effector-specific selection signals are found in FEF and, if so, whether they might be the source of similar signals found in PPC. We found effector-selection signals in FEF, but the magnitude and onset of the effector-specific signals were neither earlier nor larger in FEF than in LIP (Dickinson et al. 2003) or PRR (Calton et al. 2002). Moreover, the effector-specific signals found in FEF, unlike the effector-specific signals found in PPC, were driven largely by spatial prediction. These results suggest that the effector-selection signals found in FEF are not the source of the effector-selection signals found in LIP.

## METHODS

### *Recording procedure*

Animals were seated in a custom-designed monkey chair (Crist Instruments, Hagerstown, MD) with a fully open front that allowed for unconstrained arm movements to visual stimuli. Stimuli were back-projected by a CRT projector (Electrohome, Kitchener, Ontario, Canada) onto a touch panel (Keytec, Richardson, TX) located 25 cm in front of the animal. Unlike an LCD projector, a CRT projector casts no extraneous light, so that other than the visual stimuli, experiments took place in complete darkness in a sound-attenuated room.

FEF recordings were made from two adult male rhesus macaque (*Macaca mulatta*) monkeys. Recording chambers were placed flush with the skull (25 mm anterior and 20 mm lateral, Horsley–Clarke coordinates), contralateral to the preferred hand. The determination of

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handedness—and as a result, chamber location—was based on which hand the animal used more frequently early in training. Structural magnetic resonance imaging (MRI) was used to confirm the placement of each chamber with respect to the arcuate sulcus and also to localize recording sites (see Lawrence et al. 2005 for recording site reconstruction).

### *Stimulation procedure*

Neurons recorded within 200 microns of sites at which electrical microstimulation of $<50$ $\mu$A evoked a consistent saccadic eye movement were defined as FEF neurons (Bruce et al. 1985). To make this determination, the animal began by fixating a blue target for 400 ms. The fixation target was extinguished, and 100 ms later there occurred, with equal probability, a 70-ms interval of either stimulation or no stimulation. The fixation point reappeared 230 ms later on stimulation (biphasic, 250 $\mu$s/phase, 350 Hz, 70-ms duration) and on no-stimulation trials. The animal was rewarded on every stimulation trial, and also on every no-stimulation trial, in which the eyes remained within 4.5° of the extinguished fixation point. Because it is possible to elicit small perturbations outside of FEF, only neurons collected from stimulation cites resulting in perturbations $>2°$ were used in the analyses. Significant perturbations ($t$-test, $P < 0.05$) ranged from 2.2 to 28°, with a mean perturbation of 8.2 ± 0.3°.

### *Receptive field mapping procedure*

Spatially selective FEF neurons were then identified, and their receptive fields mapped, using a nondelayed center-out reaching task. This task required combined eye and arm movements to eccentric stimuli presented in one of eight possible directions, spaced 45° apart, at a range of three eccentricities, for a total of 24 possible targets. This mapping determined the provisional "preferred" direction (the direction with the largest response) and the "null" direction (the direction with the smallest response, with the constraint that the null direction was 180° from the preferred direction) based on the response of the neuron in the 100- to 200-ms interval after the onset of the target. An example of a response of a FEF neuron in the center-out mapping task is presented in Fig. 1. The preferred direction of the neuron is up and to the left, whereas the null direction is down and to the right. From the responses obtained 100–200 ms after target appearance in the center-out movement task, and from the size of the stimulation-evoked eye movement (FEF only), two target locations were chosen for further testing in the cue-delay-target and the target-delay-cue paradigms: one target in the preferred direction and one in the opposite (null) direction.

The preferred and null directions of spatially selective neurons were then confirmed using the target-delay-cue task (see task description below). The preferred direction of a neuron was defined as the direction associated with the largest response in any of the following three intervals of the target-delay-cue task: the early visual response (50–150 ms), the late visual response (150–250 ms) (both averaging across saccade and reach trials), and the movement-related response on saccade trials (−100 to 0 ms before the onset of the saccade). Data from 101 spatially selective FEF cells (65 from the left hemisphere of M1, 36 from the right hemisphere of M2) were recorded.

### *Cue-delay-target and target-delay-cue tasks*

A cue-delay-target trial began when the monkey fixated and reached for a centrally located blue circle. This circle turned either red or green after 500–800 ms, cueing either a saccade or reach trial (Fig. 2). (The color mapping was reversed in the second monkey.) After a variable delay (600, 900, or 1,200 ms), a blue peripheral target appeared. The monkey had 500 ms (saccade trials) or 900 ms (reach trials) to move the appropriate effector into a 6° (saccade trials) or an 8° (reach trials) window (in radius) located close to the target location.

