

Selection and Maintenance of Spatial Information by Frontal Eye Field Neurons

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Voluntary attention is often allocated according to internally maintained goals. Recent evidence indicates that the frontal eye field (FEF) participates in the deployment of spatial attention, even in the absence of saccadic eye movements. In addition, many FEF neurons maintain persistent representations of impending saccades. However, the role of persistent activity in the general maintenance of spatial information, and its relationship to spatial attention, has not been explored. We recorded the responses of single FEF neurons in monkeys trained to remember cued locations in order to detect changes in targets embedded among distracters in a task that did not involve saccades. We found that FEF neurons persistently encoded the cued location throughout the trial during the delay period, when no visual stimuli were present, and during visual discrimination. Furthermore, FEF activity reliably predicted whether monkeys would detect the target change. Population analyses revealed that FEF neurons with persistent activity were more effective at selecting the target from among distracters than neurons lacking persistent activity. These results demonstrate that FEF neurons maintain spatial information in the absence of saccade preparation and suggest that this maintenance contributes to the selection of relevant visual stimuli.

Introduction

Attention dramatically impacts visual perception, selecting signals for enhanced processing from among a continual flood of visual input. Although attention can be captured reflexively by stimulus-driven factors such as abrupt visual onsets (Yantis and Jonides, 1984), these effects can be overridden by endogenous, or “top-down,” attention, often directed according to information held in short-term, or “working,” memory (Desimone and Duncan, 1995). Evidence from human subjects points to an overlapping network of frontal and parietal brain regions underlying both spatial working memory and attention that includes the frontal eye field (FEF) in prefrontal cortex (Corbetta et al., 2002). The FEF has a well established role in the voluntary control of saccadic eye movements. Microstimulation of the FEF using high currents evokes fixed-vector saccades (Robinson and Fuchs, 1969; Bruce et al., 1985), and FEF neurons are tuned to the direction and amplitude of impending saccades (Bruce and Goldberg, 1985). In addition, many FEF neurons are modulated during memory-guided saccade tasks (Bruce and Goldberg, 1985; Sommer and Wurtz, 2000). During these tasks, in which subjects make delayed saccades to previously cued locations in space, many FEF neurons exhibit spatially selective persistent activity. In addition to its role in saccades, several recent studies have determined that the FEF is involved in the control of covert spatial attention (Moore and Fallah, 2001; Moore and Armstrong, 2003;

Thompson et al., 2005; Wardak et al., 2006). Thus, given observations that FEF neurons both exhibit persistent spatial activity and play a role in attention, the FEF provides an ideal area to explore the role of persistent activity in the general maintenance of spatial information and its relationship to the deployment of spatial attention.

We recorded neuronal activity in the FEF in monkeys trained to remember cued locations in order to detect changes in a target stimulus embedded among distracters in a task that did not involve saccades. Monkeys maintained fixation and used a manual lever to indicate whether the target underwent a change of orientation across two flashed presentations of a stimulus array (see Fig. 1A). Similar tasks have been shown to cause “change blindness,” a failure to detect localized stimulus changes when they occur simultaneously with a global visual transient, in both humans (Rensink, 2002) and monkeys (Cavanaugh and Wurtz, 2004). However, directing attention to the changing stimulus can prevent change blindness (Rensink et al., 1997; Simons, 2000). We found that FEF neurons persistently encoded the cued location throughout the trial during the delay period, when no visual stimuli were present, and during visual discrimination. Furthermore, FEF activity reliably predicted whether monkeys would detect the target change. Population analyses revealed that FEF neurons with persistent activity were better at selecting the target from among distracters than neurons lacking persistent activity. These results demonstrate that FEF neurons maintain spatial information in the absence of saccade preparation and suggest that this maintenance contributes to the selection of relevant visual stimuli.

Materials and Methods

General and surgical procedures. Two male rhesus monkeys (*Macaca mulatta*, 7 and 12 kg) were used in these experiments. All experimental procedures were in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*, the Society for Neuroscience Guidelines and Policies, and Stanford University Animal Care and Use Com-

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mittee. General surgical procedures have been described previously (Graziano et al., 1997). Each animal was surgically implanted with a titanium head post and a scleral eye coil. Surgery was conducted using aseptic techniques under general anesthesia (isoflurane), and analgesics were provided during postsurgical recovery. Structural magnetic resonance imaging was performed to locate the right arcuate sulcus in each monkey for the placement of a recording chamber in a subsequent surgery. A craniotomy was performed on each animal, allowing access to the FEF on the anterior bank of the arcuate sulcus.

Visual stimuli and behavior. Throughout the experimental session, monkeys were seated in a primate chair equipped with a manual response lever. Throughout all experiments, eye position was monitored with a scleral search coil with a spatial resolution of $\ll 0.1^\circ$ (Armstrong et al., 2006) and was digitized at 200 Hz. Monkeys were required to maintain fixation throughout the course of visual stimulus presentation. Breaks in fixation before the trial was completed were considered aborted trials and were not included in the data analysis. Monkeys were trained to fixate within a 2.3–4.9° diameter error window surrounding a central spot (0.6° diameter) and depress the lever to initiate an experimental trial. At 50–515 ms after fixation, a circular cue stimulus (1.2° diameter) was presented for 120–270 ms (“cue” epoch), indicating the target location in an upcoming array. A delay period of 600–1600 ms followed the cue (“delay period” epoch), after which a circular array comprising six circular square-wave grating stimuli (2.5–4° diameter; 0.71–0.91 cycles/°; 0.49–0.95 Michelson contrast) was flashed twice. The first flash of the array (“flash 1” epoch) lasted 285–290 ms and was followed by a 120–235 ms period during which only the fixation point remained on the screen (“interflash interval” epoch), and then the array was flashed a second time for 270 ms (“flash 2” epoch). If the target item changed orientation (20–90° rotation) between the two flashes of the array (change condition), monkeys were required to release the lever within 600 ms (monkey 1) or 1000 ms (monkey 2) after the onset of the second flash of the array to receive a juice reward. In contrast, if the target item did not change orientation between the two flashes (no-change condition), the monkeys were required to continue to depress the lever throughout the response window to be rewarded. A subset of uncued “probe” trials were included, occurring on randomly selected trials with a frequency of 0–10% for a given experiment. Probe trials had identical event timing as normal experimental trials; however, on the probe trials, the cue was not presented, and the screen was left blank during this interval. Neuronal responses on probe trials were excluded from the data analyses reported here.

