Unilateral Inactivation of Macaque Frontal Eye Field Produces an Impairment of Saccadic Target Selection as Distinct from Attentional Neglect

by

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The frontal eye field (FEF) has been implicated as a possible participant in attentional allocation. Recent studies have found that low-current stimulation of FEF results in enhanced attention and increased visual responses in extrastriate visual area V4. We investigated the necessity of FEF function for allocating attention by unilaterally inactivating FEF in two monkeys and testing the monkeys' ability on a two-alternative forced-choice saccade task. This task was designed to spatially dissociate two processes which we assessed separately: discrimination of a visual cue and generation of a saccade. Following inactivation, we determined the extent of contralesional saccadic deficits, compared to contralesional discrimination deficits, using a choice-based analysis and a reaction time (RT)-based analysis. Overall, we found that unilateral inactivation had an impact on contralesional saccadic performance corresponding to a 61.7-ms overall change in RT and a 34% change in choice probability. On the other hand, we discovered only a 7.0-ms overall change in RT and a 0% change in choice probability with respect to contralesional visual discrimination ability. We conclude that FEF function is much more important for saccadic generation than attentional allocation.

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1.0 INTRODUCTION

The frontal eye field (FEF) is considered an important site for visuomotor transformations in primates. At a critical point between sensory input and motor output, FEF receives neuronal input from visual and associative areas in the brain (Barbas and Mesulam 1981; Weller and Kaas 1987), and sends signals to oculomotor command structures (Fries 1984; Stanton et al. 1988). Electrophysiological studies have shown that FEF neurons display a wide range of responses related to visual stimuli and saccade preparation; some neurons respond best to the onset of a stimulus in their response field (RF) while some are most active before a saccade is made into their RF (Bruce and Goldberg 1985).

More recently, studies have focused on dissociating visual activity and movement-related activity in FEF, particularly in neurons which display both types of activity (Hanes et al. 1995; Schall et al. 1995, 2004; Thompson and Schall 1999; Thompson et al. 1996, 1997). In addition, visually responsive FEF neurons have been found to represent the locus of visual attention in a variety of saccadic and attentional tasks (Murthy et al. 2001; Sato and Schall 2003; Sato et al. 2003; Thompson and Schall 2000; Thompson et al. 2005).

Further experiments have suggested that FEF neurons actually participate in the allocation of visual attention (for review, see Moore et al. 2003). In particular, low-current stimulation of FEF has been shown to result in an enhancement of the monkeys' ability to detect the dimming of a visual target in the RF of the stimulated FEF site (Moore and Fallah 2001, 2004) and an enhancement of the visual response of V4 neurons with receptive fields matching the RF of the stimulated FEF site (Moore and Armstrong 2003). However, it is possible that stimulation of FEF in these experiments resulted in activation of a larger attentional network, or antidromic activation of extrastriate visual areas including V4, rather than generating a signal comparable to that produced physiologically during visual stimulation and saccades. Regardless of whether

these experiments show a true contribution of FEF in visual attention, however, it has yet to be shown whether FEF is necessary for visual attention.

To determine whether FEF is necessary for the allocation of visual attention, the function of FEF must be abolished as visual attentional abilities are probed. Many studies have addressed the behavioral impact of FEF ablation. The most profound deficits as a result of surgical unilateral FEF lesions seem to be an inability to fixate (Latto and Cowey 1971a; Ó Scalaidhe et al. 1997) and generate eye movements in the contralesional direction in response to visual stimuli (Latto and Cowey 1972; Crowne and Mah 1998; Schiller and Chou 1998). Sommer and Tehovnik (1997) reported that unilateral reversible inactivation of FEF resulted in deficits in generating saccades to contralesional targets, particularly flashed or extinguished targets, as well as maintaining fixation at a contralateral point and suppressing ipsiversive saccades. Unilateral reversible FEF inactivation has also been found to impair contraversive memory-guided saccades (Dias and Segraves 1999, Sawaguchi and Iba 2001).

Most of the FEF ablation studies to date have not dissociated between sensory and motor aspects of the task used to assess post-lesion neglect. Therefore, failure to respond to visual stimuli with a saccadic eye movement could have been due to a failure of sensory *or* motor processing in FEF. The one exception is a study by Latto and Cowey (1971b), in which monkeys were tested using manual lever response. The investigators reported that monkeys were less likely to detect contralesional visual stimuli following surgical FEF ablations; however, the measure used to detect eye movements at this time was imprecise.

In an attempt to determine whether unilateral FEF results in contralesional visual deficits as well as contralesional saccadic deficits, we designed a test in which the location of a visual cue and the location of the saccadic response were dissociated. We then used muscimol to reversibly inactivate FEF in one hemisphere, and assessed the impact of the lesion on contralesional cue detection and contralesional saccades.

2.0 METHODS

2.1 GENERAL

2.1.1 Subjects

Two adult male rhesus monkeys (*Macaca mulatta*), with laboratory designations P (8.4 kg) and N (7.0 kg), were used. Experimental procedures were approved by the Carnegie Mellon University Animal Care and Use Committee and were in compliance with the guidelines set forth in the United States Public Health Service for the Care and Use of Laboratory Animals.

2.1.2 Surgical Procedures

Before training, both monkeys underwent sterile surgeries under general anesthesia during which an acrylic cap was attached to bone screws inserted into the skull, and a head-restraint bar was embedded in the acrylic. Scleral search coils were implanted on the eyes and connected to plugs in the acrylic cap. To give access to the FEF, a 2-cm-diameter disk of acrylic and skull was removed and a cylindrical chamber was cemented over the exposed dura. The chamber was implanted over the right hemisphere in monkey N and over the left hemisphere in monkey P.

2.1.3 Behavioral apparatus

Behavioral training and experiments (including presentation of stimuli, monitoring and recording of eye movements, and delivery of reward) were controlled by a computer running Cortex software (R. Desimone, National Institute of Mental Health). Eye position was

monitored using the scleral search coil method. Stimuli were generated and displayed on a computer monitor placed 25 cm from the monkeys' eyes. Juice rewards were delivered through a spigot controlled by a solenoid valve.

2.2 BEHAVIORAL TASKS

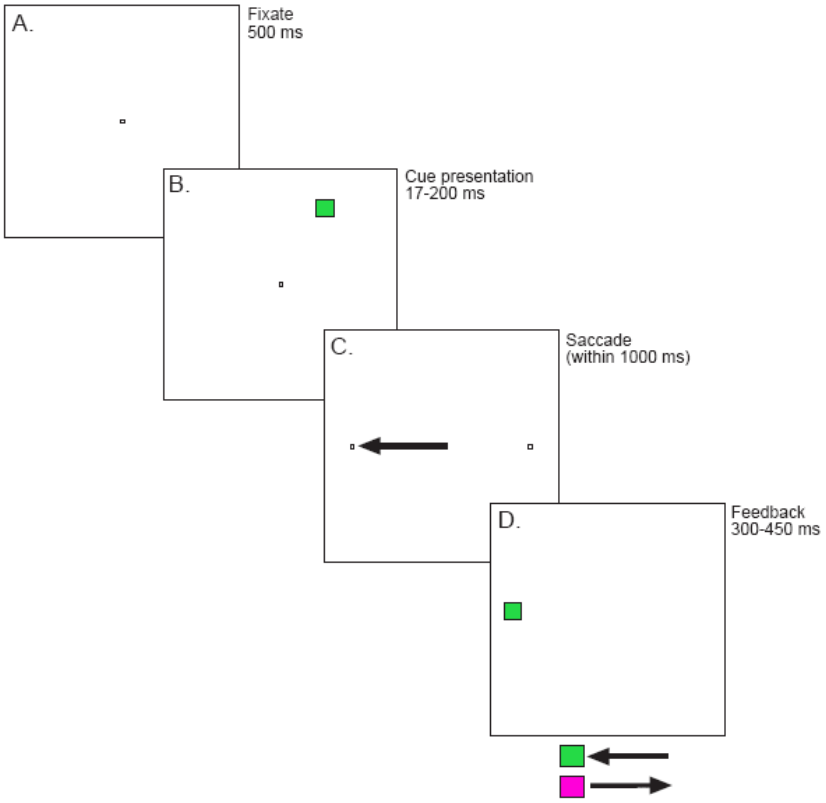

Figure 1. General format of the color rule-based saccade tasks. Panels A-D represent the computer monitor in front of the monkeys' eyes at successive stages of the task. The monkey was required to fixate a central white square for 500 ms (A), after which a cue was flashed (B). When the cue was extinguished, the fixation point disappeared, two targets appeared, and the monkey was required to make an eye movement within 1000 ms (C). When the monkey attained fixation at the correct target, a feedback stimulus was presented (D), and the monkey had to maintain fixation at this location for 300-450 ms to receive a juice reward. Green cues instructed a leftward eye movement and magenta cues instructed a rightward eye movement.

2.2.1 Features common to all tasks

The monkeys were trained to perform three variants of a color-conditional saccade task. In all three variants, the color of a cue (one of two equiluminant colors) instructed the monkey where to direct a saccade (to one of two diametrically opposed targets). The timing of events was consistent across tasks (Fig. 1). Each trial began when the monkey attained fixation on a central spot (a white 0.8° x 0.8° square with a luminance of 11.9 cd/m^2). After a delay of 500 ms, a peripheral colored cue was presented briefly, with the exact duration subject to adjustment in the range 14-200 ms as described below. At the time of offset of the cue, the fixation spot vanished and two potential saccade targets appeared at diametrically opposed locations. These were identical to the fixation spot except in being placed at 19° eccentricity. The monkey was required to maintain gaze within 3.8° of the central fixation spot until the disappearance of the cue, whereupon he was free to execute a saccade. The saccade could be initiated at any time within a grace period of 1000 ms beginning with cue offset. Gaze was required to land on target within 300 ms of saccade initiation. These unusually permissive durations were employed so as to accommodate any slowing occasioned by FEF inactivation. After a correct eye movement was executed, the monkey was required to fixate the target for a period of 100 ms, after which a feedback stimulus (a 3.8° x 3.8° square with a luminance of 6.2 cd/m^2 and of the same color as the cue) replaced the target at the same location. An additional 300-450 ms of post-saccadic fixation was required, after which the feedback cue was extinguished, the monkey was allowed to break fixation and a 0.08-0.15-ml juice reward was delivered. A delay of 1-2 s intervened between successive trials. The eight conditions to which a trial could conform (Fig. 2) were interleaved in a sequence that was random except insofar as one trial conforming to each condition had to be completed successfully before the next block of eight successful trials commenced.

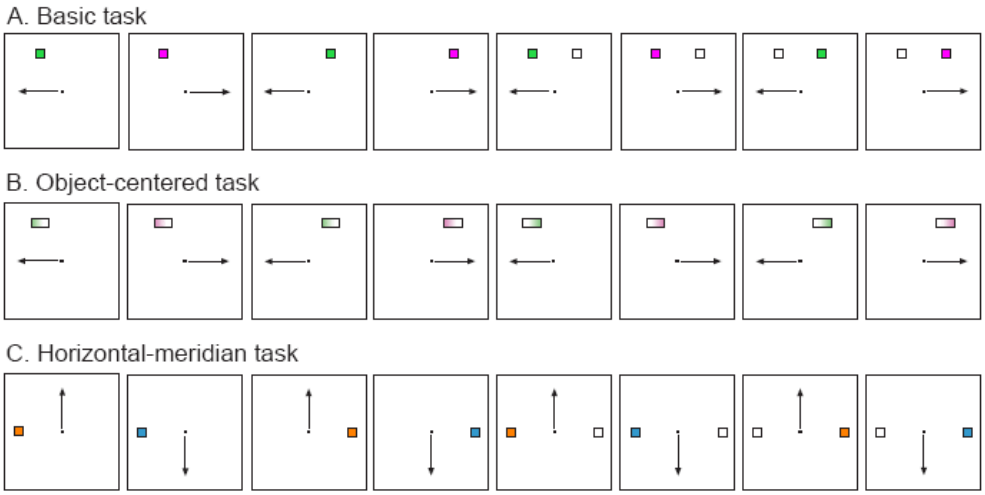

Figure 2. All conditions of the three tasks used to assess behavior. Stimuli are to scale. Arrows indicate the correct direction of saccade in response to the cue. A: Conditions comprising the Basic task. B: Conditions included in the Object-centered task.

2.2.2 Basic task

In this task (Fig. 2A), a colored cue presented in the upper left or right visual field instructed the monkey to make a saccade to one of two targets located straight to the right or left of fixation. The color of the cue (green or magenta) instructed the monkey toward which target (left or right) to direct a saccade. The cue was located at an eccentricity of 19° at an elevation of 60° from horizontal (to optimize performance for monkey N) or at an eccentricity of 13° at an elevation of 43° from horizontal (to optimize performance for monkey P). The potential saccade targets were located 19° to the left and right of fixation. On half of the trials, presentation of the cue was accompanied by simultaneous presentation of a distractor (a 3.8° x 3.8° square with a luminance of 10.6 cd/m^2) at a symmetric location in the opposite visual field.

2.2.3 Object-centered task

This task (Fig. 2B) was like the basic task in all respects except (a) that the cue was embedded as a patch of color on either the right or left side of a white rectangle elongated horizontally and (b) that no distractors were employed. Within the rectangular stimulus, color saturation was

maximal at one edge (right or left) and declined linearly to zero at the center (with luminance held constant) so that the opposite half of the rectangle was uniformly white.

2.2.4 Horizontal-meridian task

This task (Fig. 2C) was like the basic task in all respects except (a) that cues and distractors appeared on the horizontal meridian – 19° to the left and right of fixation – at locations occupied by saccade targets in the basic task, (b) that the saccade targets were located 19° above and below fixation and (c) that the color of the cue (orange or blue) instructed the monkey to which target (upward or downward) to direct a saccade.