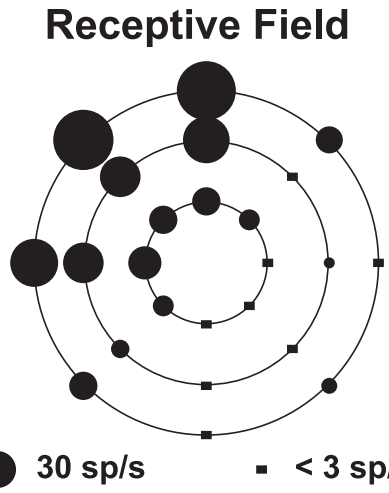


FIG. 1. Receptive field (RF) mapping. A plot of the receptive field of a frontal eye field (FEF) neuron in the center-out task. Size of the circle at each location is proportional to the firing rate of the neuron in the 100- to 200-ms interval after the onset of the target at that location, averaged across the eye and combined eye and arm movement conditions of the center-out task. Circle in the legend below the plot represents a mean firing rate of 30 spikes/s, whereas the rectangle represents a mean firing rate of $<3$ spikes/s. Eight directions were tested per eccentricity (14, 20, and 28°) for a total of 24 locations. RF and thus the preferred direction of this neuron are in the *top left* quadrant of the sampled area.

(See below for typical behavior, which far exceeded these criteria.) On any given trial, the target appeared either inside or outside the response field (RF) in the preferred or null direction of the recorded neuron. For FEF, the direction (eight possible directions, spaced 45° apart) and radial distance of the target locations was adjusted based on the size of the stimulation-evoked eye movement and on the responses in the center-out task. On cue-target trials, the target was acquired by a saccade on 92.0% of saccade trials (M1: 91.4%; M2: 93.0%) and was acquired by a reach on 83.7% of reach trials (M1: 80.8%; M2: 88.7%). In nearly 3% of these trials, the animal subsequently failed to maintain the position of the cued effector on the target location, or the position of the noncued effector on the fixation point, for the full 400 ms (M1) or 200 ms (M2) that was required. Data from these trials were not analyzed.

During FEF recording, mean saccade reaction time was 161 ± 23 ms (mean ± SD) and mean reach reaction time was 234 ± 41 ms. Saccade endpoints fell within 3.02 ± 1.62° of the visual target and reach endpoints fell within 6.29 ± 1.64°. (Animals used a splayed hand posture and "pointed" to the target with just one or two digits, allowing their other digits to contact the screen far from the target. As a result, our pressure-sensitive touch screen, equipped with a custom-made controller designed to increase temporal resolution and decrease electrical interference with single-neuron recording, transduced touch endpoints that were repeatable [SD = 1.6°] but often systematically displaced from the actual target position [mean = 6.3°].) Target-delay-cue trials were randomly interleaved with cue-delay-target trials and differed from cue-delay-target trials only with respect to the order of the stimulus presentation. That is, the target preceded the cue in target-delay-cue trials, whereas the cue preceded the target in cue-delay-target trials. A target-delay-cue trial began when the monkey fixated and reached for a centrally located blue circle. After 500–800 ms, a blue peripheral target appeared cueing the location, but not the effector, to which the monkey was to move. After a variable delay (600, 900, or 1,200 ms), the central target turned red or green, cueing either a saccade or reach trial. After the cueing at the central target, the monkey had 500 ms (saccade trials) or 1,000 ms (reach trials) to move the appropriate effector into a 6 ° (saccade trials) or an 8° (reach trials) window located close to the target location. For each task, cue-delay-



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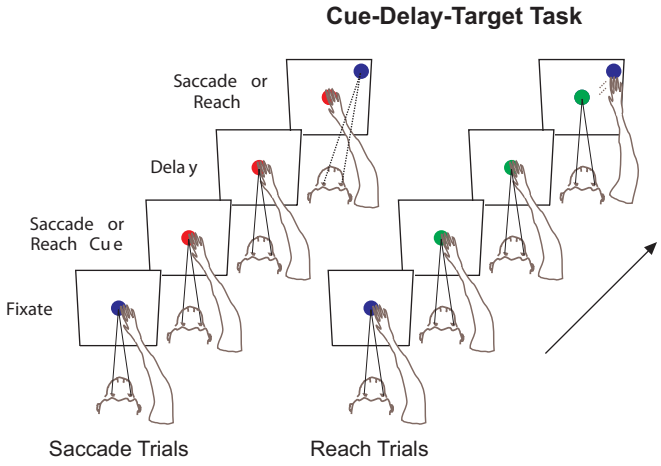


FIG. 2. Cue-delay-target task. A trial began when the monkey fixated and touched a central fixation point. After a variable interval, the blue fixation point turned red, cueing a saccade, or green, cueing a reach. (This mapping was reversed in the 2 animals.) Onset of the effector cue was followed by a variable delay period. A blue peripheral target appeared at the end of the delay, to which the monkey moved the previously cued effector. This target could appear inside or outside the RF of the recorded neuron.

target and target-delay-cue, animals performed 10 trials per direction (preferred and null) and 10 trials per effector (saccade and reach), for a combined total of 80 trials. For both tasks, correct trials were rewarded and incorrect trials (e.g., trials on which the animal moved the wrong effector, moved prematurely, moved too late, or did not move to the correct target location) were aborted (<20% of all trials).

### *Data analyses*

The responses of these 101 FEF neurons were compared with those of 66 LIP (Dickinson et al. 2003) and 138 PRR (Calton et al. 2002) neurons, recorded from the same two animals under identical conditions (with the exception that stimulation was not used in LIP and PRR). Except when otherwise noted, all recorded neurons were included in each analysis, not just those exhibiting effector-specific effects. The effector-specific response was measured in the last 300 ms of the delay period of the cue-delay-target task and significance was determined using a two-tailed *t*-test, unless noted otherwise.