On a given trial, the cue was equally likely to appear at any of the six array locations, and change and no-change trials were equally likely to occur. Each stimulus in the array was oriented at one of two angles, orientation A or orientation B, determined before the experiment began. On each trial, the orientations of the five distracter gratings were randomly assigned to either orientation A or B. The target grating was assigned to orientation A on half the trials and orientation B on the other half of trials. On change trials, the second flash of the target grating changed orientations (either A to B or B to A), whereas for no-change trials, the target grating remained the same. Orientation changes only occurred at the target location. All cue location, change and no-change, and target orientation conditions were pseudorandomly interleaved and were controlled by the CORTEX system for data acquisition and behavioral control. Each array stimulus was equidistant from the fixation point (3.6–16.8° visual angle), and each stimulus was separated from its neighbors by 60° theta. During each experiment, the array was adjusted so that one stimulus was positioned inside the response field (RF) of the FEF neuron being recorded. All visual stimuli were displayed on a liquid crystal display monitor (52 cm vertical \times 87 cm horizontal) positioned 57 cm in front of the monkey, with a background luminance of 20.5 cd/m² and a refresh rate of 60 Hz. Stimulus presentation was controlled and recorded by CORTEX, and the timing of stimulus onset and offset events was confirmed with a photodiode. Ambient illumination in the experimental room was 0.902 cd/m².

FEF neuron recordings. Single-neuron recordings in awake monkeys were made through a surgically implanted cylindrical titanium chamber (20 mm diameter) overlaying the arcuate sulcus. Electrodes were lowered into the cortex using a hydraulic microdrive (Narashige). Activity was

recorded extracellularly with varnish-coated tungsten microelectrodes (FHC) of 0.2–1.0 M Ω impedance (measured at 1 kHz). Extracellular waveforms were digitized and classified as single neurons using both template-matching and window-discrimination techniques either online or offline (Plexon).

During each experiment, a recording site in the FEF was first localized by the ability to evoke fixed-vector, saccadic eye movements with stimulation at currents of $<50 \mu\text{A}$ (Bruce et al., 1985). Electrical microstimulation consisted of a 100 ms train of biphasic current pulses (0.25 ms, 200 Hz) delivered with a Grass stimulator (S88) and two Grass stimulation isolation units (PSIU-6) (Grass Instruments). Current amplitude was measured via the voltage drop across a 1 k Ω resistor in series with the return lead of the current source. During each experimental session, we mapped the saccade vector elicited via microstimulation at the cortical site under study with a separate behavioral paradigm (Moore and Fallah, 2001). In this paradigm, the monkey was required to fixate on a visual stimulus (0.48° diameter circle) for 500 ms, after which time a 100 ms stimulation train was delivered on half the trials. For each trial, the visual stimulus was positioned at one of five locations, one at the center of gaze and one 10–13° from center along each cardinal direction. Evoked saccades had vectors with lengths ranging from 3.6–14.4° visual angle and angles of 120–270° theta.

After mapping the saccade vector, we recorded the response of any neuron that could be isolated by advancing the electrode within 0–900 μm of the stimulation site (average distance from stimulation site was 125 μm) while monkeys performed the change detection task. The array was adjusted so that one stimulus was presented inside the RF of the FEF neuron (Fig. 1B). This configuration allowed us to examine FEF neuron responses on trials in which the monkey was cued to direct attention to the stimulus appearing inside the RF of the FEF neuron (“cue RF” condition) compared with when the cue appeared at the opposite array location (180° theta away, in the opposite hemifield), indicating that the monkey should direct attention away from the RF of the FEF neuron (“cue away” condition) (Fig. 1C).

Data analysis. All data analysis was performed in Matlab (MathWorks). Only completed trials were included in the analysis. Completed trials could have one of four possible outcomes: (1) “hits,” in which the monkey released the lever within the response window after a change in the target stimulus orientation, (2) “misses,” in which the monkey failed to release the lever within the response window after a target stimulus change, (3) “correct rejects,” in which no change in target orientation occurred and the monkey continued to depress the lever throughout the response window, and (4) “false alarms,” in which no change in target orientation occurred but the monkey released the lever within the response window. Percentage correct behavior was computed as the number of hit and correct reject trials divided by the total number of completed trials. Because change and no-change trials were equally likely, chance performance corresponds to 50% correct trials. Unless otherwise indicated, data from hit and correct reject trials were included in the analysis of FEF neuronal responses. Although cues appeared at all six array locations with equal likelihood, only responses from trials in which the cue appeared inside the FEF RF (cue RF) or the cue appeared at the opposite array location (cue away) were included in the data analysis unless otherwise indicated.

A criterion level of $p < 0.05$ was used in all statistical analysis. p values $< 10^{-7}$ are reported as $p < 10^{-7}$. To compute normalized population response histograms, the average response of a neuron in each time bin was divided by the peak average response of that neuron across all time bins and conditions. Spatial tuning indices (STIs) for cue location were computed for each neuron according to the following: $\text{STI} = (\text{Response}_{\text{cue RF}} - \text{Response}_{\text{cue away}}) / (\text{Response}_{\text{cue RF}} + \text{Response}_{\text{cue away}})$. Responses during four 120 ms windows were used for the analysis of spatial tuning: aligned to the end of the delay period just before the onset of the first flash of the stimulus array (delay period); aligned to the onset of the first array presentation (flash 1); aligned to the offset of the array when the screen was blank (interflash interval); and aligned to the onset of the second array presentation (flash 2). Each window was shifted by 55 ms to adjust for the latency of visual responses. STIs for all epochs were computed using neuronal responses on both change and no-change trials, with the

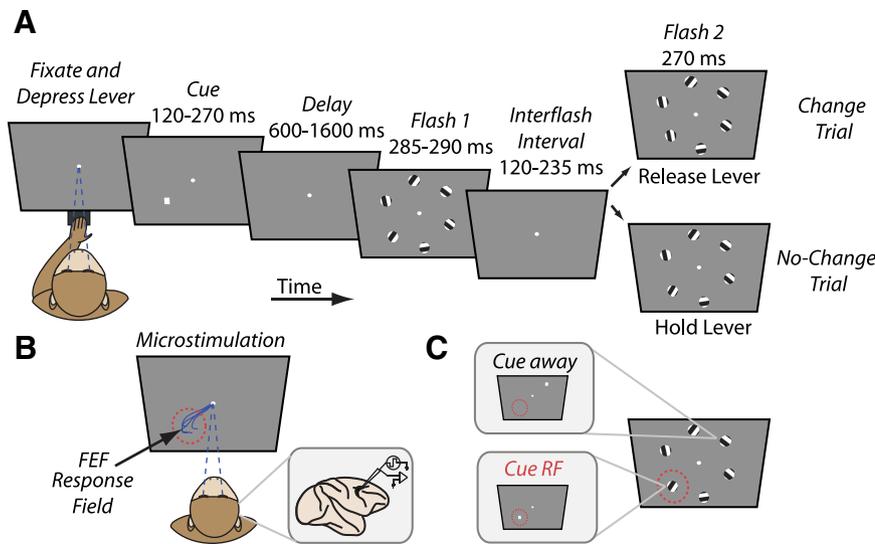


Figure 1. Experimental setup. **A**, Change detection task. The monkey maintained fixation throughout the duration of the trial. To initiate a trial, the monkey depressed a manual lever, and, after a few hundred milliseconds, a peripheral cue was presented briefly, indicating the target location. After a fixed delay period, an array of six oriented gratings was flashed twice. On trials in which the target stimulus changed orientation across flashes (change trial), the monkey was rewarded for releasing the lever. On trials in which the target stimulus did not change (no-change trial), the monkey was rewarded for continuing to hold the lever for an additional 600–1000 ms. All six locations were equally likely to be cued, and the cue was 100% valid. **B**, Stimulus alignment. The FEF RF for each recording site was determined before running the change detection task by applying microstimulation (<50 μ A) during a simple fixation task and mapping the evoked saccades. An example set of eye traces from microstimulation-evoked saccades are shown. The array of gratings was positioned such that one grating was centered at the average evoked saccade endpoint. **C**, Trials in which the monkey was cued to attend to the response field are labeled “Cue RF,” whereas trials in which the monkey was cued to attend to the opposite array location are labeled “Cue away.”