2.2.5 Lenient and stringent cues

In the first two inactivation experiments in each monkey, we used *lenient* cues, with brightness, size and duration adjusted so that performance was at around 95% correct, a standard level of accuracy for a two-choice task. The rationale for using above-threshold cues was that even these elicit robust neglect in patients. However, after the results from early sessions revealed little or no trend toward an impairment of visual discrimination, we decided to use more challenging cues. These were generated by a stepwise procedure. First, over a series of testing sessions, we varied cue size (over a range from 4° x 4° to 0.4° x 0.4°) and luminance (over a range from 6.5 cd/m^2 to 3.8 cd/m^2), holding duration at 100 ms, so as to achieve a level of performance of around 75% correct. Although performance was at 75%, the resulting cues were not at discrimination threshold. In monkeys, to a much greater extent than in humans, the percent correct score is affected by uncontrollable sources of variability, including motivational influences, as distinct from limits on discriminability. In consequence, there is no way in which to establish an entirely believable psychophysical discrimination threshold. Instead of attempting to do so, we further reduced the discriminability of the stimuli by an arbitrary but extremely stringent procedure. Each monkey performed each task over the course of a full daily session. During this session, cue duration was varied by a staircase procedure (with a precision ultimately limited by the 60 Hz screen refresh rate) so as to maintain performance at 66.7%. The duration yielding performance at this level varied markedly over the course of the session. We

processed the data from each session so as to identify that 10% of trials on which duration of the cue was shortest and noted the duration cut-off point between these trials and the remaining 90% (Fig. 3: dotted line). The *stringent* cues used during the last three inactivation experiments in each monkey were presented at this duration and at the levels of size and luminance used when it was measured. The precise size, luminance, and duration of the stringent cues for each monkey in each task are shown in Table 1. The size of the cues in the object-centered task refers to the size of the colored patch embedded in the white rectangle, which subtended 8.4° x 4.0° visual angle in total.

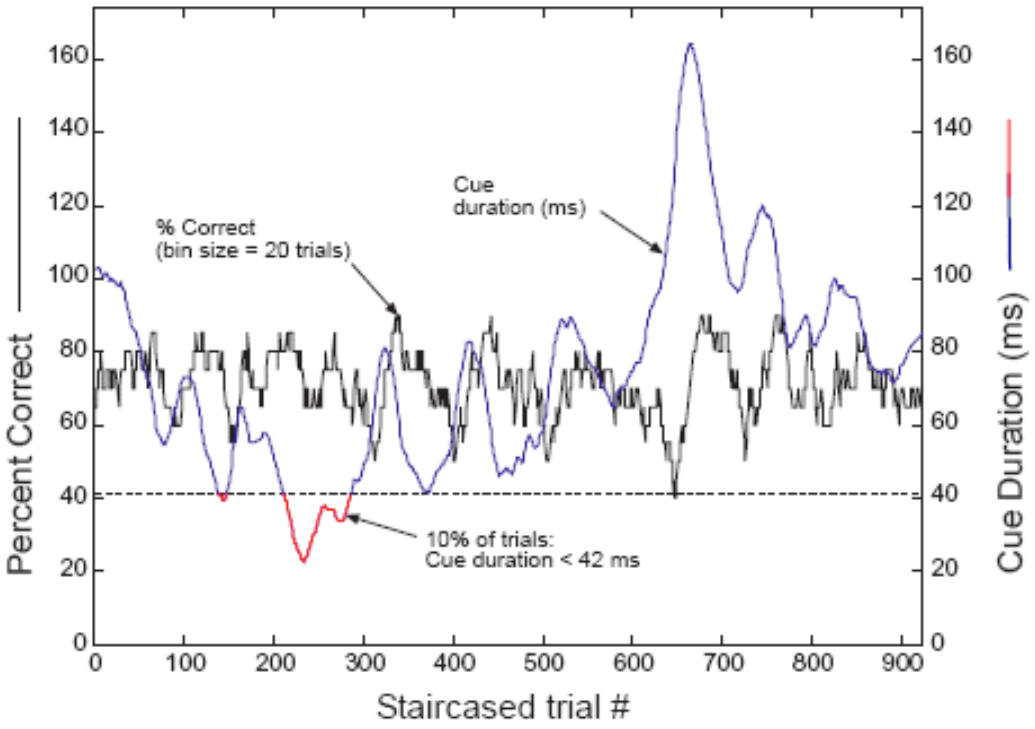

Figure 3. Performance (black trace) and duration of cue presentation time (blue trace) as a function of trial number during an example diagnostic staircasing session. Cues were presented at a size and luminance which corresponded to 75% correct when the cues were presented at 100 ms. Over the course of the staircasing session, the duration of the cue was varied systematically to ensure an overall performance level of 66.7% correct; after each correct response, the cue duration was decreased by 4 ms, and after each incorrect response, the cue duration was increased by 8 ms. The greatest cue duration of the 10% of trials with the lowest cue duration (red trace) was taken to be the monkey's threshold (in this example, 42 ms) and was used as the stringent cue in subsequent experiments.

Table 1. Parameters of stringent cues

Task	Basic		Object-centered		Horizontal meridian	
Monkey	N	P	N	P	N	P
Size	1.0° x 1.0°	1.2° x 1.2°	0.6° x 4.0°	1.8° x 4.0°	0.6° x 0.6°	4.0° x 4.0°
Luminance	5.2 cd/m^2	6.1 cd/m^2	4.6 cd/m^2	5.0 cd/m^2	3.9 cd/m^2	3.9 cd/m^2
Duration	48 ms	17 ms	42 ms	14 ms	34 ms	18 ms

2.2.6 Grouping of trials

On each day, the monkey cycled through the three tasks, completing 160-320 trials on each block, with a rest of 3-5 minutes before proceeding to the next task's block, until sufficient data had been collected. The single exception involved one experimental day, together with matched control days, on which monkey P was required to cycle between the basic task and the object-centered task without performing the horizontal-meridian task. On the series of control days preceding and/or following each inactivation experiment, the monkey typically worked for 1-3 hours per day. On the day of the inactivation, the monkey typically worked for 3-6 hours. The number of control days ranged from two to five. The number of successfully completed trials per task across the full set of control days ranged from 117 to 2928. The number of successfully completed trials per task on a given experimental day ranged from 279 to 1682. On each set of control days, together with the corresponding experimental day, all task conditions were the same. All subsequent comparisons were confined to matched experimental and control days.

2.3 FEF INACTIVATION

2.3.1 Localization of injection sites

Each injection was placed at known coordinates relative to a 1 mm square grid projected onto the cortical surface. The FEF was mapped out relative to this grid by identifying locations at which

eye movements could be elicited by low-current (< 50 μA) electrical microstimulation (1.65-ms biphasic pulses delivered through a recording microelectrode at a frequency of 300 Hz in trains 200 ms long). Gross morphological landmarks were mapped out relative to the grid by collecting magnetic resonance (MR) images with a Brükker 4.7 T magnet in which the anesthetized monkey was supported by an MR-compatible stereotaxic device. Frontoparallel and surface-parallel slices of 2 mm thickness were collected. Intra-chamber fiducial marks containing a contrast agent allowed bringing morphological features visible in the MR images into register with the reference grid. The information obtained by means of electrical-stimulation mapping and MR imaging allowed establishing the relation of each injection site to the functionally defined FEF as well as to known gyri and sulci.

2.3.2 Muscimol injection

At the beginning of each experimental day, the acrylic implant was rigidly affixed to the chair so as to prevent any movement of the head relative to the chair. A micromanipulator holding a 2 μl Hamilton syringe was affixed to a bar bolted to the chair. The syringe was oriented normal to the cortical surface, parallel to the tracks along which electrodes had been inserted during microstimulation and at known grid coordinates. The syringe was advanced under visual control through the dura and into the cortex until the lumen of the needle was at the greatest depth at which eye movements had been demonstrated to result from electrical microstimulation (commonly 5-7 mm beneath the cortical surface). This depth is similar to the depths at which inactivating agents have been placed in previous studies (Sommer and Tehovnik 1997). Electrical stimulation at the grid coordinates chosen for injection had elicited eye movements not only at the greatest depth but also along the track leading up to the cortical surface. Thus muscimol back-spreading along the track would still be confined to the FEF and back-spread would have the advantageous consequence of enlarging the inactivated region of the FEF. When the tip of the needle had been positioned as desired, 2 μl of muscimol (5 μg/μl) was injected in regular 0.1-μl increments over a period of 15 minutes. After each injection, the needle tip was inspected to ensure that all muscimol had been expelled and infused into the cortical tissue. The monkey was returned to the colony for 30-90 minutes before behavioral testing began, so as to allow the effects of the injection to stabilize.

2.4 DATA ANALYSIS

2.4.1 General

Data were pooled across all blocks of trials in which the monkey had performed a given task on a given experimental day and across all blocks of trials in which he had performed the task on the matched control days. The aim of data analysis was to determine whether selected measures of visual discrimination performance and saccadic performance were worse in the context of a given task on a given experimental day than on the matched control days.

2.4.2 Choice-based measures

Signal detection analysis (Green and Swets 1966) was applied to data from all trials in which the monkey had made a saccade (whether correct or incorrect) to one target or the other. Four analyses were carried out on data from each task, resulting in four estimates of response bias (rb) and four estimates of sensitivity (d'). Each analysis focused on a pair of conditions in which the configuration of the stimuli was identical but in which the color of the cue instructed the monkey to make saccades in opposite directions. Such pairs are depicted side by side in Fig. 2. Certain arbitrary conventions having no impact on the outcome of the analysis were of necessity adopted. Any case in which the monkey correctly made a leftward saccade in response to a leftward-instructing cue (signal) was deemed a hit. Any case in which the monkey incorrectly made a leftward saccade in response to a rightward-instructing cue (noise) was deemed a false alarm. The sign of the response bias was deemed to be positive if it conformed to the pattern expected from FEF inactivation (favoring ipsilesional saccades). The values of d' and rb were computed by the following equations:

$$rb = -0.5[z(H) + z(F)]$$

$$d' = [z(H) - z(F)]$$

where z is the inverse of the cumulative distribution function (cdf) of the two observed probabilities H (hit rate) and F (false alarm rate). H is the number of hits (N_H) divided by the number of signal trials (N_s), and F is the number of false alarms (N_{FA}) divided by the number of noise trials (N_n). For monkey P, because the chamber was over the left hemisphere, the sign of

the term on the right side of equation for rb was made positive so as to maintain consistency with the convention that an ipsilesional bias was positive.

To deal with exceptional cases that left rb and d' undefined, cases in which all signal trials resulted in hits ($N_H = N_s$) or none did ($N_H = 0$) or all noise trials resulted in false alarms ($N_{FA} = N_n$) or none did ($N_{FA} = 0$), we adopted a standard correction procedure increasing or decreasing the value of N_H or N_{FA} by 0.5 as appropriate (Green and Swets, 1966).

On the basis of the rb and d' values obtained for the four pairs of conditions, we computed two difference indices expected to be greater on the experimental day than on the control days if there were a selective impairment of (a) *contralesional saccades* $[(rb_{[IVF]} + rb_{[CVF]})/2]$ or (b) *contralesional visual discrimination* $(d'_{[IVF]} - d'_{[CVF]})$. There were two good reasons for taking this step away from the raw data and toward abstraction. First, by using the ipsilesional performance as a baseline for the contralesional performance, we compensated for day-to-day fluctuations in the monkeys' motivational level and other uncontrolled global state variables. Second, the difference index would be equally sensitive to push and pull effects that might occur if attentional or oculomotor control were dependent on a push-pull system. For example, the indices would be equally sensitive to a speeding of ipsilesional processes and to a slowing of contralesional processes.

2.4.3 Choice-based index of saccadic impairment

To test the hypothesis that FEF inactivation selectively reduced the tendency to make contralesional saccades, we computed the average of the response bias measures obtained for trials when the cue was in the ipsilesional and contralesional visual fields: $(rb_{[IVF]} + rb_{[CVF]})/2$. A selective bias against making contralesional saccades would have led to this measure's being significantly greater on experimental days than on matched control days.

2.4.4 Choice-based index of discrimination impairment

To test the hypothesis that FEF inactivation selectively impaired the processing of visual stimuli in the hemifield opposite the injection site, we computed the difference between sensitivity to cues in the ipsilesional and contralesional visual fields: $d'_{[IVF]} - d'_{[CVF]}$. A selective

reduction of sensitivity in the visual field opposite the injection site would have led to this measure's being significantly greater on experimental days than on matched control days.

2.4.5 Statistical analysis of choice effects

To determine whether the indices obtained on an experimental day and the matched control days were significantly different, we carried out a procedure involving the following steps. 1) We combined in a single set data from the experimental day and from the control days. 2) We computed, for this data set, the hit (H) and miss (1-H) rates (for signal trials) and false alarm (FA) and correct rejection (1-FA) rates (for noise trials). 3) We constructed a simulated "experimental" data set by (a) for as many signal trials as were contained in the original experimental data set, randomly assigning to the trial the status of a hit (with probability H) or else of a miss and (b) for as many noise trials as were contained in the original experimental data set, randomly assigning to the trial the status of a false alarm (with probability F) or else of a correct rejection. 4) We constructed a simulated "control" data set by an analogous procedure. Note that constructing the simulated "control" data set by the same procedure as the simulated "experimental" data set embodied the null hypothesis that the two sets arose by random sampling from a single parent population. 5) We computed, for the pair of simulated data sets difference indices identical to those computed for the actual data sets: $[(rb_{[IVF]} + rb_{[CVF]})/2]$ and $(d'_{[IVF]} - d'_{[CVF]})$. 6) We repeated the simulation procedure (steps 3-5) 10,000 times. 7) We tested the significance of each of the two observed difference indices by carrying out a two-tailed test based on where the observed value fell relative to the distribution of 10,000 simulated values.