At the single-cell level, the onset of the effector-specific response was defined as the time at which the activity on saccade and reach trials (evaluated at 1-ms intervals) differed by ≥1.33 SE for ≥400 ms. These onset times were calculated after smoothing, as described below. At the population level, the onset of the effector-specific response was defined as the time at which the activity on saccade and reach trials (evaluated at 1-ms intervals) first differed by ≥0.87 spikes/s (this arbitrary threshold level was 1.5-fold the peak firing rate in the 500-ms precue interval). For analysis of the onset of the effector-specific response, data were first filtered using a 191-point digital low-pass filter with a transition band spanning 20 to 32 Hz. For all other analyses, no filtering was used.

In the target-delay-cue task, the onset of the visual response at the single-cell level was defined as the time at which the activity (evaluated at 1-ms intervals) on trials in which the target appeared in the RF differed from zero by ≥2.5 SE for ≥25 ms. These onset times were calculated after smoothing, as described above. The criteria for determining the onset of a neuronal response were chosen to minimize the number of false positives while maintaining as much sensitivity as possible. Because responses to targets in the receptive field in the target-delay-cue task were much more robust than responses to color changes outside the classical receptive field in the cue-delay-target task, we used a more stringent criterion in the former case, compared with the latter. At the population level, the onset of the visual response was defined as the time at which the activity on trials in which the target appeared in the RF differed from trials in which the target appeared out of the RF by ≥2.0 spikes/s (this arbitrary threshold level was 1.5-fold the peak firing rate in the 500-ms precue interval). The spatial response in the target-delay-cue task was measured in the last 300 ms of the delay period of the target-delay-cue task. Because the populations of neurons of both monkeys exhibited similar patterns of activity within each area, data were pooled across animals, with the exception of the spatial prediction data collected from a single monkey.

## RESULTS

Two rhesus macaque monkeys performed interleaved saccade and reach trials of the *cue-delay-target* task (Fig. 2). In this task, a color cue signaling the type of trial (saccade or reach) is presented at fixation and, after a variable delay period, a spatial target signaling the goal of the movement is presented at a peripheral location. On any given trial, targets were presented either inside or outside the RF of the recorded neuron. The activity of FEF neurons ($n$ = 101) was recorded in the cue-delay-target task and compared with the activity recorded from LIP ($n$ = 66) (Dickinson et al. 2003) and PRR ($n$ = 138) (Calton et al. 2002) neurons in the same task and in the same two animals.

### *Single-cell responses*

Examples of responses of FEF, LIP, and PRR neurons in the cue-delay-target task are presented in Fig. 3 (*left*, *middle*, and *right*, respectively). For each neuron, the activity on saccade trials (red) and reach trials (green) is aligned on the presentation of the target. Because these data are aligned on, but do not include, the response to the presentation of the target, the

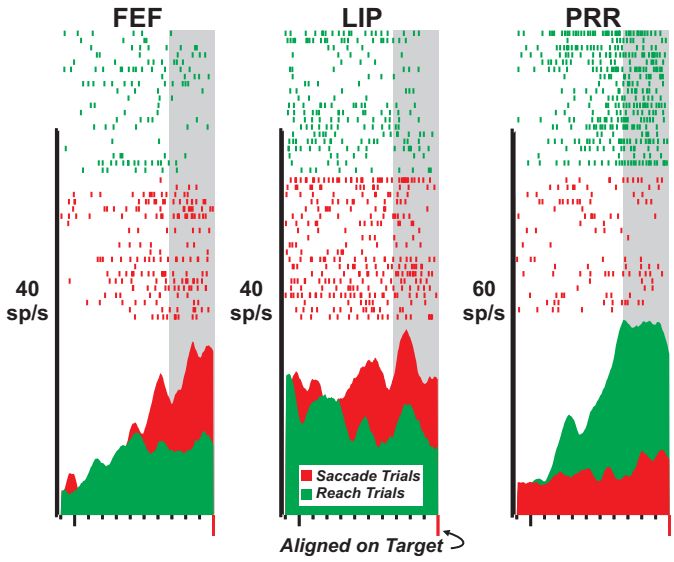


FIG. 3. Activity of single FEF, lateral intraparietal area (LIP), and parietal reach region (PRR) neurons (*left*, *middle*, and *right*, respectively) for saccade (red) and reach (green) trials of the cue-delay-target task. Response of each neuron was effector specific, with greater activity on saccade trials than on reach trials in FEF and LIP, and greater activity on reach trials than on saccade trials in PRR. Onset of the effector-specific response was earlier in the LIP and PRR neurons than in the FEF neuron. Shaded region represents the 300-ms interval before the onset of the target in which delay-period activity was averaged. Rasters and histograms are aligned on the presentation of the target. RF of the FEF neuron was shown in Fig. 1.