exception of the flash 2 epoch in which only responses from no-change trials were used (because RF stimuli never underwent a change of orientation in the cue away condition). To assess how neurons with persistent spatial signals were affected by visual distracters, neurons with positive STI values computed from both correct and incorrect trials during the interflash interval trial epoch were included in the analyses shown in Figures 2C and 3, B and C. Tuning curves were generated using responses from trials in which the cue appeared at each of the six array locations. For computing the population tuning curve, the average response of each neuron at a given cue location was converted to a z-score by subtracting the overall mean and dividing by the SD of responses at every cue location. z-scores were computed independently for each task epoch. Only neurons with at least two miss trials in both cue RF and cue away conditions were included in the analysis of behavioral performance and spatial tuning. For analysis of reaction times (RTs) and cue tuning, each experimental trial was categorized as either a “high RT” or a “low RT” trial according to whether the RT for that trial was greater than or less than the median RT for that experiment. Receiver operating characteristic (ROC) areas were used to examine whether neuronal responses on hit and miss trials predicted the monkeys change detection performance and were calculated as in previous studies (Britten et al., 1992; Armstrong and Moore, 2007) during each trial epoch. Neurons with at least five miss trials in the cue RF condition were included in the ROC analysis.

Population classifier. A support vector machine (SVM) classifier, using a linear kernel, was used to decode cue location from populations of FEF neuronal responses recorded during cue RF and cue away conditions (Hung et al., 2005). The SVM analysis was done in Matlab using the LIBSVM library (Fan et al., 2005). Only neurons with at least 10 repeated trials in each condition (cue RF and cue away) were included in the classifier analyses. We used a “leave one out” cross validation approach (Kamitani and Tong, 2005) in which the classifier was trained on responses from all but one of the trials, and then the remaining trial was used for testing classification performance. This procedure was repeated so that every trial was used for testing once, yielding 20 performance scores that were averaged to give the classifier performance for a particular sample of FEF responses. The classification procedure was repeated 500 times for different randomly selected samples of FEF neurons (sam-

pled with replacement) and for responses during different times throughout the trial. For comparison of classification performance using the responses of neurons with and without persistent delay activity, sampling was restricted to either the set of neurons that had greater average activity during the entire delay period compared with the spontaneous activity during a 250 ms baseline window preceding the appearance of the cue inside the RF ($p < 0.05$) (“delay activity”) or the remaining neurons (“no delay activity”) (Sommer and Wurtz, 2000). For comparison of classification performance using the responses of neurons with visual and delay responses versus neurons with only visual responses, sampling was restricted to either the set of neurons that had greater average activity during the entire delay period and during the cue epoch compared with the baseline window ($p < 0.05$) (“visual + delay activity”) or the neurons having only greater average activity during the cue epoch ($p < 0.05$) but not during the delay period ($p > 0.05$) compared with baseline (“visual only activity”). Classification performance comparisons were performed via a two-way ANOVA on the performance achieved using responses of 5–45 (see Fig. 5A) or 5–25 (see Fig. 5B) neurons.

Results

Change detection performance

Two monkeys were trained to perform the cued change detection task (Fig. 1A).

Both monkeys reliably detected changes at well above chance (50%) levels. Monkey 1 performed 84.6% correct (8879 trials, 55 sessions; t test different than 50%, $p < 10^{-7}$) and monkey 2 performed 83.7% correct (6225 trials, 38 sessions; $p < 10^{-7}$). To determine whether the monkeys’ performance depended on the spatial cue, we included a subset of randomly occurring probe trials in which the cue was omitted (6.3% monkey 1, 7.6% monkey 2). Both monkeys’ performance on uncued trials was significantly worse than cued trials. Monkey 1’s performance fell to 73.3% correct on uncued trials (uncued vs cued performance, $\chi^2 = 55.1, p < 10^{-7}$), whereas monkey 2’s performance was 56.0% (uncued vs cued performance, $\chi^2 = 241.7, p < 10^{-7}$). Thus, both monkeys appeared to use the cue to direct covert attention.

FEF neuron responses

We recorded the activity of 106 FEF neurons (monkey 1, 56 neurons; monkey 2, 50 neurons). Figure 2 shows the response of two example neurons, one from each monkey, for cue RF and cue away conditions during the different task epochs (Fig. 2A), and the average response of the population of FEF neurons (Fig. 2B). Each trial can be divided into six epochs: a baseline period before any visual stimuli appear; a cue period when the spatial cue is presented; a delay period after the cue offset and before the stimulus array is presented, two flashed presentations of the stimulus array (flash 1 and flash 2); and an interflash interval when the screen is blank between the two array presentations. On average, FEF neurons responded to the onset of the cue stimulus inside the RF (t test, cue response vs baseline response, $p < 10^{-7}$), and this transient visual response was followed by a sustained elevation of activity that persisted throughout the delay period (delay period vs baseline, $p < 10^{-7}$). In contrast, when the cue appeared at the opposite array location, no visual response was evoked (cue vs baseline, $p = 0.10$), and activity during the delay period was

suppressed (delay period vs baseline, $p < 0.01$), leading to a sustained difference in activity throughout the delay period for cue RF and cue away conditions ($\Delta 51.8\%$, $p < 10^{-7}$). This spatially selective persistent activity is similar to what is observed during memory-guided saccade tasks (Sommer and Wurtz, 2000, 2001), although in the change detection task, no saccades were allowed.

