Microstimulation of the Frontal Eye Field and its Effects on Covert Spatial Attention

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Abstract

Many studies have established that the strength of visual perception and the strength of visual representations within visual cortex vary according to the focus of covert spatial attention. While it is clear that attention can modulate visual signals, the source of this modulation remains unknown. We have examined the possibility that saccade related mechanisms provide a source of spatial attention by studying the effects of electrical microstimulation of the frontal eye fields (FEF) on spatial attention. Monkeys performed a task in which they had to detect luminance changes of a peripheral target while ignoring a flashing distracter. The target luminance change could be preceded by stimulation of the FEF at current levels below that which evoked saccadic eye movements. We found that when the target change was preceded by stimulation of FEF, the monkey could detect smaller changes in target luminance. The increased sensitivity to the target change only occurred when the target was placed in the part of the visual field represented by neurons at the stimulation site. The magnitude of improvement depended on the temporal asynchrony of the stimulation onset and the target event. No significant effect of stimulation was observed when long intervals (>300 ms) between stimulation and the target event were used, and the magnitude of the increased sensitivity decreased systematically with increasing asynchrony. At the shortest asynchrony, FEF stimulation temporally overlapped the target event and the magnitude of the improvement was comparable to that of removing the distracter from the task. These results demonstrate that transient, but potent improvements in the deployment of covert spatial attention can be obtained by microstimulation of FEF sites from which saccadic eye movements are also evoked.
Spatial attention refers to the selective processing of stimuli at behaviorally relevant locations at the expense of stimuli at other locations. Saccadic eye movements are the primary way by which visual resources (i.e. the foveas) are brought to bear on relevant spatial locations and are thus key exemplars of spatial attentive behavior. Much has been made of the fact that objects can be selected for attention without actually being fixated (Sperling and Melchner, 1978), i.e. selected covertly, but a wealth of evidence suggests that the mechanisms of overt and covert attention are similar, if not the same (Rizzolatti, 1983; Petersen et al., 1987; Kowler et al., 1995; Gattass and Desimone, 1996; Snyder et al., 1997; Kustov and Robinson, 1997; Corbetta et al., 1998). In extrastriate visual cortex, neural responses to peripheral visual stimuli are enhanced when monkeys are trained to attend to those stimuli while maintaining fixation (Moran and Desimone, 1985; Motter, 1993; Connor et al., 1997; Treue and Maunsell, 1999). Similar modulation in visual activity is observed immediately before saccades to visual stimuli (Fischer and Boch, 1983; Sheinberg and Logothetis, 2001). In extrastriate area V4, the strength of visual selectivity and the extent and position of receptive fields of neurons can be altered either by covert attention or by overt attention in which the monkey saccades to the relevant stimuli (Spitzer and Desimone, 1988; McAdams and Maunsell, 1999; Connor et al., 1997; Moore et al, 1998; Tolias et al., 2001). Although a link between covert attention and eye movement control is apparent, a causal relationship has yet to be established.

The involvement of the FEF in the targeting of visual stimuli and the triggering of saccadic eye movements is well established (Bruce, 1990; Schall, 1996; Tehovnik et al., 2000). The FEF contains a coherent map of visual space in oculomotor coordinates (Bruce et al., 1985). The FEF has neurons involved in saccadic eye movements as well as neurons that have been implicated
specifically in target selection (for review, see Schall, 2002). Neurons within the FEF are reciprocally connected with posterior visual areas in both the parietal and temporal lobes (Stanton et al., 1995; Schall et al., 1995). This provides a potential anatomical substrate by which top-down inputs can modulate visual representations. Consistent with this view is evidence that saccade-related FEF neurons are selectively modulated during covert attention (Kodaka et al., 1997; although see Goldberg et al., 1981). Psychophysical studies have demonstrated that visual detection not only improves at the location of covert attention (Carrasco et al., 2000), but that it also improves at the location of impending saccadic eye movements (Shepherd and Findlay, 1986; Hoffman and Subramaniam, 1996). Electrical stimulation of the FEF evokes short latency saccades in both human and nonhuman primates (Bruce et al., 1985; Blanke et al., 2000). Stimulation of the FEF with currents below the movement threshold does not evoke saccades, but nonetheless biases the selection of targets for eye movements (Burman and Bruce, 1997; Schiller and Tehovnik, 2001). We recently examined the possibility of a causal relationship between oculomotor planning and spatial attention by manipulating signals within the FEF of monkeys performing a covert spatial attention task (Moore and Fallah, 2001). We trained monkeys to make manual responses to the transient dimming of peripheral visual targets while ignoring a flashing distracter. Because it has been shown that covert attention improves contrast sensitivity (Carrasco et al., 2000; Reynolds et al., 2000), we hypothesized that by biasing saccade preparation to a particular location we could also improve the animal's ability to detect luminance/contrast changes in a visual target. We used subthreshold stimulation to test its effects on the ability of monkeys to detect luminance changes at the location represented by the stimulation site, or 'movement' field (MF). In our initial study, we found that FEF microstimulation lowered contrast thresholds within the MF, in a spatially dependent manner, when the microstimulation occurred at short intervals...
before the target event. In the present study, we examined the temporal dependence of the stimulation effect and compared the magnitude of stimulation-driven sensitivity changes to that observed when the distracter is eliminated from the task. We found that the improvement observed within the movement field was time dependent, its magnitude rapidly decreasing to zero with increasing asynchrony between the stimulation and the target event. When the stimulation train and the target event overlapped temporally, the improved sensitivity was comparable to that observed when we removed the distracter.