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differences in activity that appear in this figure should be entirely attributed to information about the chosen effector, and not the spatial goal of the upcoming movement. This figure reveals that the response of each of these neurons was effector specific, that is, the activity in the 300-ms interval before the onset of the target (gray region) depended on the trial type. The activities of both the FEF and the LIP neuron were significantly greater on saccade trials than on reach trials (by 8.9 spikes/s; $P < 0.01$ and 6.7 spikes/s; $P < 0.05$, respectively), whereas the activity of the PRR neuron was significantly greater on reach trials than on saccade trials (by 21.1 spikes/s; $P < 0.0001$). This specificity emerged much later in the FEF neuron (434 ms after cue presentation) than in either the LIP neuron (244 ms) or the PRR neuron (209 ms). Significant effector-specific modulation in the cue-delay-target task, similar to that shown in Fig. 3, was found in 22% of FEF neurons (22 of 101), 30% of LIP neurons (20 of 66), and in 40% of PRR neurons (54 of 138). In contrast, very few neurons in each area demonstrated significant modulation for the nonpreferred effector (i.e., reaches in FEF and LIP; saccades in PRR) in the cue-delay-target task. Significant nonpreferred modulation was found in only 5% of FEF neurons (5/101), 5% of LIP neurons (3/66), and in 11% of PRR neurons (15/138).

### *Population responses*

The population-averaged time courses of activity in the cue-delay-target task, aligned on the presentation of the effector cue, for FEF, LIP, and PRR, respectively, are presented in Fig. 4. As in Fig. 3, the differences in the activity being shown should be entirely ascribed to information about the chosen effector, and not the spatial goal of the upcoming movement, because that goal had not yet been specified. (Responses to the appearance of the target, not shown in these figures, will be described in a subsequent report.) In FEF, the delay-period response on saccade trials was 1.6 ± 0.5 spikes/s greater than the response on reach trials ($P < 0.01$). Effector-specific responses did not differ systematically between FEF cell types. We divided our sample of neurons into visual (31), visuomovement (30), and movement (26) categories (Bruce and Goldberg 1985; Lawrence et al. 2005). The magnitude of effector-specific modulation showed no significant differences ($P > 0.25$) across cell types (visual: 1.5 ± 0.9 spikes/s; visuomovement: 2.4 ± 0.8 spikes/s; movement: 0.7 ± 1.2 spikes/s).

In LIP, the delay-period response on saccade trials was 2.0 ± 0.6 spikes/s greater than the response on reach trials ($P < 0.01$), and in PRR, the response on reach trials was 4.0 ± 0.7 spikes/s greater than the response on saccade trials ($P < 0.0001$). The magnitude of the effector-specific response in FEF was not significantly smaller than the effector-specific response in LIP ($P > 0.5$), but was significantly smaller than the effector-specific response in PRR ($P < 0.01$).

The delay-period response in the cue-delay-target task differed from FEF to PPC in other ways as well. In LIP and PRR, the response to the nonpreferred effector was minimal. In the last 300 ms of the delay period, the response on reach trials in LIP averaged only 1.0 ± 0.5 spikes/s above baseline, and the response on saccade trials in PRR averaged only 0.9 ± 0.5 spikes/s above baseline. The response on reach trials in FEF, in contrast, averaged 3.5 ± 0.7 spikes/s above baseline. The delay-period response to the preferred effector can be thought of as the summation of two independent responses, one that is independent of effector, or effector *nonspecific* (activity on nonpreferred trials), and one that is dependent on effector, or effector *specific* (activity on preferred trials − activity on nonpreferred trials). We calculated the percentage of the delay-period response for each area that is effector specific [effector specific response/(effector response + effector nonspecific response)]. This calculation revealed that, whereas the delay-period responses in LIP and PRR are 66 and 81% effector specific, respectively, the delay-period response in FEF is only 31% effector specific.

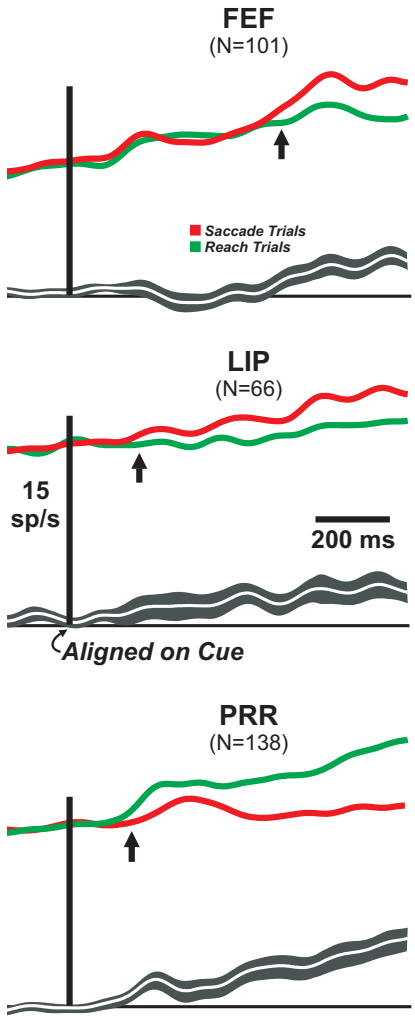


FIG. 4. Population-averaged time courses of activity for saccade (red) and reach (green) trials of the cue-delay-target task for FEF, LIP, and PRR (*top*, *middle*, and *bottom*, respectively), aligned on the presentation of the effector cue. Response of each of these populations was effector specific, with greater delay activity on saccade trials than on reach trials in FEF and LIP, and greater activity on reach trials than on saccade trials in PRR. Onset of the effector-specific response (represented by an arrow in each plot) in both LIP and PRR was hundreds of milliseconds earlier than the onset in FEF. Traces at the *bottom* of each plot represent the mean difference between saccade and reach trials (*white trace*) ± 1 SE (*gray trace*). For display purposes only, the data were smoothed using a digital low-pass filter with a −3-dB point of 9 Hz after the divergence points were determined.