After the delay period, we restricted the analysis to responses from no-change trials only, because RF stimuli never underwent an orientation change during the cue away condition. The first flash of the stimulus array (flash 1) evoked a visual response in both cue RF and cue away conditions (flash 1 vs baseline: cue RF, $p < 10^{-7}$; cue away, $p < 10^{-7}$), and this elevated activity continued throughout the interflash interval, when the screen was blank between the two flashes of the array (interflash interval vs baseline: cue RF, $p < 10^{-7}$; cue away, $p < 0.0008$) and after the onset of the second flash (flash 2) of the array (flash 2 vs baseline: cue RF, $p < 10^{-7}$; cue away, $p < 10^{-6}$). Although activity was elevated in both cue RF and cue away conditions after the onset of the array, this activity was modulated in a cue-dependent manner throughout the remainder of the trial (Δ flash 1, 31.0%, $p < 10^{-7}$; Δ interflash interval, 42.6%, $p < 10^{-7}$; Δ flash 2, 35.54%, $p < 10^{-7}$), ruling out the possibility that the spatially selective persistent activity observed after the cue was merely a sustained visual response. This cue-dependent activity differed from attentional modulations reported in visual cortex (Luck et al., 1997) in that the largest effects were observed during the delay period and interflash interval periods (51.8 and 42.6% modulation, respectively) in which no visual stimulus was present within the RF compared with the modulation of visual responses to the stimulus array (31.0 and 35.54% modulation during flash 1 and flash 2, respectively). Nonetheless, neurons in the FEF maintained a representation of cue position throughout the trial in both the presence and absence of visual stimulation.

To quantify the extent to which the first array presentation (flash 1) disrupted persistent spatial signals in the FEF, we computed an STI for each FEF neuron to measure how selective the response of that neuron was for cue location during the different task epochs (Fig. 2C). We examined spatial tuning during three 120 ms analysis windows: at the end of the delay period just before the onset of the first array presentation (delay period), immediately after the onset of the first array (flash 1), and immediately after the offset of the array (interflash interval). Spatial tuning dropped, from an average of 0.31 before the array was flashed to 0.21 immediately after the onset of the array ($STI_{\text{delay period}} - STI_{\text{flash 1}} = 0.12$, $p < 0.004$, paired t test). However, after the offset of the array spatial tuning recovered fully to 0.34 ($STI_{\text{interflash interval}} - STI_{\text{flash 1}} = 0.14$, $p < 10^{-5}$; $STI_{\text{interflash interval}}$

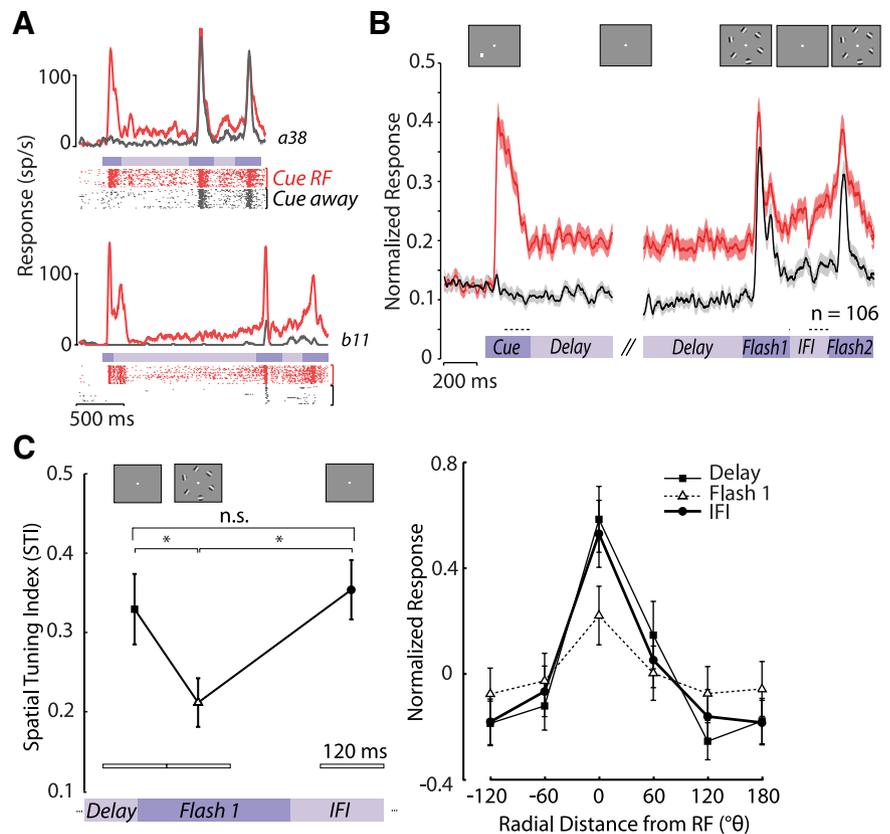


Figure 2. Example and population responses of FEF neurons during the change detection task. **A**, The spike activity of an example neuron from each monkey during the task. Histograms show the average response of each neuron on correct trials in which the monkey was cued to attend to the RF location (red) and cued to attend away (gray). Rasters show action potentials recorded on individual trials. **B**, The average normalized response of 106 FEF neurons aligned to the onset of the cue (left) and the onset of the first presentation of the stimulus array (right). Only no-change trials are included in the right. Panels along the top show a schematic diagram of the display seen by the monkey during each task epoch. Conventions for the histogram are the same as in **A**, with shading indicating SEM response. Dots above each epoch label indicate variable timing across experiments. **C**, Spatial tuning across task epochs. Left, The average STI during each of three task epochs: delay period, flash 1, and interflash interval. For each neuron, an STI was calculated using the average firing rate in cue RF and cue away conditions during three 120 ms analysis windows aligned to the delay period, flash 1, and interflash interval epochs as shown. Panels along the top show a schematic diagram of the display seen by the monkey. Right, Average normalized spatial tuning curves during the three epochs in the left plot as a function of radial distance from the RF location. For each neuron and epoch, the responses across all six array locations were converted to z-scores. Error bars indicate SEM. IFI, Interflash interval. Asterisks denote differences between epochs, $p < 0.05$.

$-STI_{\text{delay period}} = 0.02$, $p = 0.60$). Spatial tuning curves generated from the mean responses during all six cue conditions confirm this pattern of disruption, followed by recovery of spatial tuning.

FEF responses and task performance

To examine whether FEF activity was related to the monkey's change detection performance, we compared the response of FEF neurons on correct and incorrect trials. Correct and incorrect trials can be subdivided between change and no-change trials, resulting in four response categories: correct change trials (hits), incorrect change trials (misses), correct no-change trials (correct rejections), and incorrect no-change trials (false alarms). When the monkey was cued to direct attention to the RF, activity on hit trials was greater than activity on miss trials during each epoch of the trial (paired t test, $p < 0.04$; hit – miss: cue, 10.6%; delay period, 9.1%; flash 1, 13.4%; interflash interval, 14.4%; flash 2, 11.5%) (supplemental Fig. 1, available at www.jneurosci.org as supplemental material). In contrast, no difference in activity was observed between correct reject and false alarm trials during any trial epoch ($p > 0.13$). To examine how well the differences in hit and miss trial activity predicted monkeys' change detection per-