**METHODS**

**subjects**

Two male monkeys (*Macaca fascicularis*) weighing 4.8 and 5.5 kg were used as subjects in these experiments. Neither of the two monkeys (Monkey A, *Autolycus*; Monkey B, *Blacula*) had received prior behavioral training nor had they been involved in any other electrophysiological, stimulation or lesion experiments. All surgical, and behavioral procedures were approved by the Princeton University Institutional Animal Care and Use Committee and the consultant veterinarian and were in accordance with National Institutes of Health and Society for Neuroscience guidelines.

**attention task**

Monkeys were trained to detect the transient dimming of a peripheral visual target by releasing a lever (figure 1). In this task, the monkey was first required to fixate a central fixation spot. After acquiring fixation, the monkey depressed a lever that was positioned centrally below the view of a video monitor. Once the lever was held down, a peripheral visual target appeared at a fixed location and remained there throughout the trial. On two-thirds of the trials (blink trials), the target dimmed briefly (≈ 40 ms) at an unpredictable time (500 - 1800 ms) and the monkey was
rewarded for releasing the lever within a specified time window (600 - 800 ms) and the trial was completed. On one third of the trials (catch trials), the target did not dim and the monkey was instead rewarded for holding down the lever for the duration of the trial. Each trial lasted up to 2.6 seconds. During all trials, a distracter stimulus was continually flashed (at 30 Hz) throughout the display while the monkey waited for the target luminance to change. The distracter stimulus, which had a similar shape and brightness as the target stimulus, was intended to draw attention away from the target stimulus (Remington et al., 1992) thus making the detection of the target luminance change more difficult. While performing the task, the monkey was required to maintain fixation of the fixation spot throughout the trial. The trial was aborted if the eye position moved outside of a 2-3° electronic window around the fixation spot at any time during the trial. Throughout all behavioral testing, eye position was monitored and stored at 200 Hz using the scleral search coil method. Control of the display, stimulation and data storage was maintained by way of a CORTEX data acquisition system.

During stimulation experiments, the target was positioned at a location to which suprathreshold FEF stimulation shifted the monkey's gaze, referred to as the 'movement field'. On stimulation/blink trials, a 100 ms subthreshold stimulation train preceded the target luminance change. On stimulation/catch trials the stimulation train occurred at random times. The interval between the onset of the stimulation train and the luminance change, referred to as the stimulation onset asynchrony (SOA), ranged from 50 to 525 ms. Each experiment consisted of stimulation at two SOAs, one 'short' (50 - 175) and one 'long' (275 - 525).

**visual stimuli**

The target stimulus was a white square (0.25 – 1.25 deg.²) with an initial luminance of 26 cd/m² (background, 1 cd/m²) displayed on a video monitor (30 cm vertical × 40 cm horizontal, 60
Hz) positioned ≈57 cm in front of the monkey. The distracter stimulus was also a white square (0.1 – 1 deg.) displayed at the peak luminance of the target. A distracter was flashed for 16 ms and re-plotted every 32 ms at random locations excluding a 2 – 5° circular region surrounding the target stimulus. The excluded region was always larger than the spread of endpoints of the evoked saccades to the MF. All testing was performed under mesopic ambient light conditions.

**electrical stimulation and MF mapping**

Electrical stimulation consisted of a 100 ms train of biphasic current pulses (0.2 ms, 200 Hz) delivered with a Grass stimulator (S88) and 2 Grass stimulation isolation units (PSIU-6). Current amplitude was measured via the voltage drop across a 1 kΩ resistor in series with the return lead of the current source. All stimulation was delivered via tungsten electrodes (0.1 – 1.0 MΩ impedance, at 1 kHz). In each monkey, the FEF was localized on the basis of its surrounding physiological and anatomical landmarks and our ability to evoke fixed-vector, saccadic eye movements with stimulation using currents less than 150 µA, but typically around 50 µA. Stimulation of sites posterior to saccade sites evoked movements of the mouth and forelimbs (Bruce et al., 1985; Graziano et al., 2002). Stimulation evoked saccades had metrics that were similar to visually evoked saccades in the same monkeys. Moreover, the slopes of the duration-amplitude tradeoff functions (main sequence) of stimulation evoked saccadic eye movements in the two monkeys, 1.3 ms/deg. eccentricity (monkey A) and 2.2 ms/deg. eccentricity (monkey B), are within the range of visually evoked saccades (Becker, 1989). In one of the monkeys (monkey B), we confirmed histologically that our electrode penetrations were made into the FEF. At the conclusion of experiments, the monkey was given an overdose of pentobarbital and perfused transcardially with 8% paraformaldehyde. The point of electrode entry was then verified by removing the dura mater exposed by the craniotomy within the recording chamber. In this
monkey, sites from which saccades could be evoked with stimulation were located exclusively in
the anterior lateral quadrant of the craniotomy, corresponding to the location of the lateral aspect
of the genu of the arcuate sulcus.