2.4.6 Reaction time-based measures

For each task, we computed reaction time indices by the following steps. 1) For each correct trial, we computed the reaction time (RT) as the interval between cue onset and the moment at which gaze departed from the central fixation window. 2) For all trials conforming to each of the eight conditions during the experimental day and during the control days, we computed the mean of the RT. 3) For each tetrad of conditions in which cue location and saccade direction were strictly counterbalanced in a given session (the four to the left or the four to the right in each row

of Fig. 2), we computed four means of means representing the mean RT when (a) the cue was contralesional ($RT_{[CVF]}$), (b) the cue was ipsilesional ($RT_{[IVF]}$), (c) the saccade was contralesional ($RT_{[Contra]}$) and (d) the saccade was ipsilesional ($RT_{[Ipsi]}$). 4) We computed two difference indices expected to be greater on the experimental day than on the control days if discrimination were slowed in the contralesional hemifield ($RT_{[CVF]} - RT_{[IVF]}$) or if contralesional saccades were slowed ($RT_{[Contra]} - RT_{[Ipsi]}$).

2.4.7 Reaction time-based index of saccadic impairment

To test the hypothesis that FEF inactivation selectively slowed contralesional saccades, we computed the difference between the average RTs for contralesional and ipsilesional saccades: $RT_{[Contra]} - RT_{[Ipsi]}$. A selective slowing of contralesional saccades would have led to this measure's being significantly greater on experimental days than on matched control days.

2.4.8 Reaction time-based index of discrimination impairment

To test the hypothesis that FEF inactivation selectively slowed the discrimination of visual stimuli in the hemifield opposite the injection site, we computed the difference between the RT on trials when the cue was in the contralesional visual field and on trials when it was in the ipsilesional visual field: $RT_{[CVF]} - RT_{[IVF]}$. A selective slowing of visual discrimination in the contralesional visual field would have led to this measure's being significantly greater on experimental days than on matched control days.

2.4.9 Statistical analysis of reaction time effects

To assess the significance of differences in RT measures between the experimental day and the matched control days, RTs from the two data sets were randomly reshuffled 10,000 times. The reshuffling randomized which data set an RT was assigned to but retained the identity of the condition to which it belonged. For each reshuffle, the indices ($RT_{[CVF]} - RT_{[IVF]}$ and $RT_{[Contra]} -$

$RT_{[Ipsi]}$) were recalculated. A two-tailed assessment of significance was based on where the observed value for a given index fell relative to the distribution of values obtained by reshuffling.

3.0 RESULTS

3.1 OVERVIEW

The general aim of these experiments was to characterize lateralized deficits of saccade initiation and visual discrimination arising from unilateral reversible inactivation of the FEF. The studies were carried out in two monkeys: N (with a chamber over the right FEF) and P (with a chamber over the left FEF). Five FEF inactivation experiments were carried out in N and four in P. In monkey P, one inactivation was carried out in area 46 of the prefrontal cortex as a control. Each experiment spanned 2-5 days on which control data were collected and one day on which data were collected following FEF inactivation.

During data collection, each monkey cycled through three tasks: the basic task, the object-centered task and the horizontal-meridian task. The sole exception to this rule was one FEF experiment in which monkey P performed only the basic task and the object-centered task. Each task had unique design features aimed to show up in a dissociable form any deficits of saccadic or visual discrimination performance that might have resulted from FEF inactivation. All tasks, however, shared the feature that the color of a cue instructed the monkey in which direction to execute a saccade. This feature, by allowing independent manipulation of the cue's location in the visual field and of the saccade's direction, was critical for dissociating lateralized visual discrimination deficits from lateralized deficits of saccadic performance.

During the first two FEF experiments in each monkey, the design of the cues was lenient (allowing the monkeys to perform at an average level of 95% correct on control days). In later experiments (three FEF experiments in N and two FEF and one PFC experiment in P), the design of the cues was stringent (allowing the monkeys to perform only at an average level of 79% correct on control days). This manipulation did not have a large impact on the outcome of the inactivation experiments, as will be shown after the collective results have been described.

3.2 LOCATION OF INJECTION SITES

In each monkey, injections were placed at known locations relative to morphological landmarks visible in MR images of slices parallel to the cortical surface (Fig. 4A) and relative to sites at which electrical microstimulation had elicited eye movements at low threshold (Fig. 4B-C). Five injections in monkey N and four in monkey P were in the FEF as identified both on functional grounds (at a grid location where eye movements had been elicited or else between two such locations) and on morphological grounds (in the anterior bank of the arcuate sulcus). One injection in monkey P was placed intentionally in dorsolateral prefrontal cortex (area 46) as identified both on functional grounds (no eye movements elicited) and on morphological grounds (medial to the posterior tip of the arcuate sulcus).

3.3 POSSIBLE OUTCOMES

Behavioral results will be plotted as shown in Fig. 5, an example of a possible experimental outcome. For each inactivation, experimental (or post-injection) values for each choice-based and RT-based difference index will be plotted against the corresponding values for matched control days. Plots of choice-based indices are depicted on the top row, and plots of RT-based indices are on the bottom row; plots of visual discrimination measures are shown in the left column, and plots of saccade measures are in the right column. Therefore, each point represents the control and experimental value for a particular measure (choice-based or RT-based, visual discrimination or saccades). Points which fall above the dashed line, in the gray area, represent measures which were greater on experimental days than control days, indicating a behavioral deficit. The extreme example depicted in Fig. 5 shows a case in which unilateral FEF inactivation resulted in consistent deficits in both visual discrimination and saccadic performance, as indicated by the appearance of data points only in the upper, shaded portion of each plot.

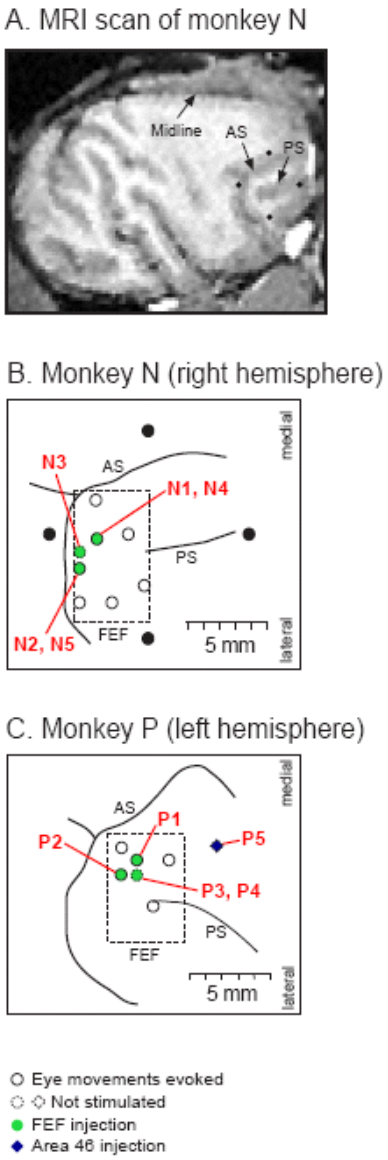

Figure 4. Muscimol injection sites. A: MR image of monkey N's right hemisphere. Arrows indicate the midline, arcuate sulcus (AS), and principal sulcus (PS). Chamber used for recording and injections was placed above the area delineated by black dots. B and C: Diagrams of stimulation and injection sites in monkey N (B) and monkey P (C). Black dots in diagram for monkey N (B) correspond to black dots in A. Circles outlined in solid black indicate sites where eye movements were evoked at low current (<50 μA) stimulation. Green circles indicate FEF injection sites; green circles with a dotted outline indicate injection sites which were not stimulated. The blue circle in C shows the location of the Area 46 injection. The red labels in B and C (N1-5, P1-5) indicate the number and order of injections made at each location. The first two injections for each monkey (N1-N2, P1-P2) used lenient cues in the behavioral tasks following inactivation, and the last three injections for each monkey (N1-N3, P1-P3) used stringent cues.

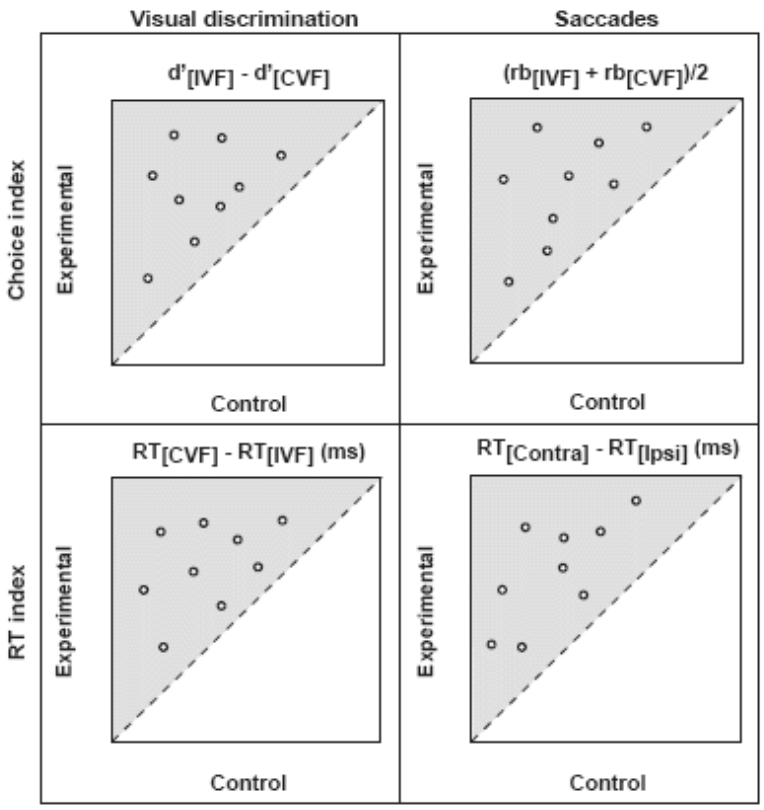

Figure 5. Expected outcomes for consistent deficits in visual discrimination and saccadic performance following FEF inactivation. Experimental values of each choice-based (top row) and RT-based (bottom row) difference index will be plotted against control values. Points falling above the dashed line, in the shaded gray area of the plot, will show cases in which unilateral FEF inactivation resulted in a decline in visual discrimination (left column) and saccadic performance (right column). In this extreme example, both visual discrimination and saccades are consistently impaired following inactivation.

3.4 BASELINE PERFORMANCE

Because pre-injection mapping of the FEF under study could conceivably cause slight visual and/or saccadic impairments, we will first consider the baseline performance of each monkey before presenting inactivation data. Overall, there was a weak trend for better discriminability in the ipsilateral than contralateral hemifield and slightly faster ipsiversive RTs in response to ipsilateral cues on control days. However, these differences were rarely significant (paired t-tests, $p > 0.05$ for nearly every comparison; see Figs. 6, 8, 10, 12, 14, and 16). Therefore,

behavioral effects due to pre-injection mapping were minor or negligible. To ensure that inactivation-related deficits (or the lack thereof) were not confounded by floor effects due to existing impairments on the contralateral side, we adopted two conservative approaches in our analysis. First, we used a comparative measure to detect discrimination impairment (comparing the difference between contralesional and ipsilesional values on control vs. experimental days), rather than an absolute measure. Second, we compared discrimination impairment to saccadic impairment. If floor effects resulted in the masking of behavioral deficits, impairments would be undetectable in both visual discrimination and saccades. However, contraversive saccadic deficits were a clear effect of FEF inactivation; this finding will be described below.

3.5 BASIC TASK WITHOUT DISTRACTORS

3.5.1 Rationale

The aim of using this task was to assess by independent measures whether unilateral FEF inactivation induced a selective impairment of (a) contralesional saccades and (b) contralesional visual discrimination. Central to achieving this aim was a feature of design whereby the location of the cue (right or left hemifield) and the direction of the saccade (rightward or leftward) varied independently across trials (Fig. 7A).

3.5.2 Performance on control days

The monkeys' level of performance on control days is summarized in Fig. 6. There were no significant differences between measures of performance in the contralateral and ipsilateral fields except for one RT measure (see asterisk, lower right).