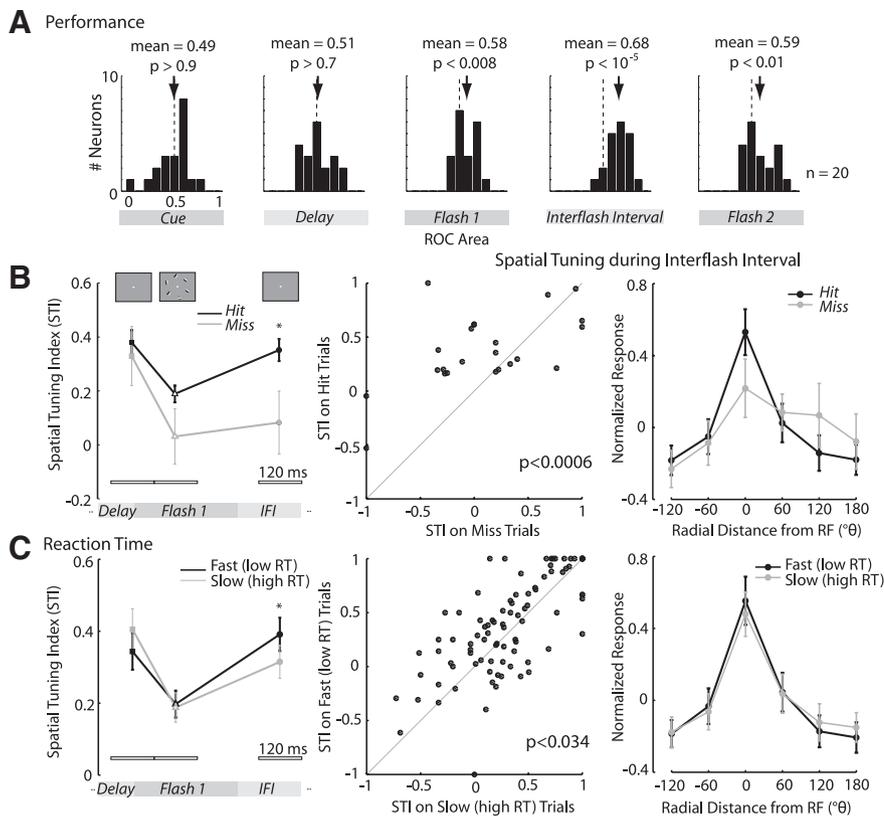


Figure 3. FEF responses and task performance. **A**, To examine the relationship between FEF responses and change detection performance, ROC areas were computed from the response of each neuron on hit and miss trials. Distributions of ROC areas for neurons with at least five miss trials in the cue RF condition ($n = 20$) during each trial epoch. The dotted lines mark an ROC area of 0.5, and the arrows indicate the means of the distributions. **B**, Spatial tuning and change detection performance. Left, Average spatial tuning index for hit trials, in which the monkey correctly responded to the target change (black), and miss trials, in which the monkey did not respond to the target change (gray) during the delay period, flash 1, and interflash interval epochs. Conventions are the same as in Figure 2C. Middle, Scatter plot of spatial tuning indices during the 120 ms interflash interval analysis window on hit trials versus miss trials. The diagonal line of unity is included for reference. Right, Average normalized spatial tuning curve during the interflash interval for hit (black) and miss (gray) trials as a function of radial distance from the response field location. Conventions are the same as in Figure 2C. Asterisks denote differences between hit and miss trials, $p < 0.05$. **C**, Spatial tuning and manual reaction time on hit trials. Left, Spatial tuning index for fast (low reaction time) trials (black) and slow (high reaction time) trials (gray) across three trial epochs. Middle, Scatter plot of spatial tuning indices during the interflash interval on fast reaction time trials versus slow reaction time trials. Right, Average normalized spatial tuning curve during the interflash interval for fast reaction time (black) and slow reaction time (gray) trials. Asterisks denote differences between fast and slow RT trials, $p < 0.05$.

formance, we computed the ROC area for the response of each neuron on hit and miss trials (Britten et al., 1992; Armstrong and Moore, 2007). The ROC area is the performance expected of an ideal observer if she were making a decision about whether the monkey would respond correctly to the changing stimulus based solely on the FEF neuron response (Green and Swets, 1974). Figure 3A shows the distribution of ROC areas computed for the population of FEF neurons during each trial epoch. During the flash 1, interflash interval, and flash 2 epochs, i.e., when the monkey was performing the visual discrimination, the responses of FEF neurons significantly predicted the hit and miss trial outcome. This effect was greatest during the interflash interval epoch, when the responses of FEF neurons could be used to predict whether or not the monkey would respond correctly to target changes with an average accuracy of 68%. Thus, FEF activity could reliably predict whether the monkey would correctly detect the change.

To test whether the disruption of persistent spatial tuning induced by the onset of the stimulus array (Fig. 2C) was related to the monkeys' ability to perform the task correctly, we compared the STIs for hit and miss trials (Fig. 3B). Spatial tuning was re-

duced during the flash 1 epoch compared with the delay period for both hit ($p < 10^{-5}$) and miss ($p < 0.04$) trials; however, the mean STI on hit trials remained reliably greater than zero ($STI_{flash\ 1} = 0.19, p < 10^{-7}$), whereas on miss trials, the mean STI was not different from zero ($STI_{flash\ 1} = 0.03, p = 0.76$). After the array offset, spatial tuning recovered fully to preflash levels on hit trials ($STI_{interflash\ interval} = 0.35, p < 10^{-7}$), whereas on miss trials, cue tuning failed to recover significantly ($STI_{interflash\ interval} = 0.08, p = 0.49$). This pattern suggests that the residual spatial tuning present during the array presentation on hit trials facilitated the recovery of spatial tuning after the offset of the array during the interflash interval. Regardless, the relationship between spatial tuning and change detection performance demonstrates that the extent to which FEF neurons maintain persistent spatial signals is correlated with whether monkeys accurately detect changes.

In addition to enhancing perception, attention is also known to decrease RT (Posner, 1980; Carrasco et al., 2006). We examined whether spatial tuning was related to the speed with which monkeys made correct judgments about changing stimuli on hit trials (Fig. 3C). Before and immediately after the first presentation of the array, spatial tuning on trials in which the monkey responded quickly (low RT trials) did not differ from tuning on trials in which the monkey responded more slowly (high RT trials) (delay period, $p = 0.11$; flash 1, $p = 0.84$). However, after array offset during the interflash interval epoch, low RT trials had greater spatial tuning than high RT trials (interflash interval, $p < 0.034$), indicating improved spatial tuning on trials in which the monkey

rapidly detected the changing stimulus. This result, together with the increased spatial tuning on hit trials compared with miss trials during the interflash interval epoch, suggests that the maintenance of a persistent representation of the cued location by FEF neurons during the blank gap between the two array presentations is important for detecting changes.