### *Onset of the effector-specific response*

Yet another difference across areas was that effector-specific response emerged later in FEF than in LIP or PRR. At the



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population level, the latency of the effector-specific response was 166 ms in PRR and 185 ms in LIP, but 562 ms in FEF (arrows in Fig. 4). By itself, this does not establish that effector specificity arises earlier in the parietal areas than in FEF. It is conceivable that very early effector-specific signals appear in a small fraction of FEF neurons. Although such early signals may not be evident at the population level, they may nevertheless be sufficient to provide "top-down" signals to the parietal cortex. To test this possibility, we measured the latency of effector-specific responses in individual neurons. A statistically significant divergence occurred in 13% (13/101) of FEF cells, 20% (13/66) of LIP cells, and 19% (26/138) of PRR cells. Cumulative histograms of the individual divergence times for each region are overlaid in Fig. 5*A*. The time at which 10% of neurons became effector specific was much earlier for parietal neurons (199 and 169 ms, respectively, for PRR and LIP) than for FEF neurons (299 ms). When considering only those neurons with significant effector-specific responses, the time at which 10% of these neurons became effector specific was also earlier for parietal neurons (96 and 194 ms, respectively, for LIP and PRR) than for FEF neurons (227 ms). Moreover, in both analyses, the neurons with the earliest divergence times were found in LIP, not in FEF. These data clearly rule out the hypothesis that effector specificity originates in FEF.

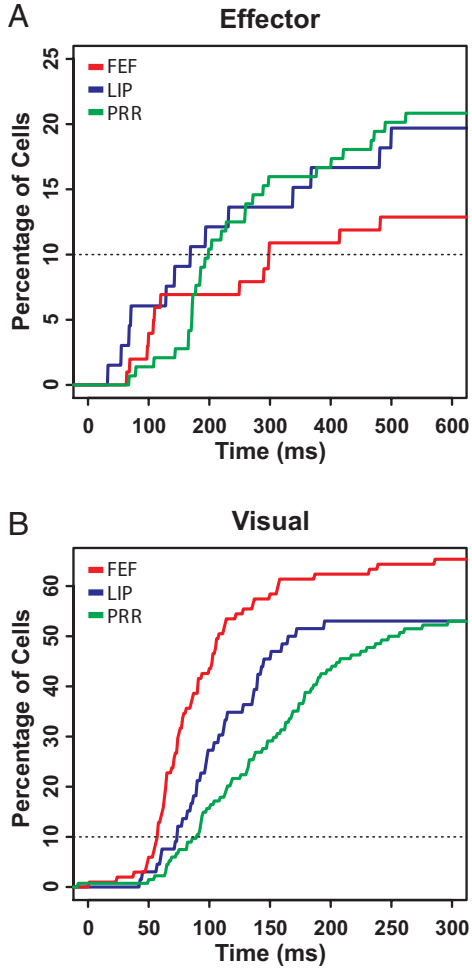


FIG. 5. Cumulative histograms of divergence times in single neurons. *A*: time at which 10% of neurons became effector specific in the cue-delay-target task was much earlier for parietal neurons (199 and 169 ms, respectively, for PRR and LIP) than for FEF neurons (299 ms). *B*: time at which 10% of neurons became visually responsive in the target-delay-cue task was earlier for FEF neurons (58 ms) than for either LIP (74 ms) or PRR neurons (90 ms).

### *Onset of the visual response*

Is it possible that the delayed onset of the effector-specific response in FEF merely resulted from a sluggish sample of FEF neurons with generally longer latencies than the sample of PPC neurons?

To test this possibility, we quantified the latency of the response to the onset of the target in the *target-delay-cue task* (see METHODS for a description of the task) in FEF, LIP, and PRR. At the population level, the latency of the visual response was 50 ms in FEF, 52 ms in LIP, and 60 ms in PRR. There was a statistically significant divergence in 72, 59, and 62% of FEF, LIP, and PRR neurons, respectively. Cumulative histograms of the individual visual response times for FEF, LIP, and PRR (red, blue, and green, respectively) are overlaid in Fig. 5*B*. The time at which 10% of neurons became visually responsive was earlier for FEF neurons (58 ms) than for either LIP (74 ms) or PRR neurons (90 ms). Thus even though the onset of the effector-specific response in FEF was no earlier than the effector-specific response in PPC, the onset of the visual response was no later in FEF than in PPC.