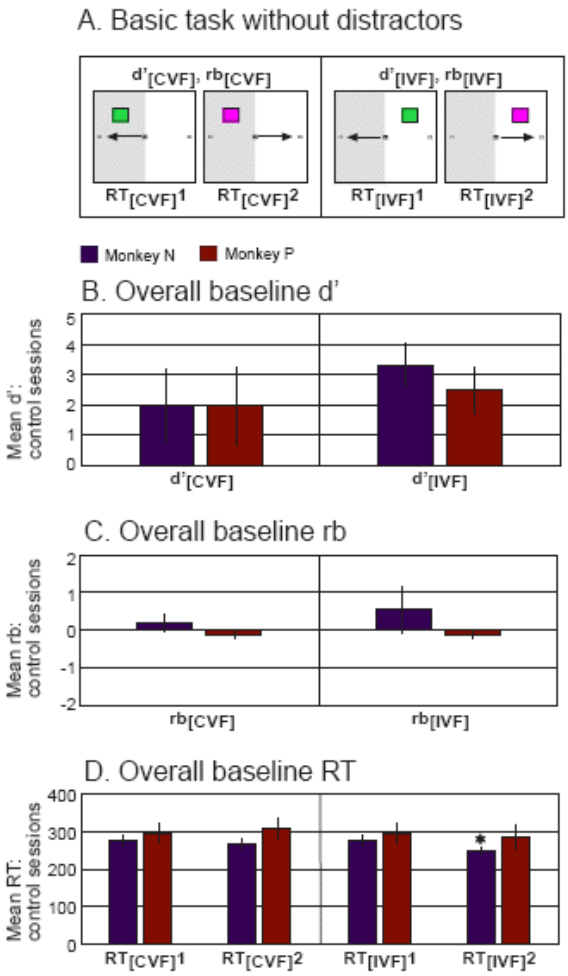

Figure 6. Baseline behavioral performance on the Basic task without distractors. A: conditions corresponding to d', rb, and RT calculations. Ability to discriminate cues in the contralesional visual field ($d'_{[CVF]}$) and response bias for cues in the contralesional visual field ($rb_{[CVF]}$) were determined using conditions in which the cues fell in the contralesional visual field (shaded portion on diagram of task conditions); $d'_{[IVF]}$ and $rb_{[IVF]}$ were determined using conditions in which cues which fell in the ipsilesional visual field (unshaded portion). $RT_{[CVF]}1$ and $RT_{[CVF]}2$ correspond to reaction time measurements for conditions in which the cue fell in the contralesional visual field, and $RT_{[IVF]}1$ and $RT_{[IVF]}2$ represent reaction times for conditions in which the cue fell in the ipsilesional visual field. B: Mean $d'_{[CVF]}$ and $d'_{[IVF]}$ on control days for monkey N (purple bar) and monkey P (red bar). C: Mean $rb_{[CVF]}$ and $rb_{[IVF]}$ on control days for each monkey. D: Mean $RT_{[CVF]}1$-2 and $RT_{[IVF]}1$-2 on control days for each monkey. Error bars show ± standard deviation for each set of control values (n = 5 for each monkey), and stars show control IVF values which were significantly different from control CVF values (paired t-tests, $p < 0.05$).

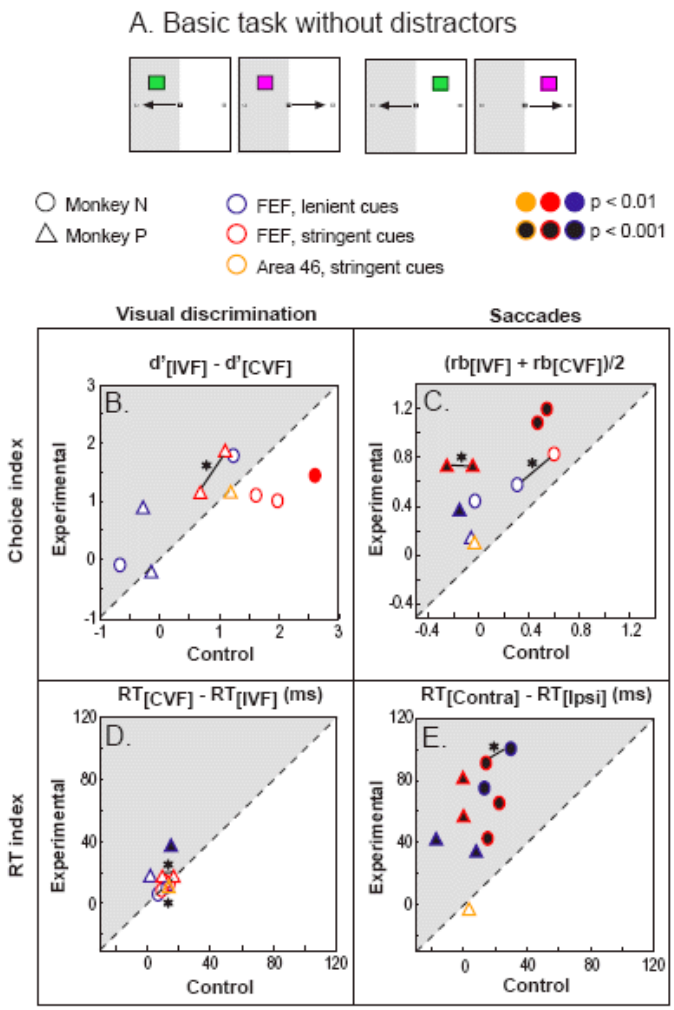

Figure 7. Basic task without distractors. A: Conditions of the Basic task in which a distractor was not present. B-E: Impact of unilateral FEF inactivation on performance. For each experimental session, the value of each choice measure and each RT measure is plotted against the matching control value. Monkey N's performance is shown represented by circular icons, and monkey P's performance is shown with triangular icons; those outlined in blue represent experiments using lenient cues, and those outlined in red represent experiments using stringent cues. Icons shaded in either blue or red indicate an effect that was significantly different from the simulated population with a p-value of < 0.01, and icons shaded in black indicate values that differed from the simulated population with a significance value of <0.001. Points that fall in the shaded area indicate a deficit in contralesional visual discrimination (B and D) or a deficit in contralesional saccadic performance (C and E) due to the muscimol injection. Points connected with a line and labeled with a star are inactivations placed in the same site in the same monkey in which the difference in the impact of inactivation (experimental-control) between the two injections was significantly smaller than that of non-matching pairs of injections. The one experiment in which muscimol was injected into area 46 of the prefrontal cortex of Monkey P is represented by the light orange triangular icon. This experiment served somewhat as a control experiment, as very little changes in the monkey's performance resulted from this injection. This point falls very close to the unity line in every case shown in Fig. 7(B-E).

3.5.3 Saccadic impairment (choice index)

This index was greater on the experimental day than on the matched control days in all nine cases (Fig. 7C: all red and blue symbols are in the shaded half of the plot). Moreover, in five of these cases, a Monte Carlo test revealed that the difference between experimental and control days was significant (symbols filled with black). We conclude that FEF inactivation induced a bias against executing contralesional saccades.

Pairs of data points which are connected with a line and labeled with a star are behavioral results of injections which were placed in the same site, the difference between the two points significantly less than the difference between all pairs of injections placed in different sites. This will be described in greater detail below (see *Consistency across Cortical Sites*).

3.5.4 Saccadic impairment (RT index)

This index was greater on the experimental day than on the matched control days in all nine cases (Fig. 7E: all red and blue symbols are in the shaded half of the plot). Moreover, the difference between experimental and control days was significant in every case as revealed by a Monte Carlo test (all red and blue symbols are filled with black). We conclude that FEF inactivation induced a slowing in the initiation of contralesional saccades.

3.5.5 Discrimination impairment (choice index)

Cases in which this index was greater on experimental than on control days (Fig. 7B: five red and blue symbols in the shaded half of the plot) were approximately as frequent as cases in which it was less (four red and blue symbols in the unshaded half of the plot). Moreover, the only case in which a Monte Carlo test revealed that the measure was significantly different on experimental and control days (red symbol filled with red) was one in which the measure was less on the experimental day than on the matched control day. The results thus provide no evidence that FEF inactivation impaired the discrimination of cues in the contralesional visual field.

3.5.6 Discrimination impairment (RT index)

Most points were clustered closely around the identity line, indicating that index values on experimental and control days were closely similar (Fig. 7D). In only one case (symbol filled with black), did a Monte Carlo test reveal that the value measured on the experimental day was significantly greater than that measured on the matched control. These results afford a weak hint that FEF inactivation slowed the discrimination of cues in the contralesional visual field.

3.5.7 Summary

Unilateral FEF inactivation induced a robust impairment in the execution of contralesional saccades but little or no impairment in the discrimination of cues in the contralesional visual field.

3.6 BASIC TASK WITH DISTRACTORS

3.6.1 Rationale

On half of all trials in the basic task, when the colored cue appeared in one hemifield, a bright distractor appeared at a symmetric location in the opposite hemifield (Fig. 9A). The aim of displaying a distractor was to enhance our ability to detect a weak impairment of contralesional visual discrimination. It is well known that patients with lateralized brain injury may exhibit extinction (failure to detect a stimulus in the contralesional hemifield when it is paired with a stimulus in the ipsilesional hemifield) even when they do not exhibit neglect (failure to detect a stimulus presented in isolation in the contralesional hemifield) (Bisiach 1991; Critchley 1953; Rafal 1994; Vuilleumier and Rafal 2000). We speculated that a distractor, by inducing extinction, might exacerbate an otherwise minor deficit in the discrimination of contralesional visual cues.

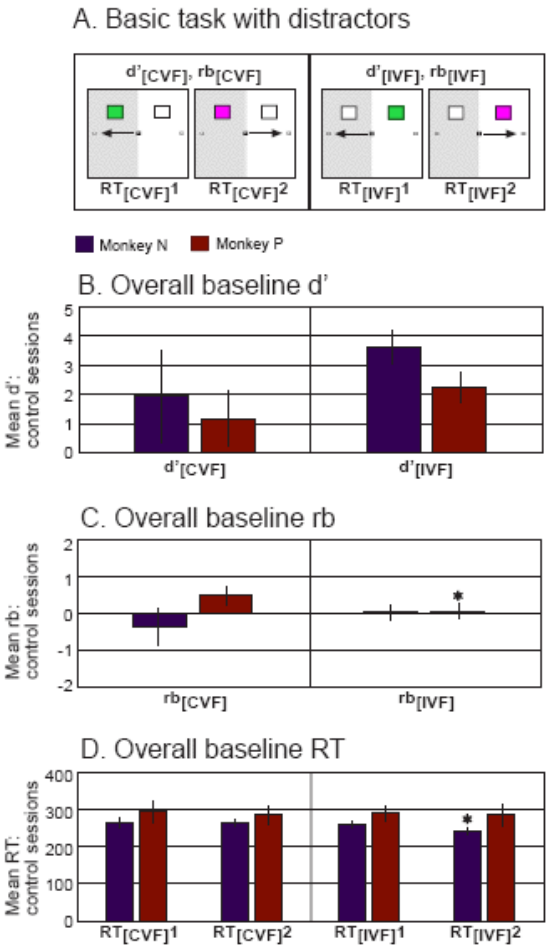

Figure 8. Baseline behavioral performance on the Basic task with distractors.

3.6.2 Performance on control days

The monkeys' level of performance on control days is summarized in Fig. 8. There were no significant differences between contralateral and ipsilateral hemifields except for one rb and one RT measure.

3.6.3 Saccadic impairment (choice index)

In all nine cases of FEF inactivation, this index was greater on experimental days than on matched control days (Fig. 9C: all red and blue symbols are in the shaded half of the plot). Moreover, in eight of these cases (filled symbols), a Monte Carlo test revealed that the measure

was significantly different on experimental and control days. We conclude that FEF inactivation induced a bias against executing contralesional saccades.

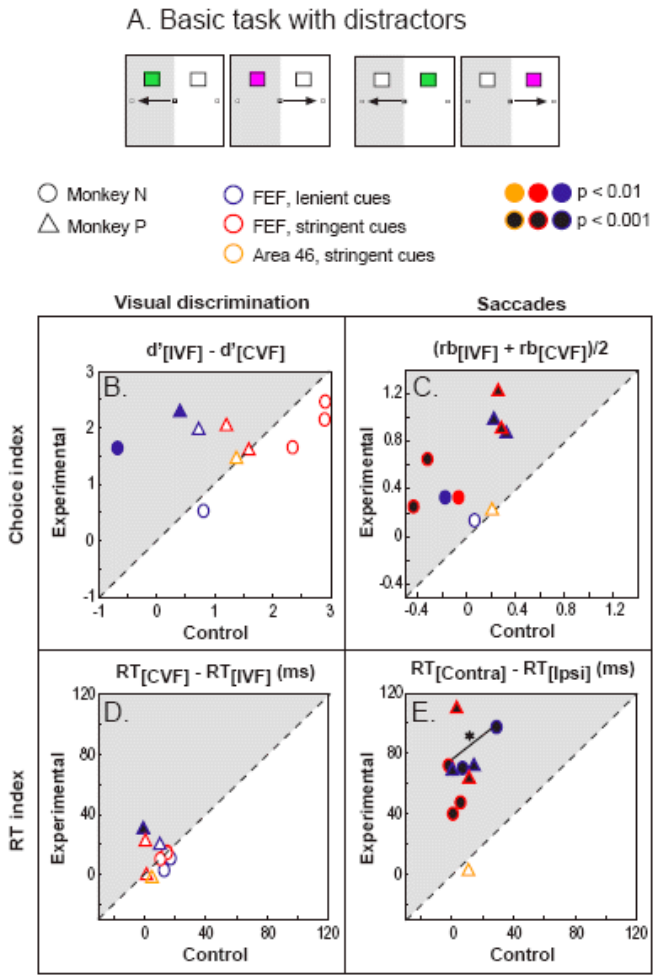

Figure 9. Basic task with distractors. A: Conditions of the Basic task in which a distractor was present. B-E: Impact of unilateral FEF inactivation on performance.

3.6.4 Saccadic impairment (RT index)

In all nine cases of FEF inactivation, this index was significantly greater on the experimental day than on the matched control day as indicated by a Monte Carlo test (Fig. 9E: all red and blue symbols occupy the shaded sector above the identity line and are filled). We conclude that FEF inactivation induced a slowing of contralesional saccades.

3.6.5 Discrimination impairment (choice index)

There were as many cases in which this index was lower on the experimental day (Fig. 9B: red and blue symbols in the unshaded half of the plot) as in which it was higher (red and blue symbols in the unshaded half of the plot). However, in both cases in which a Monte Carlo test revealed a significant difference between experimental and control days (symbols filled with blue), the value for the experimental day was higher. The results thus provide a weak indication that inactivation led to an impairment in the discrimination of contralesional cues.

3.6.6 Discrimination impairment (RT index)

Most points were clustered close to the identity line, indicating that index values on experimental and control days were similar (Fig. 9D). However, in one case (symbol filled with black), a Monte Carlo test revealed that the index was significantly greater on the experimental than on the control day. This provides a weak indication that inactivation slowed the discrimination of contralesional cues.