Decoding cue location from populations of FEF neurons

Previous studies have reported a heterogeneous population of FEF neuronal responses during visually guided and memory-guided saccade tasks (Bruce and Goldberg, 1985; Sommer and Wurtz, 2000). Consistent with these previous reports, we observed striking heterogeneity in response properties among the population of recorded FEF neurons. Figure 4A illustrates the responses of two example neurons from monkey 2. The first neuron was visually responsive to the cue and the stimulus array and had a small but reliable elevation of delay period activity during the cue RF condition. In contrast, the activity of the second neuron was suppressed by the onset of the cue and the stimulus array, although the activity of the neuron increased steadily throughout

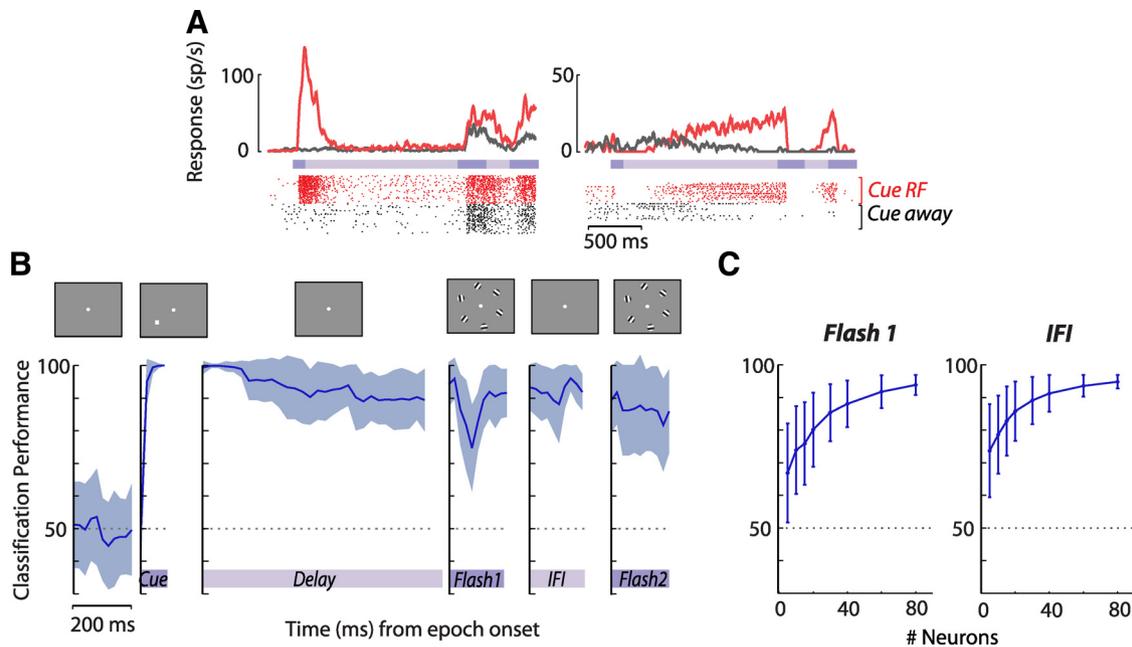


Figure 4. Decoding cue location from a heterogeneous population of FEF neurons. **A**, Heterogeneity of neuronal responses. The spike activity of two example neurons from one monkey, using the same conventions as Figure 2A. Left, A visually responsive neuron. Right, A visually suppressed neuron that showed spatial selectivity during the delay period. **B**, Time course of the average classification performance of 50 support vector machines, each trained on spike activity during cue RF and cue away trials in sliding 50 ms windows from a random subset of 40 FEF neurons, sampled with replacement. Data are aligned to the beginning of each task epoch, with panels along the top showing a schematic diagram of the display seen by the monkey during each epoch. Shading indicates SD, and the dotted line indicates chance performance. **C**, Average classification performance as a function of neuron population size during the flash 1 and interflash interval epochs. Analysis windows used are the same as in Figures 2 and 3. Error bars indicate SD, and the dotted line indicates chance performance. IFI, Interflash interval.

delay period during the cue RF condition. Because of this response heterogeneity, the responses of individual neurons can cancel one another out in the population average, reducing information about cue position in the average response. Thus, to further examine how the population of FEF neurons represents cue information throughout the trial, we used an SVM classifier to decode cue location (inside vs outside the RF) from the population of independently recorded FEF responses. Unlike simply averaging, the SVM classifier analysis leverages the response of any neuron that can distinguish between the two cue conditions. This approach involves training a classifier on a fraction of the experimental data and then using the classifier to decode the responses of the remaining trials (Hung et al., 2005; Kamitani and Tong, 2005). Figure 4B shows classification performance at different times throughout the trial. Individual time points show the average performance of 50 classifiers each trained and tested on the responses of 40 randomly selected FEF neurons. Before the onset of the cue, performance was at chance (49.44%, $p = 0.32$). However, after presentation of the cue, classifier performance reached a high degree of accuracy and remained reliably above chance throughout the remaining trial epochs. A slight decrease in decoding performance was associated with the onset of the first array presentation, consistent with the significant drop in spatial tuning we observed in the population average. The decreased classification accuracy during the flash 1 epoch compared with the interflash interval can be seen in Figure 4C, which plots average performance as a function of the number of FEF responses included in the classifier during two of the analysis windows we examined earlier. For example, during the flash 1 epoch, a sample of 20 FEF neurons could be used to decode cue location with an average accuracy of 80.02%, whereas during the interflash interval epoch, an average classification performance of 85.7% was achieved (difference in performance, $p < 10^{-7}$, signed-rank

test). Across all FEF neuron sample sizes, classification performance was lower during the flash 1 epoch compared with the interflash interval epoch (two-way ANOVA, $p < 10^{-7}$).

We also used classification performance to address the question of how functionally distinct FEF neurons represented the cued location during these epochs. We compared the performance of classifiers trained and tested using different subclasses of FEF neurons (Fig. 5). Fifty-five of 106 FEF neurons had reliably elevated activity during the delay period of the change detection task (delay period vs baseline, $p < 0.05$). During the flash 1 and interflash interval epochs, we compared the performance of classifiers decoding the responses of FEF neurons that exhibited persistent delay activity with the performance of classifiers decoding the responses of neurons that lacked delay activity (Fig. 5A). Immediately after the onset of the array, performance was greater when the responses of neurons with persistent delay activity were used for classification compared with when we used the responses of neurons without delay activity ($p < 10^{-7}$). For example, during the flash 1 epoch, decoding the responses of 20 FEF neurons with delay activity achieved an average classification accuracy of 86.9%, whereas an accuracy of only 64.7% was achieved using the responses of neurons that lacked delay activity. A similar effect was also observed during the interflash interval ($p < 10^{-7}$), when the responses of 20 FEF neurons could be decoded with classification accuracies of 89.5 and 72.6% for neurons with and without persistent delay period activity, respectively. Thus, the largest differences in classification performance between neurons with and without delay activity were observed during the flash 1 epoch ($p < 10^{-7}$).