During each experimental session, we determined the saccade vector elicited at the cortical site
under study and the current threshold to evoke a saccade using a separate behavioral paradigm. In
this paradigm, the monkey was required to fixate a visual stimulus (0.5°) for 250-500 ms after
which time a stimulation pulse was delivered. On each trial, the visual stimulus was positioned at
one of five positions, one at the center of gaze and one 10° from center along each cardinal
direction. The use of the nonzero fixation points allowed us to verify that saccades evoked were
fixed-vector (Bruce et al., 1985). The endpoints of saccades evoked from the central position were
used to define the MF. Current thresholds to evoke a saccadic eye movement were determined by
running separate blocks of trials with different current amplitudes and measuring the probability of
evoking a saccade at each current value. The metrics of the evoked saccade vector and the
corresponding threshold were determined both at the beginning and at the end of the experimental
session to ensure that neither had changed significantly throughout the session.

psychophysical performance

In most experiments, we measured the lowest target luminance change that the monkey could
detect and thus the sensitivity to target luminance changes. Thresholds were determined by way of
a simultaneous staircase method in which the size of the luminance change was increased or
decreased in steps after a block of trials, depending on the performance of the monkey. Each block
of trials consisted of two change trials and one catch trial. Blocks in which the monkey
successfully detected at least one of the target luminance changes (50%) and also successfully
completed the catch trial (100%) were followed by a decrease in the size of the luminance change.
Blocks in which the monkey failed to detect at least one change or failed the catch trial were followed by an increase in the size of the luminance change. Thus, the obtained threshold depended on both trial types. This meant that psychophysical thresholds depended exclusively on the ability of the monkey to detect the target change, and no other event. In each experiment, the monkey performed 10-25 consecutive blocks of trials, or 30-75 trials. Control and stimulation blocks were run simultaneously and were randomly interleaved. Each set of blocks consisted of one-third control blocks and two-thirds stimulation blocks. Stimulation blocks were divided between short and long SOA blocks. Thus, at the completion of a set of blocks, there were three threshold estimates, control, short SOA stimulation and long SOA stimulation, obtained from 90-225 trials.

Estimates of the luminance change threshold were obtained by fitting the staircase data with an asymptotic function. In each fit, we first interpolated the raw staircase data by computing the running average of luminance change steps \( (y) \) across blocks \( (x) \):

\[
x', y' = \left[ \frac{x_i + x_{i+1}}{2}, \frac{y_i + y_{i+1}}{2} \right]
\]

where \( i \) is the block number for \( n \)-1 blocks. This was done to allow for better asymptotic fits of the staircase data given the fact that the discrete nature of staircase data make it impossible to fit perfectly. Thus, for example, the raw staircase vector \([1 \ 2 \ 3 \ 4 \ 5 \ 6 \ 5 \ 6 \ 5 \ 6]\), which shows the discrete progression of steps to an asymptote of approximately 5.5, would result in the interpolated vector \([1.5 \ 2.5 \ 3.5 \ 4.5 \ 5.5 \ 5.5 \ 5.5 \ 5.5 \ 5.5 \ 5.5]\), one that has the same asymptotic value but can be fit perfectly. The interpolated staircase data were then least-square fitted with the asymptotic function:
where $a$ is the asymptotic luminance change and $b$ is the block number at asymptote. Note that we used a different asymptotic function than that described previously (Moore and Fallah, 2001) and that the previous fits were computed on raw staircase data and not on the interpolated data. The current method allowed us to obtain better fits (median $R^2 = 0.620$) and therefore more accurate estimates of the psychophysical threshold. Once a threshold was obtained for a given staircase function, we converted it into its corresponding sensitivity value, the reciprocal of the threshold.

RESULTS

Saccadic eye movements were evoked at 103/134 cortical sites in the two monkeys. Of the 103 sites, we were able to determine the current thresholds at 73, and thus were able to test the effect of stimulation on attention. The mean current threshold was 47 $\mu$A (s.d. = 37) and the median stimulation evoked saccade latency was 50 ms. Both sets of values are consistent with those previously reported (Bruce et al, 1985). The mean amplitude of saccades evoked was 13.2° (range 5 - 20°) into the contralateral hemifields and the distribution of saccade direction included both upper and lower quadrants of the visual field (-85° to 90°).

Initial tests: optimizing subthreshold current

Although our experiment was designed to test the effect of subthreshold stimulation on attention, at the outset we did not know how far below threshold the test current should be. Therefore, our initial tests were designed, in part, to optimize the subthreshold current value. In these experiments, we did not measure psychophysical thresholds but instead compared the percent
correct performance of control and stimulation trials. In this case, performance was measured as the mean of the blink and catch trials. During each experiment, the level of stimulating current used, expressed as a fraction of threshold current, was varied arbitrarily between 46 and 88% (25 - 150 µA, median = 73 µA). Figure 2A shows the effect of stimulation as a function of normalized current level for 17 of these initial experiments. The mean difference between stimulation and control trials, although small (4%), is statistically significant (t test, P < 0.05). But more importantly, the effect of stimulation depended significantly on the fractional current level used (Kendall Rank correlation, $R = 0.770$, P < 0.05). This result suggests that the positive effect of FEF stimulation on performance can only be observed when the current is sufficiently below the movement threshold. In the data shown, the linear best fit of the effect over current level has an x-intercept at $\approx 80\%$. This result is consistent with our observation that during experiments using near threshold currents, the monkey frequently broke fixation on stimulation trials, often making saccades to the target stimulus. Stimulation at near threshold currents thus appeared only to make carrying out the task more difficult. In all subsequent experiments, we therefore used currents that were $\approx 50\%$ of the movement threshold. In addition, we changed our dependent variable from a performance measure to that of a psychophysical threshold, and its corresponding measure of sensitivity, to obtain a more precise measure of the effects of stimulation.

Stimulation of FEF at $\approx 50\%$ of the movement threshold did not disrupt the ability of monkeys to maintain fixation while performing the attention task. Figure 2B shows both the mean eye velocity and eye position with respect to the MF during and after a 100-ms stimulation train. Data from subthreshold stimulation trials were obtained during 1,424 stimulation trials (catch and blink). Data from suprathreshold stimulation trials were obtained during 376 calibration trials in which the stimulation evoked saccadic eye movements 100% of the time. The latter shows the
mean eye velocity and displacement for evoked movements with a range of metrics. At the same
FEF sites, subthreshold stimulation, however, did not disrupt fixation. During subthreshold
stimulation, the component of eye velocity in the direction of the MF remained well below the
range in which saccades are detected. Moreover, throughout the stimulation trial, the eye position
data showed no evidence of drift toward the MF. Instead, however, there appeared to be a very
small shift in eye position away from the MF (< 0.1 deg), and this drift began ≈ 75 ms after the
completion of the stimulation train. The lack of any disruption in fixation during subthreshold
stimulation indicates that the position and stability of the visual target on the retina during the
attention task were identical in control and stimulation trials.