3.6.7 Summary

In trials on which a distractor was displayed, just as in trials involving no distractor, there was a robust and consistent impairment of contralesional saccades but only a weak and inconsistent impairment of contralesional visual discrimination.

3.7 OBJECT-CENTERED TASK

3.7.1 Rationale

In the object-centered task, the cue was a colored patch occupying either the contralesional or the ipsilesional half of an otherwise white rectangle (Figs. 11A and 13A). The aim of using this task

was twofold. First, by incorporating a distractor (the white region of the rectangle) into the very object that contained the cue (the colored region of the rectangle) it might make discrimination of the cue's color more difficult and so reveal an otherwise latent deficit in visual discrimination. Second, it might reveal signs of object-centered neglect. It is well known that in some patients neglect takes the form whereby the contralesional half of any object tends to be neglected regardless of the object's location in the visual field (Arguin and Bub 1993; Driver et al. 1992; Driver and Halligan 1991; Halligan and Marshall 1994; Humphreys et al. 1996; Rapcsak et al. 1989; Walker 1995; Young et al. 1992). If unilateral inactivation of the FEF induced an object-centered neglect, then the monkeys' performance would be worse when the colored cue occupied the contralesional side of the rectangular object than when it occupied the ipsilesional side.

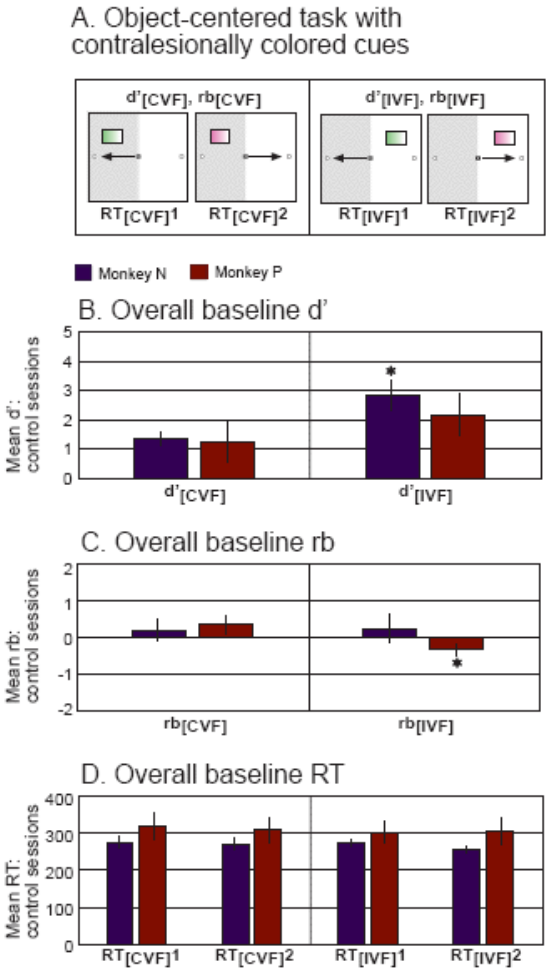

Figure 10. Baseline behavioral performance on the Object-centered task with contralesionally colored cues.

3.7.2 Performance on control days

The monkeys' level of performance on control days is summarized in Figs. 10 and 12. In each figure, the only significant differences between contralateral and ipsilateral hemifields were the d' measure in monkey N and the rb measure in monkey P. The significant difference in monkey P's rb measure, however, indicates only a reversal in the direction of the bias (ipsiversive to contraversive), rather than a reduction in overall bias, when comparing CVF to IVF.

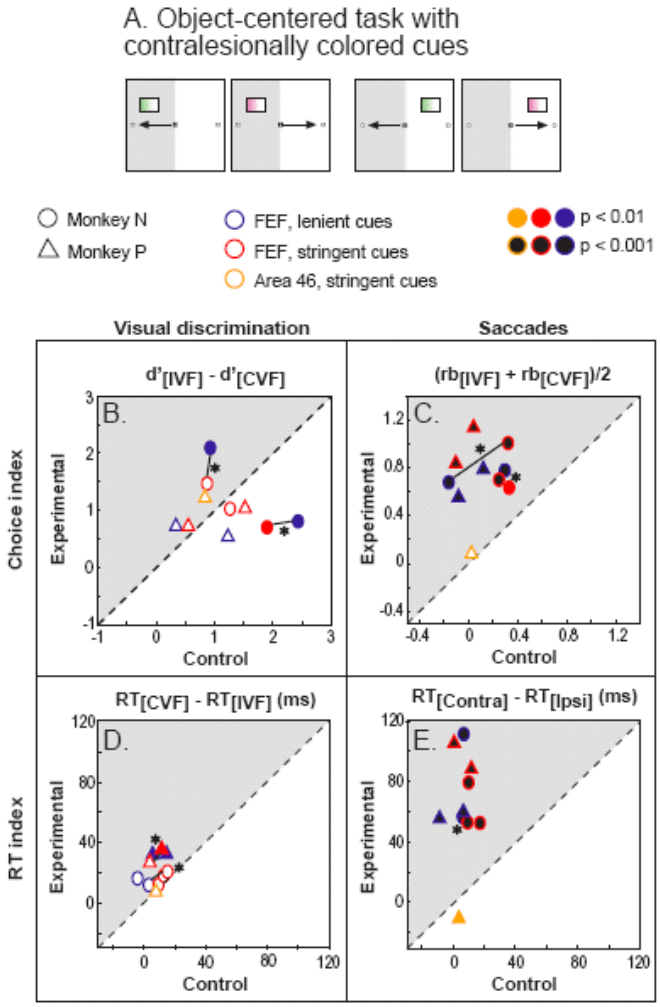

Figure 11. Object-centered task with contralesionally colored cues. A: Conditions of the Object-centered task in which cues were colored contralesionally. B-E: Impact of unilateral FEF inactivation on performance.

3.7.3 Saccadic impairment (choice index)

In all nine cases of FEF inactivation, this index was significantly greater on experimental days than on matched control days, as indicated by a Monte Carlo test, regardless of the object-centered location of the cue (Figs. 11C and 13C: all red and blue symbols are in the shaded half of the plot and are filled). We conclude that FEF inactivation induced a bias against executing contralesional saccades.

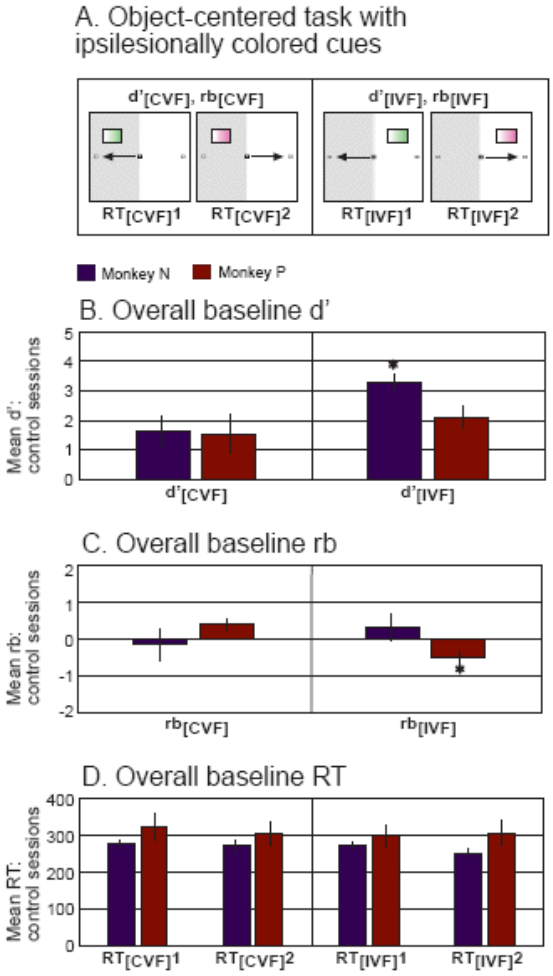

Figure 12. Baseline behavioral performance on the Object-centered task with ipsilesionally colored cues.

3.7.4 Saccadic impairment (RT index)

In all nine cases of FEF inactivation, this index was significantly greater on the experimental day than on the matched control day, as indicated by a Monte Carlo test, regardless of the object-centered location of the cue (Figs. 11E and 13E: all red and blue symbols occupy the shaded sector above the identity line and are filled). We conclude that FEF inactivation induced a slowing of contralesional saccades.

3.7.5 Discrimination impairment (choice index)

There were as many cases in which this index was lower on the experimental day (Figs. 11B and 13B: red and blue symbols in the unshaded half of the plot) as in which it was higher (red and blue symbols in the unshaded half of the plot). This was true regardless of whether the cue was on the contralesional or the ipsilesional side of the object. Moreover, out of four cases in which a Monte Carlo test revealed a significant difference between experimental and control days (filled symbols), there was only one case in which the index was higher on the experimental day. The results provide no evidence for the existence of a discrimination deficit specific either to the contralesional visual field or to the contralesional side of the object containing the cue.

3.7.6 Discrimination impairment (RT index)

There was a consistent tendency for the index to be higher on the experimental day than on the matched control day (Figs. 11D and 13D: red and blue symbols in the shaded half of the plot). This was true regardless of whether the cue was on the contralesional (Fig. 11D) or ipsilesional (Fig. 13D) side of the object. In four out of eighteen cases, a Monte Carlo test revealed that the difference between the experimental and control days was significant (filled symbols). These results indicate that inactivation of the FEF slightly slowed the discrimination of cues in the contralesional visual field. They provide no evidence for a slowing in the discrimination of cues on the contralesional side of the object.

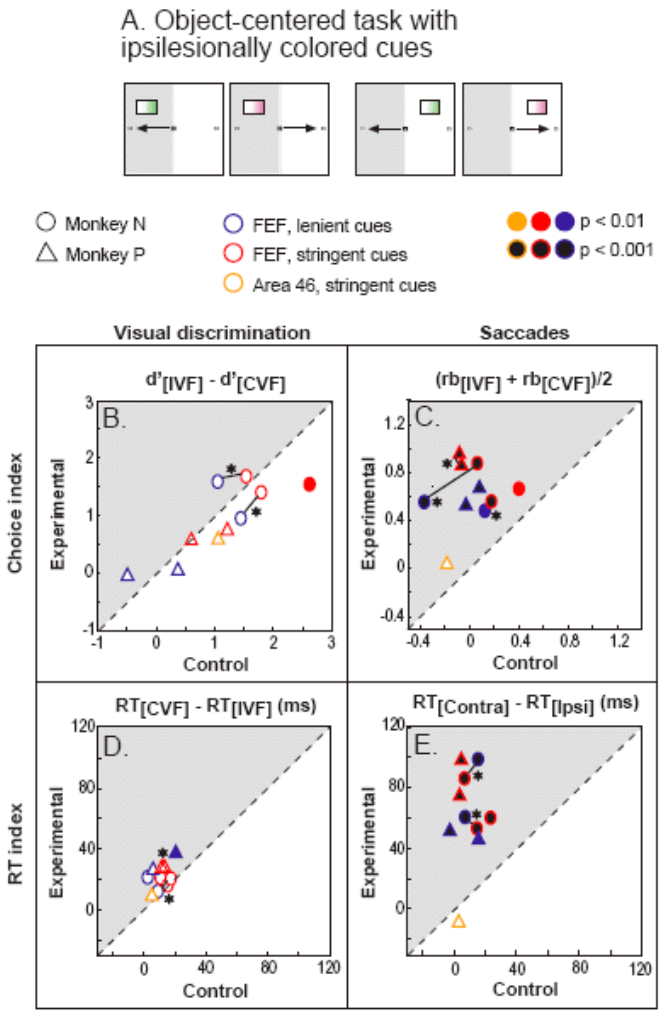

Figure 13. Object-centered task with ipsilesionally colored cues. A: Conditions of the Object-centered task in which cues were colored ipsilesionally. B-E: Impact of unilateral FEF inactivation on performance.

3.7.7 Summary

There was a robust and consistent impairment of contralesional saccades. This was accompanied by an apparent subtle impairment of visual discrimination in the contralesional visual field manifest as a slowing of the behavioral response but not as a reduction of sensitivity. The slowing of discrimination was specific to the contralesional visual hemifield and not to the contralesional side of the object containing the cue.

3.8 HORIZONTAL-MERIDIAN TASK WITHOUT DISTRACTORS

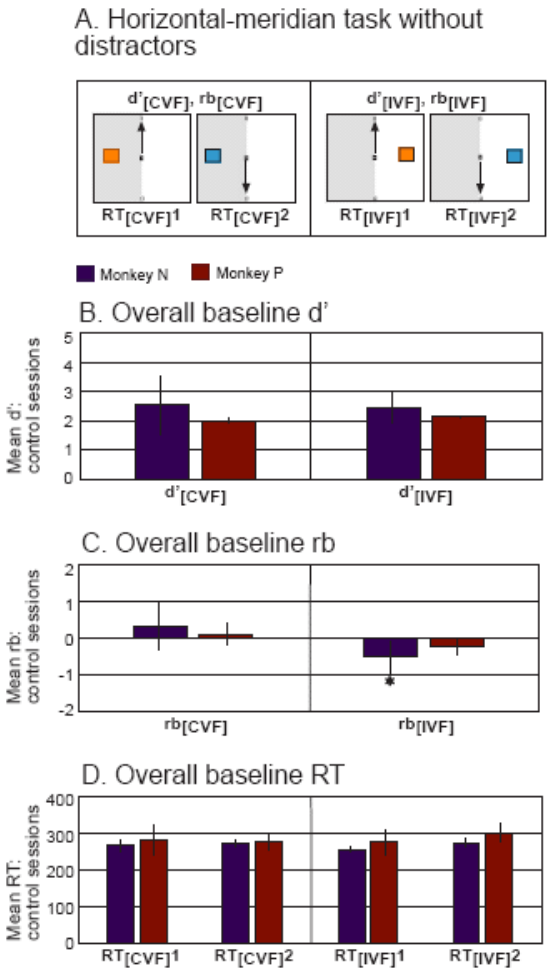

Figure 14. Baseline behavioral performance on the Horizontal meridian task without distractors.