### *Effector and spatial responses*

For comparison across cortical regions, we normalized the effector-specific delay-period activity evoked in the cue-delay-target task by the spatial delay-period activity evoked in the target-delay-cue task. All three areas showed strong spatial tuning. Delay-period activity in the target-delay-cue task was significantly greater when the target appeared inside compared with that outside the RF in FEF ($4.5 \pm 0.9$ spikes/s; $P < 0.0001$), LIP ($5.2 \pm 1.0$ spikes/s, $P < 0.0001$), and PRR ($9.5 \pm 1.3$ spikes/s, $P < 0.0001$). A comparison of effector signals (in the cue-delay-target task) with spatial signals (in the target-delay-cue task) reveals that, in FEF, effector information was 35% as effective as spatial information (an evoked response of 1.6 spikes/s compared with 4.5 spikes/s) in evoking a delay-period response. In LIP and PRR these values were 38% (2.0/5.2) and 42% (4.0/9.5), respectively. Thus the effector-specific responses in LIP and PRR were as great as or greater than the effector-specific response in FEF even when normalized to the spatial responses in each region.

The results presented thus far are summarized in Table 1. Although the responses of each population were effector specific, the effector-specific response was no more prominent in FEF than in PPC on all measured accounts. The percentage of cells in each area with effector-specific responses, the magnitude and timing of those effector-specific responses, the magnitude of effector-nonspecific responses, and the ratio of effector-specific responses to spatial responses in each area are all inconsistent with the idea that saccade-related effector-specific responses originate in FEF.

### *Spatial prediction*

Effector-specific delay-period activity in LIP and PRR occurs even in the absence of an explicit spatial target (see Fig. 4). Previous reports tested, and firmly rejected, the possibility



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TABLE 1. *Summary of effector-specific and -nonspecific responses in FEF, LIP, and PRR*

| Area | Preferred Effector | Effector-Specific | | Effector-Nonspecific Response, spikes/s | Onset of Effector Specificity, ms | Sustained Spatial Response (Effector/Spatial) |
|---|---|---|---|---|---|---|
| | | Cells (*n*) | Response, spikes/s | | | |
| FEF | Saccade | 22% (101) | 1.6 | 3.5 | 562 | 4.5 spikes/s (35%) |
| LIP | Saccade | 30% (66) | 2.0 | 1.0 | 185 | 5.2 spikes/s (38%) |
| PRR | Reach | 40% (138) | 4.0 | 0.9 | 166 | 9.5 spikes/s (42%) |

that this activity is related to an internally generated trial-by-trial prediction of where the target might appear (Calton et al. 2002; Dickinson et al. 2003). However, this explanation might apply to delay-period activation found in FEF. The notion here is that a prediction that the target would appear within the RF of a particular neuron could cause that neuron to be active during the delay period (provided, of course, that the appropriate effector had been cued at the start of the trial). In fact, related effects were previously reported in FEF (Umeno and Goldberg 2001) and downstream of FEF in the superior colliculus (Basso and Wurtz 1997, 1998).

To test this possibility we used the manipulation of spatial prediction reported by Dickinson and colleagues (2003). We presented three different blocks of the cue-delay-target task. To look for effects of spatial prediction, we presented long blocks of trials in which targets appeared both inside and outside the RF ("preferred and null"), only inside the RF ("preferred"), or only outside the RF ("null"). If spatial prediction was at play, there should have been greater delay-period activity in the preferred block than in the preferred and null block and no delay-period activity in the null block. Additional data from 12 FEF neurons, prescreened for effector-specific delay-period activity, were collected from one animal. The preferred and null block was always performed first, followed by either the null and then the preferred block or the preferred and then the null block. Each block consisted of 60 (30 saccade and 30 reach) cue-delay-target trials. Because a number of trials were necessary for the animal to become familiar with the target location(s) in a particular block, the analysis excluded the first 10 trials of each block.

An example of an FEF neuron in the preferred, preferred and null, and null blocks (*left*, *middle*, and *right*, respectively) of the cue-delay-target task is presented in Fig. 6. The activity on saccade trials was significantly greater than the activity on reach trials for preferred (31.5 ± 5.1 spikes/s; $P < 0.0001$), preferred and null (16.0 ± 6.1 spikes/s; $P < 0.05$), and null blocks (10.5 ± 3.5 spikes/s; $P < 0.01$). The effector-specific response in the preferred block was significantly greater than the effector-specific response in both the preferred and null block ($P < 0.05$) and the null block ($P < 0.001$). The decrease in the effector-specific response from preferred to null blocks is consistent with the modulation of the effector-specific response by spatial prediction.

Population-averaged responses are presented in Fig. 7*A*. Significant effector-specific responses were found in all three blocks ($P < 0.05$). The effector-specific response in the preferred block (left) was 3.1 ± 1.7 spikes/s greater than the effector-specific response in the preferred and null block (center; $P < 0.05$, one-tailed) and 6.1 ± 2.3 spikes/s greater than the effector-specific response in the null block (right; $P < 0.05$, one-tailed). The decrease in the effector-specific response from the preferred to the null block is consistent with modulation by spatial prediction. The presence of an effector-specific response in the null block, however, suggests that effector specificity is not *entirely* dependent on spatial prediction.