**Psychophysical effects of stimulation: response criterion**

We measured the monkey's sensitivity to target changes in the MF during a staircase procedure
in which the task difficulty was increased or decreased according to the monkey's performance.
Throughout this procedure, the monkey's performance (% correct) was held constant at 66.6%.
This performance was determined both by the blink and catch trial performance. Subthreshold
stimulation of FEF during the attention task did not affect the monkey's response criterion.
Relative performance on catch and blink trials during control and stimulation trials were
statistically indistinguishable during the staircase procedure (92 % catch, 49% blink, *control*; 91%
catch, 51% blink, *stimulation*; t-test, *p*>0.05). Thus, stimulation did not alter the likelihood that
the monkey would release the lever. In addition, comparison of the latencies of lever releases
allowed us to rule out any effect of stimulation on the release of the lever. During trials on which
the target blinked, the mean latency of lever releases (reports of a target blink) was 471 ms without
stimulation as compared to 469 ms during stimulation trials, a difference that is not significant (t-test, p>0.05).

**Psychophysical effects: sensitivity to target luminance changes**

Using current levels ≈50% of the movement threshold, we compared the luminance change thresholds obtained during stimulation trials with that of control (no stimulation) trials using the peripheral attention task. Figure 3 illustrates the experimental procedure and an example of the effect of microstimulation. In this example, stimulation of the FEF site using a current of 25 µA, evoked saccadic eye movements, shifting the direction of gaze to a location 8° into the contralateral field. With progressively lower currents, fewer saccades were evoked. For this site, the movement threshold, or current at which saccades were evoked half the time, was about 18 µA. During the attention task, microstimulation with a 9 µA (subthreshold) current preceded the luminance change (blink trials), or occurred without a luminance change (catch trials). During control trials, the monkey was able to reliably detect a 45% change in target luminance. In contrast, during stimulation trials the monkey was able to detect a 30% change in target luminance. In this case, the luminance change required to obtain equal performance between the two experimental conditions differed by 15%, stimulation trials yielding a lower threshold. The corresponding measures of sensitivity for the control and stimulation conditions were 2.22 (1/0.46) and 3.03 (1/0.34), respectively. Stimulation thus raised the relative sensitivity by 37%.

We conducted a total of 59 tests of the effect of microstimulation on detection inside the MF at 49 FEF sites (mean threshold current = 35; s.d. = 23; mean test current = 15; s.d. = 12). Stimulation of FEF increased the monkey's sensitivity to the luminance change, relative to the control trials, when the target was positioned within the MF. Figure 4A shows a distribution of
sensitivities relative to the control trials obtained for all 59 experiments. The shift in the distribution above 0 indicates a general increase in sensitivity to the luminance change with stimulation relative to the control condition (t-test, p < 0.0001). Relative sensitivity data are shown log-transformed to permit symmetric values on either side of zero, and thus to normalize the distributions of the obtained values. When the data from the two monkeys were analyzed separately, each set showed a significant increase in relative sensitivity (monkey A, n = 38, t-test, p < 0.0006; monkey B, n = 21, t-test, p < 0.03). The mean relative sensitivity for all experiments, expressed logarithmically, was 0.048 signifying a 12% increase in sensitivity. This increase was identical in the two monkeys (mean = 11 ± 2.8%, monkey A; mean = 12 ± 5.2%, monkey B; Factorial ANOVA, F = 0.010, p > 0.9).

In contrast to the effects observed inside of the MF, we found no effect of stimulation on the sensitivity to luminance changes outside of the MF. During these experiments, we attempted to place the target at a location 90° θ from the MF (relative to the fixation point), but at the same eccentricity and within the same hemifield. In some cases, the dimensions of the monitor constrained the placement of the target and thus other locations distant from the MF were chosen. The average absolute distance (in degrees of visual angle) between the MF and the outside location was 17° (range 7° - 27°). In all but one case, the outside target was placed in the same visual hemifield as the MF (i.e. contralateral to the stimulated FEF). The distribution of relative sensitivity values was centered at -4.7% (Figure 4B), but was not significantly different from zero (t-test, p > 0.36). Thus, sensitivity to the target change was unaltered by stimulation in this configuration.

We considered the possibility that a failure to find an effect of stimulation on the monkey's performance in the outside configuration might have been due to the fact that we conducted fewer
experiments \( (n = 28) \) than with the *inside* configuration \( (n = 59) \). Therefore, we directly compared the results obtained with the *inside* configuration with the results obtained with the *outside* configuration when both experiments were performed at the same FEF site. This comparison consisted of 26 experiments in which all experimental conditions were identical (i.e. test current, SOA, target size, distracter size, etc) except for the location of the target with respect to the MF. For the subgroup of *inside* experiments with corresponding *outside* tests, sensitivity to the luminance change was significantly elevated above the control (mean = 0.064 ± 0.014; t-test, \( p < 0.0001 \)) by approximately 16%. This observation indicates that neither the sample size nor the particular experimental conditions could account for the absence of stimulation effects in the *outside* configuration. Furthermore, a (nonparametric) paired comparison of the relative sensitivities obtained in the *inside* and *outside* conditions (*inside* - *outside*) reveals a significantly larger change in sensitivity when the target was positioned inside the MF (Wilcoxon signed-rank test, \( p < 0.002 \)) (Figure 4C). Thus, the position of the target with respect to the MF was a critical factor in determining the magnitude of the stimulation effect.