3.8.1 Rationale

In the basic task and the object-centered task, the cues were in the upper visual field whereas the targets of saccades were on the zero degree horizontal meridian. That visual processing of contralesional cues was relatively intact whereas execution of contralesional saccades was grossly impaired might simply reflect a form of retinotopic specificity in which inactivation of the FEF interfered with attention to contralesional locations close to the zero degree horizontal meridian. The aim of using the horizontal-meridian task (Fig. 15A) was to pose the question

whether visual processing of the cues would be impaired if the cues were presented on the zero degree horizontal meridian at the same eccentricity as the saccade targets in the preceding tasks. An orange (or blue) cue, whether on the right or left, now signaled the monkey to make an upward (or downward) saccade.

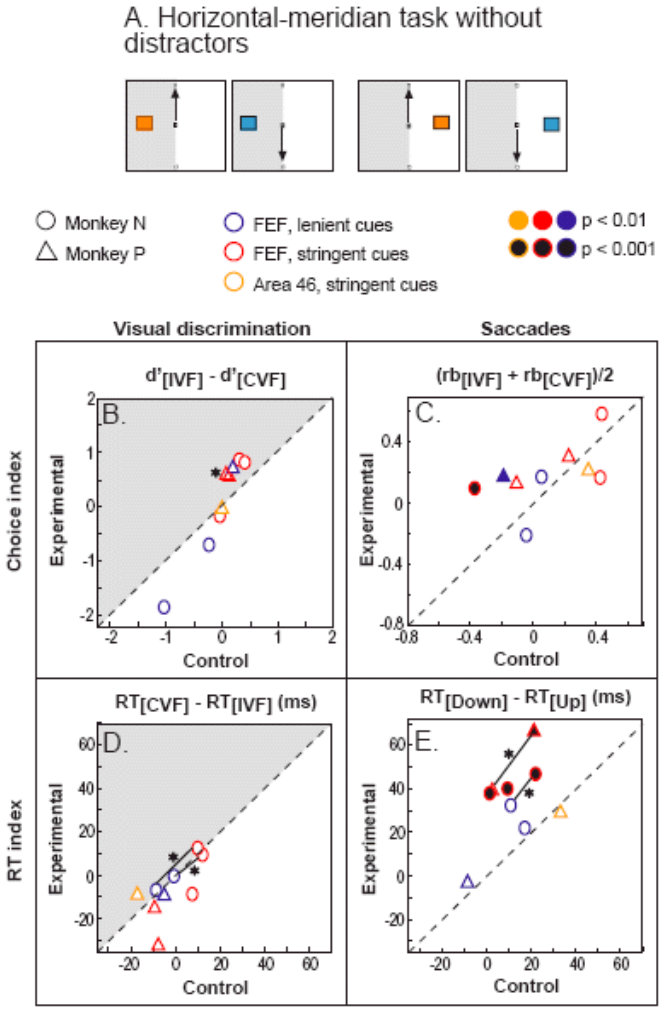

Figure 15. Horizontal meridian task without distractors. A: Conditions of the Horizontal meridian task in which a distractor was not present. B-E: Impact of unilateral FEF inactivation on performance.

3.8.2 Performance on control days

The monkeys' level of performance on control days is summarized in Fig. 14. The only significant difference between contralateral and ipsilateral hemifields is in one rb measure, but

this difference was barely significant ($p = 0.04$), and indicates a reversal in the direction of bias (ipsiversive to contraversive) rather than an overall reduction in bias.

3.8.3 Saccadic impairment (choice index)

Because saccades were in an upward or downward direction in this task, it was not possible to pose the question whether there was a contraversive impairment. Instead, we asked whether there was a downward impairment, treating downward as equivalent to contralesional saccades and upward as equivalent to ipsilesional saccades in all quantitative and statistical tests. To our surprise, there was a trend for the bias index to be greater on experimental than on matched control days. The bias index was greater on experimental than on matched control days in six out of eight cases (Fig. 15C: red and blue symbols above the identity line). The difference achieved significance, as indicated by a Monte Carlo test, in two of those cases (filled symbols). The results thus suggest that FEF inactivation induced a bias against making downward saccades, although this bias was much weaker overall than the biases we observed for ipsiversive saccades following inactivation (see Figs. 7C, 9C, 11C, and 13C).

3.8.4 Saccadic impairment (RT index)

This index was greater on the experimental day than on the matched control day in six of eight cases (Fig. 15E: red and blue symbols above the identity line) and attained significance as indicated by a Monte Carlo test in four of those cases (filled symbols). The results thus suggest that FEF inactivation induced a selective slowing of downward saccades; however, this slowing was not as pronounced as that observed for contraversive saccades (see Figs 7E, 9E, 11E, and 13E).

3.8.5 Discrimination impairment (choice index)

This index was greater on the experimental than on the control day in five out of eight cases (Fig. 15B: red and blue symbols above the identity line). However, the effect was not significant, as

revealed by a Monte Carlo test, in any case. The results provide no compelling evidence for the existence of a discrimination deficit specific to the contralesional visual field.

3.8.6 Discrimination impairment (RT index)

This index was greater on the experimental than on the control day in only a minority of cases (Fig 15D: red and blue symbols above the identity line). Furthermore, in no case did the difference achieve significance as indicated by a Monte Carlo test. The results thus provide no evidence for a slowing of visual discrimination in the contralesional visual field.

3.8.7 Summary

On one hand, there was an unexpected trend toward an impairment of downward (as opposed to upward) saccades. On the other hand, the signs indicating an impairment of contralesional visual processing were subtle and inconsistent.

3.9 HORIZONTAL-MERIDIAN TASK WITH DISTRACTORS

3.9.1 Rationale

On half of all trials in the horizontal-meridian task, when the colored cue appeared in one hemifield, a bright distractor appeared at a symmetric location in the opposite hemifield (Fig. 17A). For reasons explained above (Basic Task with Distractors), we expected that the presence of a distractor might bring out an otherwise latent impairment of contralesional visual discrimination.

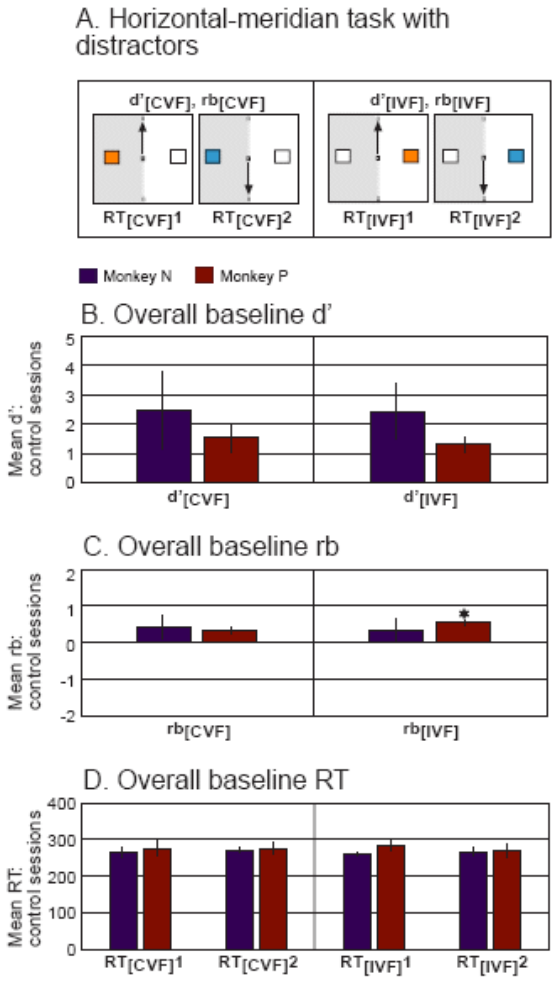

Figure 16. Baseline behavioral performance on the Horizontal meridian task with distractors.

3.9.2 Performance on control days

The monkeys' level of performance on control days is summarized in Fig. 16. There were no significant differences between contralateral and ipsilateral hemifields, except for one rb measure.

3.9.3 Saccadic impairment (choice index)

The bias index was greater on experimental than on matched control days in six out of eight cases (Fig. 17C: red and blue symbols above the identity line). The difference achieved significance, as indicated by a Monte Carlo test, in four of those cases (filled symbols). The results thus suggest that FEF inactivation induced a bias against making downward saccades.

3.9.4 Saccadic impairment (RT index)

This index was greater on the experimental day than on the matched control day in all eight cases (Fig. 17E: red and blue symbols above the identity line) and attained significance as indicated by a Monte Carlo test in five of those cases (filled symbols). The results thus suggest that FEF inactivation induced a selective slowing of downward saccades.

3.9.5 Discrimination impairment (choice index)

This index was greater on the experimental than on the control day in five out of eight cases (Fig. 17B: red and blue symbols above the identity line). In one of those cases, the effect achieved significance as revealed by a Monte Carlo test (filled symbol). The results provide a weak hint of a discrimination deficit specific to the contralesional visual field.

3.9.6 Discrimination impairment (RT index)

This index was greater on the experimental day and on the control day in equal numbers of cases (Fig. 17D: red and blue symbols above and below the identity line). In no case did the difference between experimental and control days achieve significance as indicated by a Monte Carlo test (no symbol is filled). The results thus provide no evidence for a slowing of visual discrimination in the contralesional visual field.

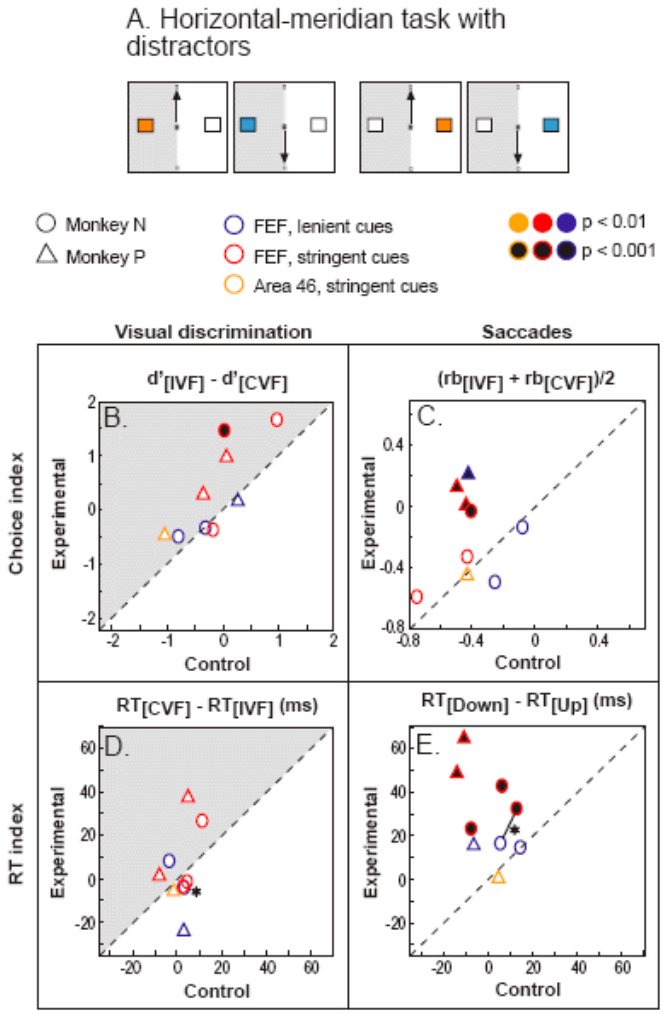

Figure 17. Horizontal meridian task with distractors. A: Conditions of the Horizontal meridian task in which a distractor was present. B-E: Impact of unilateral FEF inactivation on performance.

3.9.7 Summary

The results were little altered by the presence of distractors. There was still an unexpected trend toward an impairment of downward (as opposed to upward) saccades. There were still only subtle and inconsistent signs of an impairment affecting contralesional visual processing.

3.10 COMPARING SACCADIC AND DISCRIMINATION IMPAIRMENTS ON A COMMON SCALE

How severe was the impairment of contralesional visual discrimination as compared to the impairment of contralesional saccades? To answer this question requires measuring the two effects on a common scale. In the case of *reaction time-based* measures, to do so is straightforward. It requires only assessing by how many milliseconds the indices of contralesional discrimination impairment ($RT_{[CVF]} - RT_{[IVF]}$) and contralesional saccadic impairment ($RT_{[Contra]} - RT_{[Ipsi]}$) increased on experimental as compared to control days. The results (summarized in Fig. 18) indicate that the impact on discrimination in the contralesional visual field, as averaged across all three tasks, was 7.0 ms, whereas the impact on the execution of contralesional saccades, as averaged across the two tasks requiring horizontal saccades, was 61.7 ms. Thus, so far as this reaction time-based measure is concerned, the effect of FEF inactivation on saccades was approximately tenfold greater than its impact on visual discrimination.

The *choice-based* measures of discrimination performance (sensitivity: d') and saccadic performance (response bias: rb) are not directly comparable. Accordingly, as a basis for comparison, we will focus on other choice-based measures. In particular, we will compare inactivation-induced increases in (a) the probability that visual discrimination in the contralesional visual field would fail and (b) the probability of succumbing to a bias against contralesional saccades. These two measures, being both in the form of a probability, are directly comparable. However, to derive them from the monkeys' recorded behavior requires making certain assumptions.