In addition, to examine the extent to which all visually responsive neurons were enhanced with attention, regardless of whether or not the neuron also exhibited persistent activity, we compared the performance of classifiers decoding the responses of visually responsive FEF neurons that had persistent delay period activity

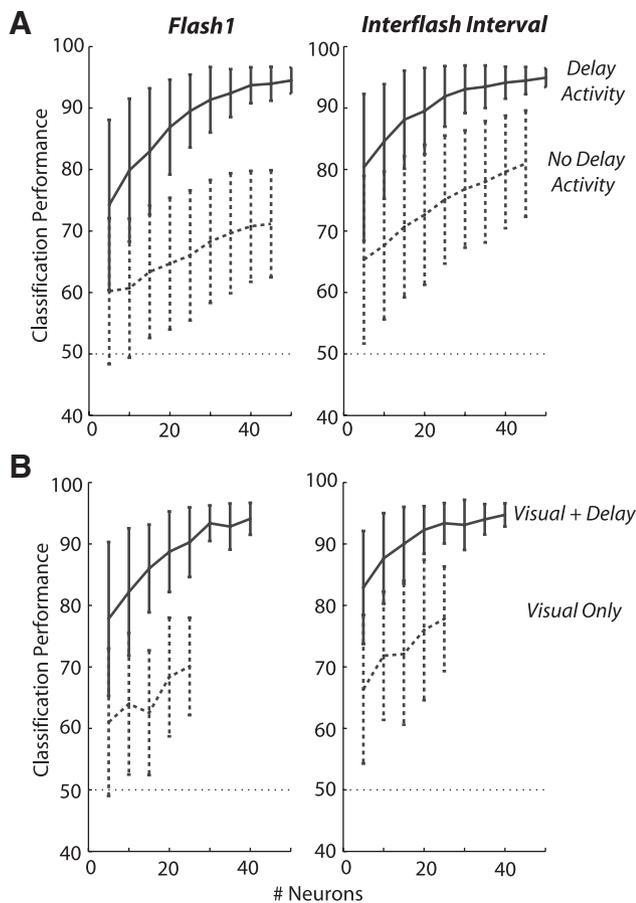


Figure 5. Cue location classification performance varies for different subgroups of FEF neurons. Average classification performance shown as a function of neuron population size during the flash 1 and interflash interval epochs. **A**, Solid lines show the average performance of 500 classifiers trained and tested on the responses of FEF neurons that had persistent spatial activity during the delay period (“Delay Activity”). Dashed lines show the average performance of classifiers trained on the responses of neurons that lacked persistent delay period activity (“No Delay Activity”). Analysis windows used are the same as in Figures 2–4. Error bars indicate SD, and the thin dotted line indicates chance performance. **B**, Solid lines show the average performance of 500 classifiers trained and tested on the responses of FEF neurons that were visually responsive and had persistent spatial activity during the delay period (“Visual + Delay”). Dashed lines show the average performance of classifiers trained on the responses of visually responsive neurons that lacked persistent delay period activity (“Visual Only”).

(visual + delay neurons, $n = 44$) with those decoding the responses of purely visual FEF neurons that lacked persistent delay period activity (visual only neurons, $n = 30$) (Fig. 5B). Decoding accuracy was greatest for visual + delay neurons compared with visual only neurons during both the flash 1 ($p < 10^{-7}$) and interflash interval ($p < 10^{-7}$) epochs. To relate this result to the STIs we examined previously, we compared spatial tuning during the flash 1 and flash 2 epochs for visual + delay and visual only neurons (Fig. 6). Spatial tuning during the flash 1 and flash 2 epochs quantifies the attentional modulation of visual responses occurring during target discrimination, when the monkey was making a judgment about whether or not the RF stimulus changed orientation. Although one might expect any visually responsive neuron to be enhanced with attention, during the flash 1 and flash 2 epochs, the average STI of visual + delay neurons was more than double that of visual only neurons (flash 1: $STI_{\text{visual + delay}} = 0.27$; $STI_{\text{visual only}} = 0.12$; delay activity vs no delay activity, $\Delta STI = 0.15$, t test, $p < 0.03$; flash 2: $STI_{\text{visual + delay}} = 0.33$; $STI_{\text{visual only}} = 0.12$; delay activity vs no delay activity: $\Delta STI =$

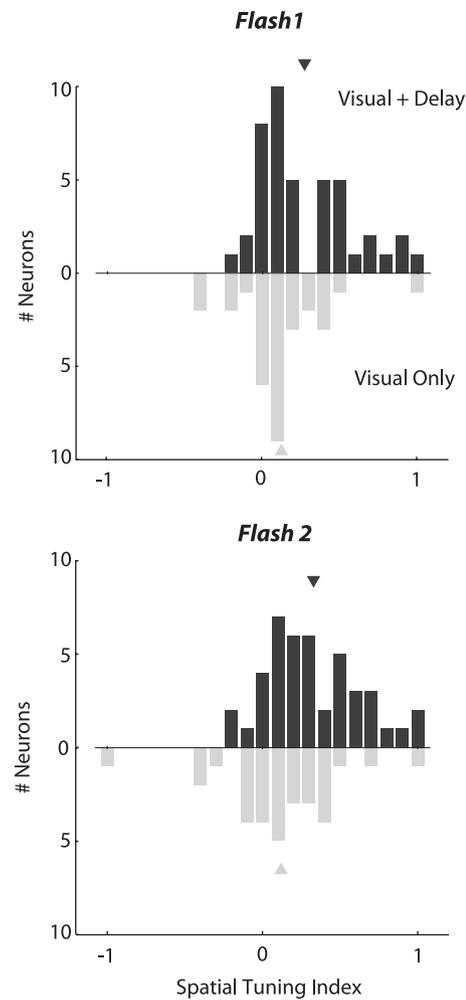


Figure 6. Spatial tuning during visual discrimination varies for different subgroups of FEF neurons. STIs were computed for each neuron by taking the difference of the average visual response to the flashed stimulus array during the cue RF and cue away conditions and dividing by the sum of the two responses. Dark and light gray histograms show the distribution of STIs during the flash 1 (top) and flash 2 (bottom) epochs for “Visual + Delay” and “Visual Only” neurons, respectively. Triangles indicate the means of the distributions.

0.21, t test, $p < 0.01$). This effect cannot be explained by an overall increase in visual responsiveness of visual + delay neurons compared with visual only neurons, because the magnitude of the flash 1 visual response was statistically indistinguishable between the two subgroups (visual + delay neurons, 27.9 spikes/s; visual only neurons, 31.8 spikes/s; t test, $p > 0.51$). Thus, neurons with persistent activity not only maintained cue information throughout the delay period but also showed more attentional enhancement during target discrimination.