*Effect of stimulation onset asynchrony*

By systematically varying the onset of the stimulation relative to the target luminance change (SOA) we were able to examine the effect of biasing oculomotor preparation at different times relative to the target event. Each stimulation experiment consisted of two different widely spaced SOAs, one 'short' and one 'long'. Data considered thus far represent only short SOA conditions; that is, conditions in which the stimulation train began 50 to 175 ms prior to the target luminance change. During interleaved trials, we also examined the effect of stimulation on psychophysical thresholds when the stimulation train began from 275 to 525 ms before the target
change. The total range of SOAs thus allowed us to examine the effect of stimulation from -525 ms to -50 ms relative to the target change.

In contrast to the results with short SOAs, stimulation at long SOAs did not significantly affect sensitivity to the target luminance change (t-test, p > 0.47). The relative sensitivity obtained with stimulation at longer SOAs averaged only 2.1 ± 3%. Moreover, a paired comparison of the relative sensitivity obtained with short and long SOAs during the same experiments revealed an effect of the time (short vs. long SOA) of stimulation (mean difference in relative sensitivity = 9.5%, t-test, p < 0.004). The effect of stimulation was greatest when the onset of stimulation and the target change differed by only 50 ms and decreased exponentially with longer SOAs (Figure 5). At the shortest SOA, the 100 ms stimulation train temporally overlapped the target change and the monkey's sensitivity to the change improved by 18% (0.073 log relative). Overall, mean relative sensitivity was significantly correlated with SOA (R² = 0.85, p < 0.01) reflecting a decreasing effect of stimulation with increasing SOA. Data plotted in figure 5 are shown fit with an exponential function (R² = 0.93) in which the relative sensitivity peaks at 22% (0.088 log relative) when extrapolated to an SOA of 0 ms and decays half way at an SOA of 165 ms.

Comparison of stimulation effects with distracter removal

Although we believed that our use of a distracter made the task more difficult, we nonetheless sought to verify that this was indeed the case. Moreover, we sought to compare the effect of FEF stimulation, increased sensitivity to target changes in the MF, with the effect of distracter removal. We therefore conducted a small number of experiments (n = 23) in which we measured each monkey's psychophysical performance in the presence or absence of the distracter during interleaved trials. In these experiments, we placed the target at a fixed location 5° from the
fixation point. During this manipulation, there was no FEF stimulation. As expected, the monkey was more sensitive to the target luminance change when the distracter was removed. Shown in figure 6A is the result of one such experiment. Overall, the monkey's sensitivity to the target change was increased by 21% when the distracter was removed (t-test, p<0.001). More importantly, the improvement observed after complete removal of the distracter was not significantly greater than when FEF stimulation was applied at the shortest SOA (t-test, p>0.05) (Fig. 6B).

DISCUSSION

Our results demonstrate that visual detection can be enhanced by subthreshold stimulation of FEF sites from which saccades are evoked. Our results show that when a target luminance change was preceded by subthreshold stimulation of FEF, monkeys were able to detect smaller changes in target luminance. This improved performance only occurred when the target was placed in the part of visual space represented by neurons at the stimulation site. The improvement depended on the temporal asynchrony of the stimulation onset and the target event, the largest facilitation occurring at the shortest asynchrony. The magnitude of the improvement at the shortest asynchrony was comparable to the improvement observed after removing the distracter from the task. Below, we discuss the possible mechanisms underlying the effects of stimulation and suggest how covert oculomotor signals might be involved in modulating visual representations.

Underlying mechanisms

Electrical stimulation of neural tissue activates all neural elements in the vicinity of the electrode tip (Tehovnik, 1996). It is therefore important to consider the degree to which the
stimulation effects were due to direct activation of FEF neurons, as opposed to other brain structures. The FEF is heavily interconnected with other cortical and subcortical structures, such as the superior colliculus and parietal lobe area LIP, both of which have a known involvement in oculomotor behavior and are believed to be involved in spatial attention (Bushnell et al., 1981; Kustov and Robinson, 1996). Our effects could have resulted from activation of neurons within the FEF and the subsequent activation of structures to which the FEF projects as well as from direct antidromic stimulation of neurons forming connections with the FEF. Thus, FEF stimulation may have indirectly produced attentional modulation by orthodromic or antidromic recruitment of other structures that in turn directly act to increase spatial attention. If the observed effects were exclusively due to antidromic activation of areas projecting to FEF, it is possible that FEF neurons themselves play no role in allocating covert spatial attention.

If we assume that the results implicate the FEF in the control of covert attention, we must also take into account the heterogeneity of function among FEF neurons. Several studies have obtained evidence suggesting that neural activity correlated with covert selection is dissociable from neural activity correlated with saccade execution (Thompson et al., 1997; Murthy et al., 2001). Thus, we must consider that the psychophysical effects observed might represent two separate, and independent, outcomes of microstimulation, one being an increase in the strength of a specific saccade command, and the other being an increase in the allocation of covert attention. Our results are limited in that they merely demonstrate that attentional facilitation can be generated from the same cortical sites from which saccades can be evoked. Our results do not establish that this facilitation is accomplished via activation of only motor related FEF neurons, or motor related neurons with inputs to the FEF. On the contrary, the attentional facilitation may have operated independently of the motor effects of microstimulation. Although we suspect that the two
subpopulations of FEF cells, those more directly involved in saccade commands and those more
directly involved in covert attention, are functionally coupled under normal behavioral
circumstances, and that modifying the activity of one results in activity changes in the other, the
possibility that this is not the case remains open. Indeed, future studies will need to directly
determine the degree of interdependence of the subpopulations of neurons within the FEF.