We assume, in particular, (a) that on all trials in which discrimination was successful the monkey made the correct response and (b) that on trials in which discrimination failed the selection of the target was determined by a probability function reflecting the monkey's bias (Fig. 19). This set of assumptions is conservative in that it maximizes the estimate of the contribution made by to the monkey's choice behavior by his capacity for discrimination. The probability of discrimination's being successful (D) and the probability, if discrimination fails, of the saccade's being in an ipsilesional direction (B) are derivable from the measured hit rate (H) and false alarm rate (F) as D = H-F and B = (1-H)/(1-H+F), where hits are defined, in accordance

with the convention established above, as contralateral saccades executed in response to cues instructing contralateral saccades, and false alarms are defined as contralateral saccades executed in response to cues instructing ipsilateral saccades.

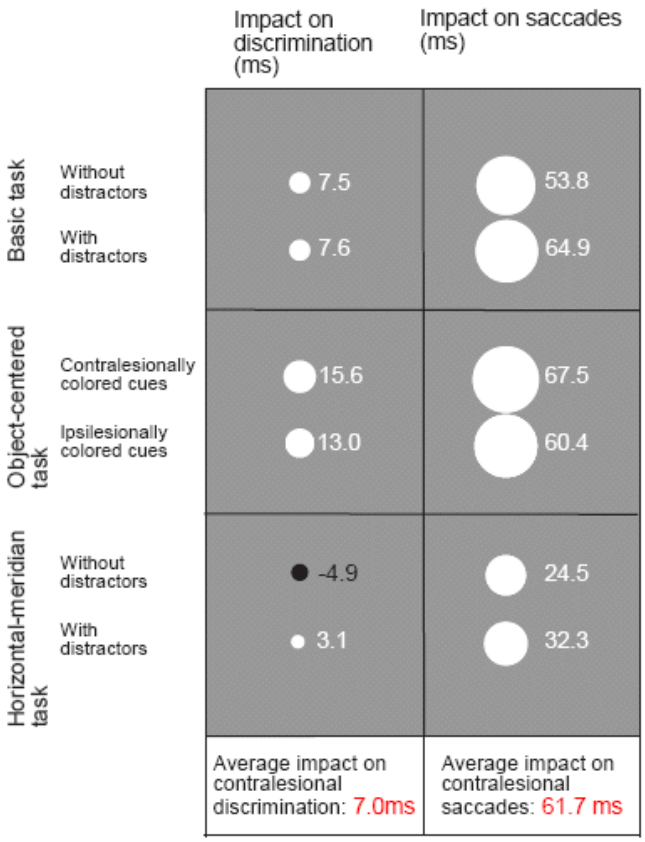

Figure 18. Overall impact of unilateral inactivation on discrimination (left column) and on saccades (right column) with respect to reaction time. Impact on discrimination was assessed by taking the difference in the disparity between reaction time for cues in the contralesional and ipsilesional visual field ($RT_{[CVF]} - RT_{[IVF]}$) between control and experimental days. Impact on saccades was assessed by taking the difference in the disparity between reaction time for contralesional and ipsilesional saccades ($RT_{[Contra]} - RT_{[Ipsi]}$) between control and experimental days. The diameter of the circles represent the magnitude of the impact; white circles indicate an impairment in discrimination or saccades, while black circles indicate an enhancement.

The inactivation-induced increase in the rate at which contralesional discrimination failed is computed as: $D_{[IVF]} - D_{[CVF]}$ on the experimental day minus $D_{[IVF]} - D_{[CVF]}$ on the control day. The inactivation-induced increase in the rate at which the monkey succumbed to a bias against contralesional saccades is given by: $(D_{[IVF]} - D_{[CVF]})/2$ on the experimental day minus($D_{[IVF]}$ –

$D_{[CVF]}$)/2 on the control day. The results (summarized in Fig. 20) indicate that the increase in the probability that discrimination would fail was markedly less than the increase in the probability that the monkey would succumb to a bias against contralesional saccades. Across all three tasks, the average value of indices reflecting the tendency for inactivation to impair discrimination in the contralesional visual field was zero. Across the two tasks requiring horizontal saccades, the average of the indices reflecting the tendency for inactivation to induce a bias against contralesional saccades was 0.34. Thus, so far as this choice-based measure is concerned, the only effect of FEF inactivation was on saccades.

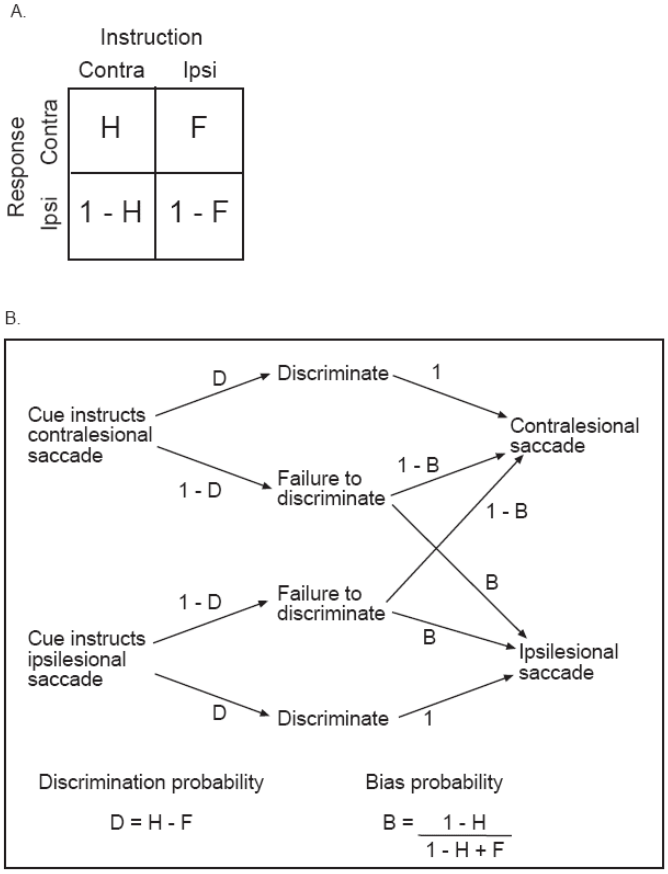

Figure 19. Model of discrimination and response selection process. A: All possible combinations of instructions and responses on a given trial. B: Diagram of the two-step process of discrimination and response selection. The result is a discrimination probability (D = H-F) and a bias probability (B = (1-H)/(1-H+F).

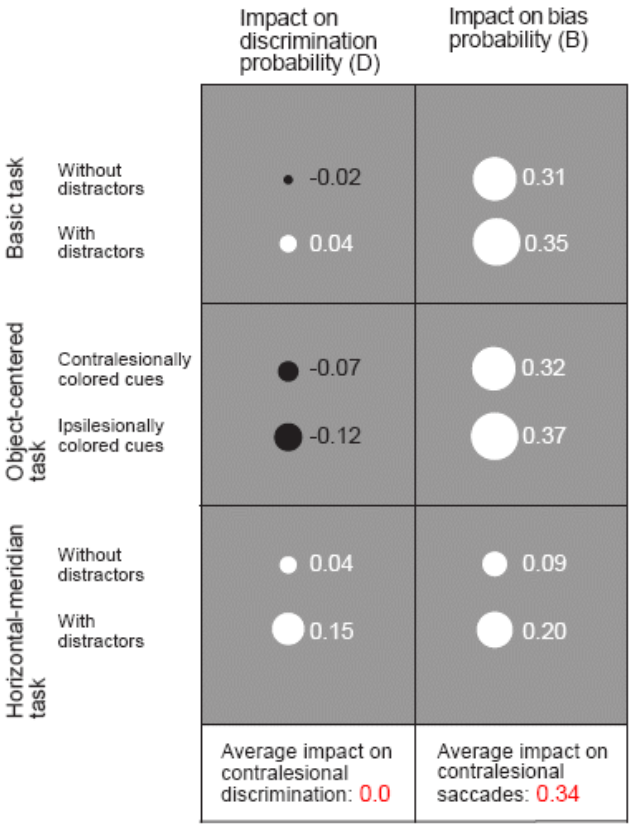

Figure 20. Overall impact of unilateral inactivation on discrimination probability (left column) and on bias probability (right column). Impact on discrimination probability was assessed with the following formula: $(D_{[IVF]} - D_{[CVF]})_{Exp} - (D_{[IVF]} - D_{[CVF]})_{Cont}$, using the discrimination probability (D) described in Fig. 19. Impact on bias probability was assessed with the following formula: $[(D_{[IVF]} - D_{[CVF]})/2]_{Exp} - [(D_{[IVF]} - D_{[CVF]})/2]_{Cont}$, using the bias probability (B) described in Fig. 19.

3.11 CONSISTENCY ACROSS CORTICAL SITES

In three pairs of inactivations (two in monkey N and one in monkey P), the muscimol injection was placed at the same location and depth for a single pair (see Fig. 4B and 4C). Consistent behavioral impairments following FEF inactivation at same injection site would indicate that our method of inactivating FEF and measuring behavior were reliable. To determine the level of uniformity within injection sites, we took the difference between each control and experimental index of saccadic and discrimination impairment for each experiment. We then took the difference between this value for each within-injection site pair and across-injection site pair for

each monkey and performed a one-tailed t-test to determine whether this difference was significantly smaller for inactivations performed at a single site compared to inactivations performed at different sites. In Figs. 7B-E, 9B-E, 11B-E, 13B-E, 15B-E, and 17B-E, inactivation pairs from the same injection site which showed significantly similar control-experimental differences ($p < 0.05$) are connected with a line and labeled with a star. In several cases, within-injection sites pairs fell so closely together on the plot that it was impossible to connect them with a line; these are labeled with only a star.

Overall, the differences between the effects of FEF inactivation located at the same injection site were significantly smaller than the difference between the effects at different sites 30 out of a possible 72 measurements. In other words, the behavioral effects of inactivation at the same FEF site were significantly similar nearly half the time. This indicates a reasonably high level of consistency within FEF injection sites.

3.12 CONSISTENCY OVER TIME DURING THE EXPERIMENTAL SESSION

The dynamics of muscimol diffusion in the brain are not well-known. It is possible, however, that our results were impacted by a slow spread of muscimol inactivation, or a gradual re-activation as the effects of muscimol wore off. To explore this possibility, we calculated the RT-based discrimination impairment ($RT_{[Contra]} - RT_{[Ipsi]}$) for each individual block within each experimental session. We chose the RT-based discrimination impairment measure because it was this that showed the most robust effect overall following FEF inactivation. For blocks of the Basic task and the Object-centered task (for which saccades were direct to the right or the left), we calculated the average of the RT measure for those blocks which fell within the first four blocks of the entire session, the last four blocks of the session, and the remaining blocks in the session. We did consider blocks of the Horizontal meridian task in determining the point at which blocks fell during the session, although we did not consider the average RT measure in this analysis.

In monkey N, we found a trend for the RT-based discrimination impairment to increase over the course of the experimental sessions. The average impairment was 51.1 ± 14.5 ($\alpha = 0.05$, $n = 11$) ms for the first four blocks, 78.3 ± 8.2 ($\alpha = 0.05$, $n = 22$) ms for blocks in the middle of the

session, and 81.2 ± 17.1 ($\alpha = 0.05$, n = 11) ms for the last four blocks. In monkey P, however, we discovered a trend for the effects to increase toward the middle of the session, and decrease toward the end of the session. The average impairment for monkey P was 62.8 ± 22.6 ($\alpha = 0.05$, n = 9) ms for the first four blocks, 78.2 ± 11.7 ($\alpha = 0.05$, n = 18) ms for blocks in the middle of the session, and 69.2 ± 10.9 ($\alpha = 0.05$, n = 14) ms for the last four blocks in the session. The difference between these trends may be explained by the observation that monkey P usually worked for a longer period of time during experimental sessions, and therefore the effects of muscimol may have faded after several hours. However, we did not systematically explore this possibility.

3.13 CONSISTENCY ACROSS LEVELS OF CUE DISCRIMINABILITY

Overall, on control days with lenient cues, performance was at 95% correct (d' = 3.3), whereas on control days with stringent cues, performance was at 78.5% (d' = 1.6). If inactivation of FEF resulted in a disruption of attentional selection in the contralesional visual field, we would expect that our measures of impairment would be greater when stringent cues were used than when lenient cues were used.

To ask whether there was a difference in impairment following inactivation for lenient vs. stringent cues, we first calculated the fraction of inactivations resulting in a significant expected impact on RT-based and choice-based saccade and discrimination impairment, as shown by the filled symbols in Figs. 7B-E, 9B-E, 11B-E, 13B-E, 15B-E, and 17B-E. We found that overall, the effect on RT-based saccade impairment was significant in 16/22 cases (72.7%) for lenient cues, while the effect on RT-based saccade impairment was significant in 29/30 cases (96.7%) for stringent cues. The effect on choice-based saccade impairment was significant in 14/22 cases (63.6%) for lenient cues, and 23/30 cases for stringent cues (76.7%). The effect on RT-based discrimination impairment was significant in 5/22 cases (22.7%) for lenient cues, and 1/30 cases (3.3%) for stringent cues. The effect on choice-based discrimination impairment was significant in 3/22 cases (13.6%) for lenient cues, and 1/30 cases (3.3%) for stringent cues. Note that in each fraction, only significant cases in the expected direction were counted.

We also calculated the average impact on contralesional discrimination and contralesional saccades using the common-scale method outlined above and summarized in Figs. 18 and 20. The average impact on contralesional discrimination with respect to RT was 9.8 ms for lenient cues and 4.6 ms for stringent cues. The average impact on contralesional saccades was 43.6 ms for lenient cues and 54.9 ms for stringent cues. The average impact on discrimination probability (D) was 0.03 for lenient cues and -0.01 for stringent cues. The average impact on bias probability (B) was 0.28 for lenient cues and 0.23 for stringent cues.