Time courses of the predictive effects in FEF and LIP are compared in Fig. 7*B*. Each data point represents the difference

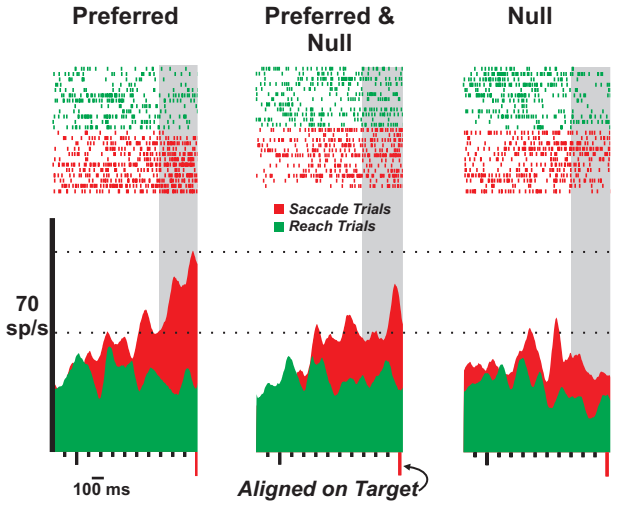


FIG. 6. Response of a single FEF neuron in the preferred, preferred and null, and null blocks (*left*, *middle*, and *right*, respectively) of the spatial prediction manipulation of the cue-delay-target task. Although the response in each block was effector specific, with greater activity for saccade than for reach trials, the magnitude of the effector-specific response decreased from preferred to null blocks, consistent with spatial prediction. Rasters and histograms are aligned on the presentation of the target.

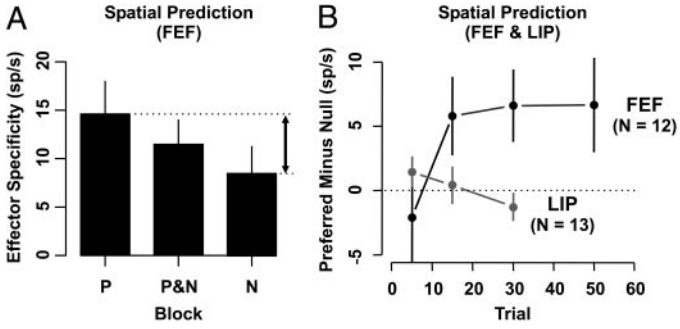


FIG. 7. *A*: response of a sample of 12 FEF neurons decreased from the preferred (P) to preferred and null (P&N) to null blocks (N) of the cue-delay-target task. These results demonstrate that the effector-specific response in FEF was modulated, at least in part, by spatial prediction. The arrow represents the statistically significant difference in the effector-specific response between preferred and null blocks ($P < 0.05$). *B*: this difference is plotted across trials of the cue-delay target task for FEF and LIP. Effector-specific response of FEF neurons was clearly modulated by spatial prediction, with activity that was significantly greater than zero after only 15 trials. In contrast, the effector-specific response of LIP neurons was not modulated by spatial prediction, with activity remaining around zero across trials.



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between preferred (P) and null (N) blocks in the effector-specific response. In FEF, this difference started around zero but increased quickly, deviating significantly from zero and reaching asymptotic levels after only 15 trials ($P < 0.05$). This indicates that, over the course of 15 trials, the animal developed a prediction regarding the location in which a target would be presented. It should be noted that this prediction is effector specific; the effector-*non*specific response (reach preferred − reach null) failed to deviate significantly from zero across trials (data not shown). In contrast to FEF, neither the effector-specific (Fig. 7*B*) nor the effector-nonspecific response (not shown) deviated significantly from zero across trials in LIP. These results reveal an important qualitative difference in the effector-specific responses of FEF and LIP. Whereas the effector-specific response in FEF is driven by both spatial and nonspatial signals, the effector-specific response in LIP is driven by only nonspatial signals.

## DISCUSSION

In the present study, we examined whether neurons in FEF were effector specific and, if so, whether these effector-specific signals might exert a "top-down" influence on LIP. Although Goldberg and Bushnell (1981) reported that FEF neurons were effector specific in the presence of explicit spatial information, we now report that FEF neurons are effector specific even in the absence of explicit spatial information. There was, however, no evidence that these effector-specific signals originate earlier in FEF than in PPC (Fig. 5*A*). To the contrary, we found that the effector-specific signals in PPC were larger in magnitude, present in more neurons, and appeared earlier than the effector-specific signals in FEF (Table 1). In particular, only three quarters as many cells were effector specific in FEF compared with LIP; the population-averaged effect was only 80% as large in FEF as in LIP, and only 69% as large when normalized to sustained spatial activity; and the onset of specificity was about 400 ms earlier in LIP than in FEF. In contrast, the response to explicit spatial information occurred in FEF as early as or earlier than that in LIP (Fig. 5*B*). Finally, effector-nonspecific activity was more than threefold larger in FEF than in LIP, and effector-specific activity in FEF included large spatially predictive signals that were not present in LIP. Taken together, these data rule out the hypothesis that effector-specific signals found in LIP reflect a "top-down" influence from FEF.