Mode of action

As it is unclear which pathways activated by stimulation of the FEF sites are sufficient to
explain the improvement in psychophysical performance, it is also important to consider the
impact of stimulation on perception in general. Neurons within the FEF include those that respond
in relation to saccades as well as those that respond to the appearance of visual stimuli (Bruce et
al., 1985) and thus one must consider the role of the FEF in vision, not merely motor preparation.
For example, the possibility that stimulation of the FEF produces a visual percept must be
carefully considered. It might be argued that the improvement in sensitivity to target changes
observed in the MF could have been produced indirectly by eliciting a visual percept, or
phosphene, that in turn heightened the monkeys' sensitivity to an impending target luminance
change (Posner, 1980). This hypothesis would also predict the spatial dependence of the observed
effects. While it should be stressed that one cannot determine the impact of FEF stimulation on a
monkey's visual experience, there are several reasons that make the above hypothesis unlikely.

First, the design of our behavioral task is not compatible with those in which effects of
visual cueing are obtained. Typically, when visual cueing is used to shift attention the subject is
uncertain of the target location on any given trial (e.g. Eriksen and Hoffman, 1973; Posner, 1980).
In contrast, the position of the target in our task was known throughout the entire block and the
monkey had to maintain attention at that position as best it could while the distracter was presented. Human psychophysical studies demonstrate that attention effects with visual cues depend critically on uncertainty of the target location (Nazir, 1992; Shiu and Pashler, 1994). Moreover, even when visual cues elicit greater psychophysical performance at a cued location that is already known, they require a substantial cue-target SOA (> 200 ms) (Luck et al., 1996). This observation contradicts those of the present paper in which the largest effects were obtained when the target event and FEF stimulation temporally overlapped. Furthermore, stimulation on both blink and catch trials prevented it from reducing any temporal uncertainty.

Second, by stimulating at varying times with respect to the target event, we were able to examine how the signals it produced interacted with the veridical luminance change. Thus, stimulation could improve, interfere with or have no effect on the detection of target events. If stimulation of the FEF evokes visual sensations, we should expect it to mask the target event when the two overlap temporally. A wealth of psychophysical evidence has established that simultaneously presented visual stimuli mask one another (Breitmeyer, 1990). Furthermore, at least one recent attention study found that visual cues would mask the target when presented at the target location at very short SOAs (Luck et al., 1996). In our task, the monkey was required to detect only the veridical target event (luminance decrement), and thus extraneous visual signals occurring at the same location should only impede, not improve, performance. If FEF stimulation had injected a visual signal, one should expect the monkey to perform more poorly on blink trials and on catch trials, failing to report actual target changes and reporting changes that did not occur, respectively, thereby decreasing its sensitivity to the veridical target event. Our results demonstrate a peak in the psychophysical improvement when the stimulation and the luminance change overlapped in time, thus contradicting a visual sensation hypothesis.
Third, stimulation of human FEF does not evoke visual sensations. Stimulation of human FEF elicits short-latency saccadic eye movements into the contralateral hemifield, just as it does in nonhuman primates (Foerster, 1931; Penfield and Rasmussen, 1950; Godoy et al., 1990; Blanke et al., 2000). The region from which saccades can be evoked is responsive to visual stimuli as well (Blanke et al., 1999). However, during stimulation subjects do not report visual sensations, just that their eyes are moving beyond their control (Penfield and Rasmussen, 1950; Blanke et al., 2000; O. Blanke, personal communication). Visual hallucinations can be elicited by stimulation of cortical sites anterior or lateral to human FEF (Blanke et al., 2000), sites homologous with dorsolateral prefrontal cortex in the monkey (Miller, 1999), but these hallucinations are extremely complex in nature and include at least the entire contralateral hemifield. Therefore, insofar as human and monkey FEF are homologous one should be confident that FEF stimulation was not associated with visual sensations, particular at subthreshold currents.

It is ultimately impossible to determine precisely the subjective effects of FEF microstimulation in monkeys, owing to the animal's marked inability to describe them to us. However, we believe that a hypothesis attempting to explain our psychophysical effects as due to categorically visual phenomena is not parsimonious. Instead, we interpret our observations in the light of evidence of the FEF's role, and its immediate connections, in visuomotor transformations (Bruce, 1990; Schall, 1995). Neurons within the FEF respond to the appearance of visual targets and in relation to purposive saccades to them. Visual responses exhibit little or no visual selectivity (Mohler et al., 1972), but presaccadic activity is highly tuned to the direction and amplitude of saccades (Bruce et al., 1985; Schall et al., 1995). These properties suggest that activation of sites within the FEF can specify a location in space without specifying a particular visual stimulus or stimulus attribute. If so, the effect of FEF stimulation might be to increase the salience of visual
representations via known feedback projections to posterior visual areas (Stanton et al., 1995). This view is consistent with both the visual and the motor properties of the area. It is also consistent with recent work from our laboratory demonstrating that the effect of subthreshold stimulation on responses in visual cortex is to change the gain of visual responses in a spatially selective manner (Moore and Armstrong, 2003).