Taken together, these results suggest that using stringent cues increased the effect of FEF inactivation on saccade impairment (particularly with respect to the fraction of inactivations showing a significant effect), but decreased the effect of inactivation on visual discrimination. The latter finding is directly contrary to the trend expected from an attentional deficit.

3.14 CONSISTENCY BETWEEN MONKEYS

To compare the effects of FEF inactivation on each monkey, we also calculated the fraction of inactivations resulting in a significant impact on behavior, as well as the overall impact on contralesional discrimination and saccades for monkey N and monkey P separately. Overall, the effect of inactivation on RT-based saccade impairment was significant in 26/30 cases (86.7%) for monkey N, and 19/22 cases (86.4%) for monkey P. The effect on choice-based saccade impairment was significant in 18/30 cases (60.0%) for monkey N and 19/22 cases (86.4%) for monkey P. The effect on RT-based discrimination impairment was 0/30 cases (0.0%) for monkey N, and 6/22 cases (27.3%) for monkey P. Finally, the effect of choice-based discrimination impairment was significant in 3/30 cases (10.0%) for monkey N, and 1/22 cases (4.5%) in monkey P. Again, only significant cases in the expected direction were counted.

The average impact on contralesional discrimination with respect to RT was 2.9 ms for monkey N and 12.2 ms for monkey P. The average impact on contralesional saccades was 45.5 ms for monkey N and 54.5 ms for monkey P. The average impact on discrimination probability (D) was -0.06 for monkey N and 0.09 for monkey P. The average impact on bias probability (B) was 0.15 for monkey N and 0.33 for monkey P.

These results suggest that the fraction of inactivations resulting in significant impairments, as well as the overall impact on contralesional discrimination and saccades, were comparable between the two monkeys. However, monkey P seemed to display a greater degree of impairment of contralesional discrimination and discrimination probability, as well as contralesional saccades.

3.15 DECREASES IN IPSIVERSIVE SACCADIC RT VS. INCREASES IN CONTRAVERSIVE SACCADIC RT

Although our method of subtracting discrimination and saccadic measurements in the contralesional direction from corresponding measurements in the ipsilesional direction was designed for its tolerance for day-to-day fluctuations and sensitivity to push-pull mechanisms (see *Methods*), it is critical to discern whether the predominant effect was an impairment in the contralesional direction or an enhancement in the ipsilesional direction. Prior work has found both tardier contraversive saccades and disinhibited ipsiversive saccades during FEF inactivation (Sommer and Tehovnik 1997). To determine the extent of contraversive delays and ipsiversive hastening, we calculated average contralesional and ipsilesional RTs for both monkeys and compared the control value to the experimental value. For the Basic task, on conditions with no distractor, contralesional saccades were slowed an average of 54.4 ms, and ipsilesional saccades were slowed an average of 0.7 ms. For conditions with a distractor, however, contralesional saccades were slowed an average of 58.3 ms, while ipsilesional saccades were speeded an average of 6.5 ms. For the Object-centered task, contralesional saccades were slowed an average of 66.5 ms, and ipsilesional saccades were slowed an average of 2.6 ms (no difference was apparent between conditions with contralesionally colored cues and ipsilesionally colored cues). For the Horizontal meridian task, downward saccades were slowed an average of 56.4 ms, and upward saccades were slowed an average of 31.9 ms (no difference was apparent between conditions with and without distractors).

These results suggest that the predominant effect of unilateral FEF inactivation was a slowing of contralesional and downward RTs. However, a subtle slowing of ipsilesional RTs also occurred when no stimulus was present in the ipsilesional visual field (as in the Basic task

with no distractors and in the Object-centered task). When an ipsilesional saccade was required and an ipsilesional stimulus was present, as in the Basic task with distractors, RTs were slightly decreased (6.5 ms). In addition, a slowing of upward RTs also occurred, though this effect was not as great as the slowing of downward RTs.

3.16 FIXATION PERFORMANCE

In general, we found that monkeys were able to maintain fixation properly after unilateral FEF inactivation. There was no significant difference in the number of fixation breaks during the task for either monkey on experimental as compared to control sessions. For monkey N, the percentage of trials in which the monkey broke fixation was 5.4 ± 0.9% ($\alpha = 0.05$, $n = 43$) on control days and 5.3 ± 0.7% ($\alpha = 0.05$, $n = 57$) on experimental days. For monkey P, the rate of fixation breaks was 9.2 ± 2.1% ($\alpha = 0.05$, $n = 32$) on control days and 11.2 ± 0.9% ($\alpha = 0.05$, $n = 50$) on experimental days.

3.17 DORSOLATERAL PREFRONTAL INJECTION

We deliberately placed a single injection of muscimol rostral to the FEF in periarcuate prefrontal cortex (PFC) of monkey P. The aim of doing so was to investigate the possibility of eliciting a contralesional saccadic impairment from inactivation of tissue outside the FEF. The unilateral injection in PFC in fact elicited no consistent impairment either of contralesional visual discrimination or of contralesional saccades. The contrast between PFC and FEF emerged particularly strikingly from the analysis of saccadic performance in the context of the object-centered task. In this task, there was a significant impairment of contralesional saccades, indicated both by choice-based and by reaction time-based measures, both in trials with distractors and in trials without distractors, after each of nine FEF injections (Figs. 15E and 17E: filled red and blue symbols). In contrast, the impact of the PFC injection on the contralesional saccadic reaction time was, if anything, a speeding (Figs. 15E and 17E: orange symbols beneath

the identity line). Although we did not follow up on this observation, we consider it worth noting because of the strong suggestion that the increase of contralesional saccadic reaction times is specific to inactivation of the FEF.

4.0 DISCUSSION

4.1 IMPAIRMENT OF CONTRALESIONAL SACCADES VS. IMPAIRMENT OF CONTRALESIONAL DISCRIMINATION

Our results indicate that unilateral inactivation of the FEF leads to a strong deficit in contralesional saccades. Following FEF inactivation, contralesional saccades were less likely to occur, and when they did occur, their RTs were greater. In contrast, a deficit in contralesional visual detection following from unilateral inactivation of FEF was very weak, if present at all.

The critical difference between our task design and those used earlier to detect visuomotor deficits resulting from FEF lesions was that in our task, the spatial locations of the visual cue and the saccade target were dissociated. The consistent and significant finding that contralesional saccades were impaired, while virtually no contralesional visual deficits occurred, indicates that FEF has a much more powerful impact on the saccadic system than on visual discrimination. Furthermore, the profound impact on contralesional saccades indicates that our muscimol injections were sufficient to impair function in FEF; the lack of an impairment in discrimination cannot be attributed to an inadequate degree of inactivation.

Because we did not map out the RFs of each FEF injection site with stimulation immediately prior to each experiment, it may be argued that in every case, the inactivated area only contained neurons whose RF fell at the location of the contralesional saccade target, and never the location of the contralesional visual cue. However, the visual cues used in Task 3 were centered at the exact location of the saccade targets in Tasks 1 and 2. With the exception of one injection performed on monkey P, both monkeys were required to perform all three tasks during each experimental session. Therefore, because monkeys were impaired at making saccades to the contralesional targets in Tasks 1 and 2, they should have been equally impaired at discriminating contralesional cues in Task 3, if discrimination were equally affected by inactivation. However,

we saw very little evidence of a contralesional discrimination deficit; in only one session did a monkey display a significantly decreased ability to detect contralesional stimuli, and this was only when an ipsilesional distractor was present.

4.2 IMPAIRMENT OF DOWNWARD SACCADES

We also discovered a weak impairment in downward saccades following inactivation of both the right FEF (monkey N) and the left FEF (monkey P). There are at least two possible explanations for this finding. First, it could be that neurons at each cortical site at which we induced lesions are important for downward eye movements. Blanke and Seeck (2003) found that stimulation of human FEF in superficial layers resulted in contralesional and either horizontal or oblique upward eye movements, and suggest that superficial neurons may code for upward saccades. The sites that we chose for inactivation were always 5-7 mm beneath the surface of the cortex; however, because monkey FEF is located along the bank of the arcuate sulcus, the cortical layer in which the injection was placed depends more on the anterior-posterior location than the depth of the syringe. In each monkey, we placed multiple injections at FEF sites which were at least one mm apart in anterior-posterior coordinates, and the horizontal spread of each injection was at least 1.5 mm, according to the cubic relationship described by Tehovnik and Sommer (1997). Therefore, the span of inactivated tissue was at least four 4 mm in each monkey, which is sufficient to span several cortical layers.

A more likely possibility is that inactivating FEF revealed an overall upward bias in the saccadic system. If downward saccades are inherently more difficult to generate, a lesion in either hemisphere may impair downward saccades simply by a decrease in cortical activity. That this explanation is feasible is evidenced by the well-known difference in upward and downward saccadic performance. When saccades are initiated from the center of gaze, upward saccades are shorter in latency than downward saccades (Payne 1967), and have higher peak velocities, shorter durations, and smaller errors (Zhou and King 2002). In addition, there is evidence of an upward bias in memory guided saccades. When saccades are directed to a remembered target, the saccade endpoint is generally deviated upward (Gnadt et al. 1991; White et al. 1994). In addition to suggesting a superficial arrangement of upward-coding neurons, as described above,

Blanke and Seeck (2003) proposed that FEF may simply contain more upward-coding neurons than downward-coding neurons. Taken together, these findings support an inherent upward bias in the saccadic system which may have been revealed following inactivation of either FEF.

4.3 LACK OF EVIDENCE FOR IMPAIRMENT OF CONTRALESIONAL ATTENTION

Intrinsic in our analysis of the impact of FEF inactivation on visual discrimination is an assessment of the extent to which FEF neurons are involved in allocating attention to visual stimuli. Several experiments have examined the possible role of FEF in attentional selection of visual stimuli. Moore and Fallah (2001, 2004) found that by stimulating neurons in FEF at a current lower than that required for evoking saccades, they could enhance performance of a stimulus-detection task when the stimulus was located in the RF of the FEF site that was stimulated. Moore and Armstrong (2003) demonstrated that the same type of FEF stimulation could enhance the response of V4 neurons to a visual stimulus. However, a possible explanation of these experiments is that FEF stimulation antidromically activated extrastriate visual areas, which could result in increased attention and enhanced visual responses. Controls in the FEF stimulation-V4 recording study (Moore and Armstrong 2003) attempted to eliminate this possibility by showing that V4 neurons' responses to FEF stimulation were dependent on the neurons' visual responses to stimuli in their response fields. However, because FEF stimulation occurred after the visual stimuli were presented, this result merely shows that FEF stimulation had a greater impact on neurons which were already active, perhaps because the neurons were already in a more excitable state. Therefore, an antidromic explanation of these experiments is still a possibility.

Moreover, even if the artificial activation of FEF neurons does contribute to the enhancement of a sensory representation, it does not necessarily follow that this is an active mechanism of attentional allocation which occurs during actual eye movements. Our results suggest that allocation of attention to a visual stimulus is certainly possible without full function of FEF; this is indicated by the observation that monkeys were clearly able to attend and discriminate cues

which fell within the RFs of neurons which were evidently inactivated (as demonstrated by an impairment to generate saccades to those locations).

Similar to the argument above regarding selective inactivation of only downward-coding neurons, we considered the possibility that our injections inactivated only neurons which occupied a laminar position projecting to oculomotor areas and not those projecting to extrastriate areas such as V4. However, we believe this was not an important factor in our results. First, as explained above, the horizontal spread of muscimol most likely spanned at least 4mm. In addition, Hupé et al. (1999) demonstrated that substances injected into cortical tissue diffuse in a vertically oriented ellipsoid shape, much of the solution moving upward along the micropipette or syringe. Therefore is it reasonable to assume that the vertical spread of muscimol exceeded 4mm, and that regardless of the orientation of the syringe to the surface of the cortex, several layers of FEF were inactivated by each muscimol injection. Indeed, it would be a technically challenging experiment to reproducibly inactivate only FEF neurons which do not project to V4, and we are doubtful that this occurred accidentally for each of our nine FEF inactivations.

Related to attentional allocation is the idea that FEF is involved in saccadic target selection; this idea allows that the visual activity reflected by many FEF neurons is related to attention, but that this activity serves the primary goal of generating a saccadic signal. Thompson and colleagues have found that some FEF neurons respond rapidly to the onset of any sudden visual stimuli in their RFs, and a cell with an oddball target (where a saccade is to be initiated) in its RF subsequently displayed build-up increased activity (Thompson et al. 1996; Thompson et al. 1997). This implies that a visual stimulus elicits a nonspecific, transient response in any neurons with a corresponding RF, and this is followed by a selective narrowing down of activation to a subset of neurons when a direction of saccade is actually chosen. This selection occurs even when the location of the oddball is switched suddenly, and the direction of saccade changes (Murthy et al. 2001). Furthermore, a stimulus which must be attended, but is never the target of a saccade, is selected by FEF neurons (Sato and Schall 2003; Sato et al. 2003; Schall et al. 2004). Recently, Thompson et al. (2005) found that when monkeys performed an attentional task in which no saccade was required, nor were monkeys ever trained to make a saccade during the task, visually responsive FEF neurons selected the attentional cue, but movement neurons displayed no activity. The most distilled motor signal in FEF therefore appears to have no role in

attentional selection unrelated to saccadic generation. While the visually responsive neurons do appear to be involved in selecting an attentional target, it is clear from our experiment that these neurons are not necessary for attentional selection. We almost certainly inactivated both movement-related and visually responsive FEF neurons, and observed dramatic saccadic deficits but virtually no changes in visual discrimination ability. Therefore, we conclude that although many FEF neurons appear to select the location of an attentional target, those neurons are not necessary for the allocation of attention into their RFs.

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