Discussion

We recorded the responses of FEF neurons in monkeys performing a change detection task that required the covert deployment of attention to a previously cued location. On correct trials, the population of FEF neurons persistently encoded the cued location throughout the trial, during both delay period and visual discrimination epochs. Cue-related activity was reduced after the onset of the distracters regardless of whether the monkey detected the change or not. However, on trials in which the monkey correctly detected the change, cue-dependent activity recovered

fully. In contrast, on trials in which the monkey failed to detect the change, the representation of the cued location was completely disrupted by the onset of the distracters, and it did not recover. FEF neuron responses during the interflash interval could be used to predict whether the monkey would detect the change with an accuracy of 68%. We also found that the persistent representation of the cued location was correlated with the monkey's speed at detecting target changes. Finally, we used a classifier analysis to decode the cue location from the population of recorded FEF responses. This analysis confirmed the persistence of a cue representation throughout the trial and showed that FEF neurons with persistent activity were better at selecting the target from among distracters than neurons lacking persistent activity. Below, we discuss the current results and relate them to studies of attention and working memory.

Mechanisms of covert spatial attention in the FEF

Most early studies of the FEF tended to focus on its role in saccades (Robinson and Fuchs, 1969; Schiller et al., 1979a,b; Bruce and Goldberg, 1985); however, some initial evidence suggested that FEF neurons might also encode the salience of visual stimuli (Wurtz and Mohler, 1976). More recently, a variety of different experimental techniques have been used to demonstrate a causal role of the FEF in covert spatial attention (Moore and Fallah, 2001, 2004; Moore and Armstrong, 2003; Armstrong et al., 2006; Awh et al., 2006; Wardak et al., 2006; Armstrong and Moore, 2007). Although these causal experiments have clearly implicated the FEF as a source of attentional control, they do not reveal how individual FEF neurons participate in the allocation of attention. Although early single-neuron studies in the FEF did not find a clear correlate of covert attention (Goldberg and Bushnell, 1981), more recent studies reported attentional modulation of FEF visual responses (Thompson et al., 2005; Monosov et al., 2008). The current results suggest that persistent coding of spatial information may contribute to visual response modulation in FEF neurons.

Neuronal responses in the FEF recorded during saccade tasks tend to fall along a visuomotor continuum, with some neurons exhibiting purely visual responses and others firing exclusively before a saccade is made (Bruce and Goldberg, 1985; Sommer and Wurtz, 2000). Previous work has found that visual- and movement-responsive neurons are equally likely to exhibit persistent delay activity (Sommer and Wurtz, 2000). Thus, where along the visuomotor continuum the persistently active neurons we observed in the current study would lie is uncertain. One study found that only visually responsive FEF neurons were modulated during a pop-out covert visual search task (Thompson et al., 2005). It is possible that the pattern of attentional modulation across different subtypes of FEF neurons may depend on task parameters. For example, as implied by the observations of the current study, when attention must be deployed without explicit visual cues, persistently active FEF neurons may maintain an internal representation of the attended location that is relatively impervious to disruption by distracting visual events.

Interpreting the classifier results

We used a classifier analysis to decode the remembered location from the population response. This approach has been used previously to decode object and category information from the responses of neurons in inferotemporal cortex (Hung et al., 2005) as well as perceived and remembered orientation information from functional magnetic resonance imaging blood oxygenation level-dependent responses in human visual cortex (Kamitani and

Tong, 2005; Harrison and Tong, 2009). In the current study, single-neuron recordings were typically collected in independent sessions, and therefore the FEF responses used for decoding were independent. However, simultaneously recorded neuronal responses are known to exhibit correlated variability (Zohary et al., 1994). Some controversy exists regarding the impact of these "noise" correlations on coding accuracy in neuronal populations (Abbott and Dayan, 1999; Romo et al., 2003; Hung et al., 2005), precluding straightforward implications about the accuracy of decoding single-trial responses based on the current findings in independently recorded FEF neurons. As such, it is difficult to make strong interpretations about the absolute number of FEF neurons required to encode the attended and remembered location. Nonetheless, the classifier approach allowed us to examine how the sample of FEF neurons represented cue location throughout the trial without losing information by averaging across heterogeneous response properties. Moreover, this issue should not undermine the comparison of decoding accuracy achieved using different FEF neuronal subsets. Using this approach, we found greater classification performance for neurons with delay activity compared with neurons that lacked delay activity during both the array presentation and the subsequent interflash interval. Thus, persistently active neurons not only maintain a stable representation of the cued location, but they are also better at selecting the target from among distracters than neurons lacking persistent activity.

Working memory and attention

Although several recent studies have begun to explore the neuronal basis of attention in the FEF using a variety of experimental approaches, the possible role of FEF neurons in working memory has been primarily examined in the context of memory-guided saccade tasks (Bruce and Goldberg, 1985; Funahashi et al., 1989; Sommer and Wurtz, 2000) (but see Sommer and Wurtz, 2001). This task is not ideally suited for assessing working memory involvement because it cannot distinguish retrospective encoding of the visual stimulus from prospective encoding of a movement plan (Funahashi et al., 1993). One study attempted to dissociate working memory- and attention-related responses in dorsolateral prefrontal cortex (dlPFC) by having monkeys hold a target location in memory while discriminating a stimulus at another location (Lebedev et al., 2004). Despite the fact that dlPFC is often associated with the maintenance of short-term memories (Funahashi et al., 1989, 1993), most neurons responded to the attended location rather than the memorized location, although many neurons responded to both the attended and memorized locations. Similar approaches might be used to clarify the role of persistently active FEF neurons in working memory, since the current experimental design cannot determine whether the persistent spatial information is best characterized as sustained attention or also contributes to working memory tasks without an attention component. Nonetheless, the current results demonstrate that persistent spatial activity in the FEF is not limited to saccade tasks, suggesting that it may have a more general role in working memory. Moreover, the fact that neurons with persistent FEF activity were better at selecting the target from among distracters than neurons lacking persistent activity suggests that the presence of persistent activity contributes to attention. Although it is possible that attention and working memory rely on different subpopulations of FEF neurons, the current findings are consistent with a model in which the maintenance of spatial information by FEF neurons biases visual processing at remembered locations (Awh et al., 2000; Jha, 2002; Soto et al., 2008).

Saccade preparation, spatial working memory, and spatial attention

Evidence of a role of the FEF in saccade preparation, spatial working memory, and spatial attention raises the question of how these seemingly disparate functions are related. Considering the current findings in the context of the known roles of the FEF in saccades and attention, one possible model is that persistent FEF activity reflects saccade plans that can be maintained in the absence of visual cues and that this activity may provide a top-down influence on visual cortex (Luck et al., 1997; Kastner et al., 1999). The influence of movement preparation on movement execution has been widely studied (Rosenbaum, 1980; Wise, 1985; Churchland et al., 2006). In general, increased planning duration decreases movement reaction time (Rosenbaum, 1980) and is believed to facilitate the sensory guidance of coordinated movements (Wise, 1985). In the case of eye movements, the ability to behaviorally dissociate the preparation of saccades from their execution may also provide a convenient means of achieving both the selection of visual representations and the maintenance of spatial information. Persistent plan activity in the FEF may serve an attentional or mnemonic function depending solely on the presence or absence of a visual stimulus at the saccade goal.

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