**Suppressed saccades and covert attention**

Although relevant stimuli usually require orienting responses in which movements bring the targets of interest onto the foveas, sometimes such movements need to be suppressed. Gaze direction is often deliberately averted from the subject of attention, particularly during social interactions in primates. In monkey and man, direct gaze is often a sign of aggression and thus subdominant monkeys often avoid the gaze of more dominant monkeys (van Hooff, 1972). Some patients with frontal cortex lesions are unable to suppress reflexive saccades to salient targets (Guitton et al., 1985; Holmes, 1918) suggesting that the frontal lobe, and possibly the frontal eye fields, is also involved in suppressing inappropriate saccades. Consistent with this observation is the finding that microstimulation of the FEF can delay saccades to locations that differ from that represented at the stimulation site (Burman and Bruce, 1997). Stimulation of the more foveal representation of the FEF delayed contraversive saccades up to a half of a second. At sites from which saccades could be evoked, stimulation below the movement threshold delayed saccades to locations outside of the MF. One interpretation is that the relative strength of oculomotor plans within FEF is crucial in the triggering of saccades and thus the suppression of a saccade is the result of competing plans within FEF.
In the present study, monkeys fixated while covertly attending to a peripheral target stimulus and this task might have thus required maintaining a balance of two competing oculomotor plans, the fixation plan being slightly stronger, and therefore being carried out. One simple view would be that covert and overt spatial attention mechanisms differ only in terms of motor input. Accordingly, the strength of covert spatial attention would be directly proportional to the strength of motor preparatory signals and the probability of those signals being carried out. This relationship is shown schematically in figure 7. In this descriptive model, the present result of enhanced psychophysical performance in the MF is explained by assuming a direct relationship between visual sensitivity and the strength of the movement plan to the target stimulus, relative to the fixation command. In both control and stimulation conditions the relative movement plan is always less than 1, since the monkey remains fixated, but it is elevated by FEF stimulation. The elevated oculomotor signal elicited by FEF stimulation thus results in an increased sensitivity to visual events within the MF. Note that the model illustrated also suggests even greater improvements in sensitivity when FEF is stimulated at or near the movement threshold. Our initial observations actually suggested a performance decrement with near threshold stimulation (fig. 2A). However, this was due to the fact that such stimulation prevented the monkey from carrying out the fixation component of the task and thus prevented us from adequately measuring the monkey's performance. The descriptive model predicts that the greatest improvement would have been observed had it been possible to measure performance when saccades were actually evoked. This component of the model is based on previous psychophysical evidence of improved visual detection immediately prior to saccades (e.g. Hoffman and Subramaniam, 1995).

The model also predicts that when the monkey performs the task outside of the MF, the effect of stimulation should be reversed. However, given that the efficacy of FEF stimulation is
known to be greatly reduced when the evoked behaviors are not compatible with the rewarded task behavior (Goldberg et al., 1986; Tehovnik et al., 1999), one should expect a similar reduction in the effects of stimulation when the monkey performs the task outside the MF. Current thresholds to evoke a saccade are elevated by a factor of 3 if the saccade keeps the monkey from completing the rewarded task (Tehovnik et al., 1999). Thus, the expected decrease in the relative movement plan in the outside configuration should be only 1/3 of what it is in the inside configuration. Given the observed 12% change in sensitivity inside the MF, one should expect a change of -4% outside of it. Although our tests outside of the MF yielded no significant effect of stimulation, the mean change in sensitivity was -4.7%.

In a recent study, we found that subthreshold microstimulation of the FEF was followed by gain changes in the visual responses of V4 neurons (Moore and Armstrong, 2003). In this study, monkeys were not trained to attend to peripheral visual stimuli, but an attention-like enhancement could be evoked by FEF microstimulation when the receptive fields of V4 neurons and the FEF representations overlapped spatially. Unlike what the results of the outside experiments might predict, microstimulation of non-overlapping FEF representations resulted in a significant suppression of visual responses of V4 neurons. However, in the electrophysiological study the behavioral conditions of the overlap and non-overlap conditions were identical in terms of the impact of stimulation on the rewarded task. Nevertheless, the suppression effect appeared to be only half the magnitude of the enhancement effect. Both enhancement and suppression effects observed lasted at least 100 ms following the end of microstimulation. This observations suggests a physiological basis for the temporal dependence of the psychophysical effects observed in the present study. Both results are consistent with the time scale of psychophysically determined shifts of attention during change detection tasks (Rensink, 1999) and the dynamic changes in the
representation of oculomotor commands within the FEF (Schlag et al., 1998; Seidemann et al., 2002).

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Figure 1. Diagram of the attention paradigm used to measure the effects of stimulation. A, The display used in the spatial attention task. In the task, the monkey attends to a peripheral target (indicated by searchlight) while maintaining central fixation and signals a transient dimming of the target with a lever release. During the task, a distracter is flashed in rapid succession at random locations throughout the display. The distracter is shown as scattered throughout the display to convey the its appearance due to visual persistence. To test the effect of FEF stimulation on attention, the target was placed at the location to which suprathreshold stimulation would shift the monkey's gaze, referred to as the 'movement field' (MF). B, The timing of events in the spatial attention task. The top set of traces illustrates the sequence of events on trials in which the target dims ('Blink' trial), the monkey correctly releases the lever and a reward is delivered. The bottom trace illustrates the same but for trials in which the target does not dim ('Catch' trial) and the monkey is rewarded for holding down the lever. When testing the effect of FEF stimulation on task performance, stimulation occurred before the target change, or at random times during catch trials.