The present results differ from those of a recent human functional magnetic resonance image (fMRI) experiment by Connolly and colleagues (2002) in which preparatory activity was found in FEF but not in the intraparietal sulcus (IPS), which includes the putative human homologue of LIP. There were, however, important differences in the design of the two experiments that could account for the differences in results. The present experiment required selection between two effector systems (saccade or reach), whereas the fMRI experiment required selection between two types of saccades (pro- or antisaccade). It is conceivable that these two types of selection processes, one between effectors and one within effector, have distinct neuronal correlates. Moreover, the fMRI experiment used a "gap" paradigm in which the offset of the fixation point precedes the onset of a peripheral target (Fischer and Weber 1993). In monkeys, this manipulation is associated with an increase in neuronal activity not only in FEF (Dias and Bruce 1994) and SC (Dorris et al. 1997), but also in LIP (Ben Hamed and Duhamel 2002). Thus the lack of modulation in human IPS during the gap period is somewhat surprising. A recent fMRI study (DeSouza et al. 2003), the design of which was very similar to the experiment just described, except that the fixation point was not terminated before the onset of the peripheral target (resulting in an "overlap" task rather than a "gap" task), suggests that human IPS is modulated during the selection of a saccade. These results raise the possibility that the presence of a gap period in the study by Connolly et al. abolished selection-related signals in human parietal cortex. The differences between this study and the current study may also reflect the different species and/or different methodologies (single-neuron recording vs. fMRI).

Although the present results demonstrate that effector-specific activity does not originate in FEF, it is nevertheless possible that effector-specific activity originates elsewhere in the frontal lobe. An area specifically hypothesized to play a role in top-down control is the dorsolateral prefrontal cortex (Fuster 1997). Work from Goldman-Rakic's laboratory does not support this hypothesis, suggesting instead that the functional relationship between area LIP and areas FEF and the dorsolateral prefrontal cortex is reciprocal (Chafee and Goldman-Rakic 1998, 2000). Other evidence implicates the supplementary eye fields (SEFs) as a possible source of selection signals. Coe and colleagues (2002) compared activity in LIP, FEF, and SEF during the preparatory period of a "free-choice" paradigm, in which monkeys freely chose to direct a saccade toward one of two targets. Whereas the magnitude and the onset of the selection responses in LIP and FEF were similar, the selection response was both earlier and larger in SEF. Whereas the study of Coe and colleagues addressed spatial selection rather than effector selection, the results are compatible with the idea that saccade-selection signals may originate in SEF. Of course, our results are also compatible with the hypothesis that nonspatial effector-specific signals arise de novo in LIP from relevant sensory inputs and contextual cues.

Neurons in FEF are known to anticipate the location of an upcoming saccade target based on previous experience (Bruce and Goldberg 1985; Umeno and Goldberg 2001). We manipulated the probability that a target would appear inside or outside the RF of a neuron to determine whether this anticipation or prediction could underlie effector-specific responses in FEF. We hypothesized that if spatial prediction was at play, activity would be greatest for blocks in which the target consistently appeared inside the RF, least for blocks in which the target consistently appeared outside the RF, and intermediate for blocks in which the target could appear either inside or outside the RF (Dickinson et al. 2003; Umeno and Goldberg 2001).

The results of this manipulation demonstrate that effector-specific responses in FEF can be evoked by implicit spatial information (Fig. 7*A*). The source of the spatially predictive signals in FEF (Umeno and Goldberg 2001) and SC (Basso and Wurtz 1997) remains unknown. In contrast, in LIP, the results of the identical manipulation demonstrate that effector-specific responses are not evoked by implicit spatial information. Although anticipatory or predictive responses have been reported in LIP, these responses occurred only when there was certainty that a target for an upcoming saccade would appear at a particular location (Colby et al. 1996). In the spatial prediction



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manipulation, because saccade and reach trials were interleaved, the probability of the appearance of a target for a saccade was only 50% even in the null and the preferred blocks. We found that spatial prediction does not occur under these circumstances and, as a result, cannot account for the effector-specific responses found in LIP in mixed blocks.

The effector-specific signals in FEF and LIP are qualitatively different. In addition to a difference in magnitude and timing, FEF but not LIP contains substantial nonspecific modulation, and the effector-specific modulation in FEF, unlike the modulation in LIP, shows a pronounced effect of spatial prediction. Thus FEF appears to combine a signal encoding spatial prediction with an effector-specific signal from the parietal cortex, resulting in modulation in FEF that is not inconsistent with a motor preparation signal.

It is interesting that LIP, in contrast to FEF, shows so little spatial modulation during the delay period of the cue-delay-target task (compare Colby et al. 1996). One possible interpretation of this finding is that signals in LIP represent the task instruction or task rule itself (e.g., red = saccade trial; green = reach trial). Whereas abstract rules are generally thought to be represented in prefrontal cortex (e.g., Wallis et al. 2001), recent research from our laboratory suggests that, under some circumstances, abstract rules may be represented in PPC (Stoet and Snyder 2004). In that study, cells representing different rules were interspersed within areas. The coding in the present study is much more straightforward: neurons that increase their firing for the saccade task compared with the reach task are segregated by area. It is conceivable that differences in the complexity of coding between the two studies reflect differences in the complexity of the paradigms. Future research will be required to determine whether the effector-specific signals in parietal cortex reflect an abstract rule and, furthermore, whether such rule-related signals may be found elsewhere in prefrontal cortex.

In summary, the present results support the hypothesis that posterior parietal cortex is involved in the nonspatial effector-specific selection processes (Calton et al. 2002; Dickinson et al. 2003) and contradicts the hypothesis that these processes reflect a top-down influence from FEF.

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