Figure 2. A, Effect of FEF stimulation on attention task performance (% correct) during initial experiments in which the stimulation current varied with respect to the current threshold. Points represent the differences between stimulation and control task performance (stimulation - control) across varying current. Current is shown normalized to the movement threshold (i.e., current used/threshold current). The mean difference in performance was significantly greater than zero, but this difference depended on the current used relative to the threshold current. Subsequent experiments were therefore carried out using currents at ≈50% of threshold current (arrow). B,
Stability of fixation during suprathreshold and subthreshold stimulation. Stimulation evoked saccades during suprathreshold stimulation and failed to disrupt active fixation during subthreshold stimulation. The top set of traces plots the component of velocity in the direction of the MF during suprathreshold (gray), subthreshold (black) and non-stimulation trials (dashed). Note that the subthreshold and control traces are grossly overlapping. The bottom traces plots the eye displacement (position). Suprathreshold plots, which are clipped, show the means of 376 stimulation-evoked saccades obtained during calibration trials. Subthreshold and non-stimulation plots are the means of 1,424 each, and were obtained during the attention task. Note that the subthreshold trace deviates from zero and from the control trace by ≈-0.05° beginning 75 ms following the end of the stimulation train.

Figure 3. Illustration of a typical experiment and the effect of stimulation on psychophysical performance. A, Top, individual saccade vectors obtained during suprathreshold stimulation of an FEF site illustrating how the MF was mapped. Vector traces show 8 saccades evoked on 8 trials at a (suprathreshold) current of 25 µA. Calibration bar indicates 2 degrees, vertical and horizontal. Bottom plot shows the proportion of evoked saccades measured at different current levels to determine the current threshold. The open arrowhead indicates the subthreshold current (9 µA) used during the spatial attention task. B, Top, depiction of the attention task performed with the target positioned in the MF. Bottom plot shows staircase functions used to obtain target change thresholds (% Michaelson contrast from background) with (filled symbols) and without microstimulation (open symbols). Each set of points is fitted with an asymptotic function to estimate the threshold.
Figure 4. The effect of microstimulation on sensitivity to target luminance changes. A, Histogram shows the distribution of the log relative sensitivity ( \( \log \frac{\text{sensitivity}_{\text{stimulation}}}{\text{sensitivity}_{\text{control}}} \) ). The distribution shows data obtained during 59 experiments in which the task was performed with the target in the MF (icon on right). A lack of an effect of stimulation would result in a distribution centered on zero. The distribution of relative sensitivity shown has a mean at 0.048 (arrow) signifying a 12% increase in sensitivity to the target change with stimulation. B, Effect of stimulation when the target was positioned outside of the MF. Distribution of relative sensitivity values for 28 experiments in which the target was positioned outside of the MF. The distribution is centered on zero, illustrating no significant effect of stimulation. C, Comparison of effects of stimulation on relative sensitivity when the target was either positioned inside or outside of the MF. Scatter plot shows the relative sensitivity values obtained from experiments with the target inside the MF (abscissa) and those obtained outside of the MF (ordinate) when both experiments were performed at the same FEF site (n = 26). Arrows on the right and top indicate the mean inside and outside values.

Figure 5. Comparison of the effects of stimulation at different stimulation onset asynchronies (SOAs). On stimulation trials, the interval between the onset of the stimulation train and the target luminance change was either short or long (top diagram). Bottom plot shows the effect of specific SOAs on mean relative sensitivity. The upper three SOAs represent the long SOAs, and the lower three represent the short SOAs. The effect of stimulation increased as the SOA approached zero and peaked at 0.073, or 18% above control.
Figure 6. The effect of removing the distracter on the detection of target luminance change. A, Example of thresholds obtained during blocks of trials in which the monkey had to detect a target luminance change in the presence of the flashing distracter (open symbols) or without the distracter (filled symbols) during interleaved trials. Diagrams at top illustrate the display as viewed by the monkey and the presence (left) or absence of the distracter (right). The plot shows the interpolated staircase data obtained during 20 blocks of trials in each condition. B, Effect of removing the distracter on sensitivity to target change compared with the effect of FEF stimulation (microstim) at the shortest SOA.

Figure 7. Descriptive model of the effect of FEF stimulation on covert and overt spatial attention. Icons at the top depict the inside and outside MF task configurations. Plots below show theoretical curves in which the sensitivity to target changes is a function of the strength of preparation of saccades to the target, relative to the strength of the fixation plan. Shown in red is a plot of the monkey's discrete eye position, at either the fixation point (FP) or at the target. When the relative movement plan exceeds 1, the monkey initiates a saccade to the target half of the time. Open and black arrows indicate the strength of the relative movement plan expected during control and stimulation trials, respectively. Note that when the task is performed with the target in the MF, left, the effect of FEF stimulation is to increase the relative movement plan substantially, while when it is performed with the target elsewhere, the effect is to decrease it by only a small amount. This prediction is based on the observation that the effect of FEF stimulation depends on the degree to which the evoked behaviors are consonant with the rewarded task (Tehovnik et al., 1999). Both plots explain changes in visual sensitivity at the target location by the changes in the monkeys relative movement plan initiated by FEF stimulation.
Figure 1
Moore and Fallah
Figure 2
Moore and Fallah

A

![Graph showing Performance Difference (% correct) vs. Normalized Current](image)

B

![Graphs showing Velocity and Position](image)
Figure 3
Moore and Fallah
Figure 4
Moore and Fallah

A

Number of experiments

Log relative sensitivity

B

Number of experiments

Log relative sensitivity

C

Log relative sensitivity (outside)

Log relative sensitivity (inside)
Figure 5
Moore and Fallah
Figure 6
Moore and Fallah

A

![Graph showing the effect of luminance change on log relative sensitivity.](image)

B

![Bar graph showing log relative sensitivity.](image)
Figure 7
Moore and Fallah

A

B

Eye position

Relative movement plan [target/fixation spot]

Sensitivity at target location

Relative movement plan [target/fixation spot]

Eye position