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Research report

The effects of combined superior temporal polysensory area and frontal eye field lesions on eye movements in the macaque monkey

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Abstract

We previously found [42] that lesions of the superior temporal polysensory area (STP) cause temporary deficits in the production of eye movements. In order to both define regions participating in the ensuing recovery and to further explore the cortical control of eye movements, we examined the effects of addition of frontal eye field (FEF) lesions to STP lesions, on visual fixation, saccadic eye movements, and smooth pursuit eye movements. Three monkeys received bilateral STP lesions followed by a FEF lesion and as a control, an additional monkey received a bilateral inferior temporal cortex (IT) lesion followed by a FEF lesion. All animals had a profound impairment in foveating the central fixation point. This impairment was completely eliminated by turning on a dim light in the testing chamber. Large neglect-like impairments in making saccades were only seen after combined STP and FEF lesions. Impairments in making smooth pursuit eye movements after combined lesions of STP and FEF were larger than those seen after STP lesions but within the range of deficits that have been reported after FEF lesions alone. The impairment of visual fixation in darkness and the lack of impairment under conditions of dim illumination appear to reflect a specific role for the FEF in spatial orientation in the absence of visual landmarks. The FEF also appears to play a more critical role than STP in smooth pursuit. By contrast, STP and the FEF appear to work cooperatively with respect to the production of saccades. We suggest that cortical oculomotor control can flow either through the midbrain or through the FEF and that the FEF pathway is specifically involved in tasks with a discontiguity between the stimuli and the behavioral response while the midbrain pathways are preferentially involved in more stimulus-driven eye movements.

Keywords: Saccades; Smooth pursuit; Lesion; Oculomotor; Localization; Cortex; Macaque

1. Introduction

A number of cortical areas in the monkey have been implicated in oculomotor control. Nevertheless, the effects of lesions of individual cortical areas (other than striate cortex) on eye movements are typically small and transient. Posterior parietal cortex lesions [35] and frontal eye field (FEF) lesions [9,24,33] have been shown to cause small or no impairments in making saccadic eye movements. Lesions of the superior temporal polysensory area (STP: [5]), an area located in the superior temporal sulcus which has visual response properties and connections similar to those of posterior parietal cortex, also produce small deficits in making saccades [42]. Similarly, lesions of posterior parietal cortex [31], the FEF [24,32,34,36], STP [42], MT and MST [10,41] have all been shown to produce impairments in making smooth pursuit eye movements. Two possible reasons exist for the relatively small size of deficits on simple eye movement tasks after lesions restricted to one cortical area: first, there may exist a large amount of equipotentiality within the aforementioned areas on these tasks, and alternatively, each area may be a specialized for specific aspects of eye movement control that have not been isolated by simple oculomotor tasks.

Hemidecortication [54], combined lesions of two cortical areas involved in eye movements, or combined

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lesions of cortical tissue and the superior colliculus produce deficits that are substantially larger than those that follow individual cortical lesions. For example, combined posterior parietal cortex and FEF lesions produce deficits both in making saccades and in making smooth pursuit eye movements that are much larger than those seen after either lesion alone [33,34]. Moreover, while lesions of either the superior colliculus or the FEF produce small to moderate deficits in making saccadic eye movements as monkeys remove pieces of apple from slots in a board, combined superior colliculus and FEF lesions yield a severe deficit in making exploratory eye movements that is much larger than the deficit after either lesion alone [47]. Comparable results were obtained in a study of the effects of lesions and cooling of the frontal eye fields, superior colliculus, or both, on saccades [25]. The intermediate and deep layers of the superior colliculus receive input from a large number of extrastriate visual areas, the FEF, and the supplementary eye fields [12]. In addition to cortical output via the superior colliculus, the FEF projects directly to the brainstem para-oculomotor areas [19,28,29,52]. The finding that combined lesions of the superior colliculus and FEF produce a nearly complete loss of scanning eye movements suggests that while there are a number of cortical areas involved in making eye movements, the cortical control of saccadic eye movements flows largely through these two areas. Similarly, posterior visual areas appear to be capable of mediating smooth pursuit eye movements either via their connections to the FEF [1,3,20,21,23,38,49] or directly via their connections to the pons [4,15,55,56]. The existence of multiple cortical output pathways for the control of eye movements further motivated us to attempt to determine what areas are involved in the recovery seen after STP lesions and what differences, if any, there are between the effects of lesions of the FEF and STP.

We have now begun to examine which cortical areas are involved in mediating eye movements in the absence of STP and to elucidate the respective contributions of these areas to different aspects of eye movement control by investigating the effects of combined removal of STP and the FEF on visual fixation, saccades to visual targets, and smooth pursuit eye movements.

A preliminary report of this study in abstract form has been presented previously [50].

2. Methods

2.1. Subjects

The subjects were 4 macaque monkeys: 1 *Macaca mulatta* and 3 *Macaca fascicularis*, ranging in weight from 4.0 to 6.5 kg. All animal handling, surgical procedures, training and testing was done in accordance with protocols following NIH guidelines and approved by the Princeton University Institutional Animal Care and Use Committee and the consulting veterinarian. At the beginning of this study STP had been removed from monkeys 1, 2 and 3 bilaterally in either two stages (1 and 2) or one stage (3) (see Histology, below). Monkey 4 at the beginning of the study had IT removed from both hemispheres in two stages. All monkeys had been tested until they met our criterion for recovery from the effects of their STP or IT lesions. In the present study, monkeys 1 and 3 received a bilateral FEF lesion and monkeys 2 and 4 received a unilateral FEF lesion (see Table 1).

2.2. Methods for measurement and control of eye movements

The monkeys were implanted with a head bolt and a scleral eye coil [22] for measuring eye position. Surgery was performed under sodium pentobarbital anesthesia using standard sterile procedures [see [42]]. The head bolt was implanted onto the skull with skull screws covered with dental cement to yield a strong, stable and painless means of head restraint. Following recovery from the surgery, the animals were put on a controlled drinking schedule and began training.

During all training and testing the animal sat in a primate chair with its head held in a fixed position by an implanted head bolt. In a dark room the animals faced a 98×98 degree translucent screen. An optic bench behind the tangent screen was used to project the fixation and target stimuli (0.3 degree diameter spots of light generated by LEDs). Eye position was monitored to within 0.5 degrees accuracy by a magnetic search coil apparatus [13]. A PDP-11/73 computer monitored eye position, presented stimuli, controlled reinforcement contingencies, and collected performance and eye movement data. The PDP-11/73 also presented an on-line x–y display of the monkeys' eye position with a persistent trace that was cleared at the end of each trial. This display also showed the target locations and the windows in which the animal was required to fixate. Throughout all behavioral training and testing the monkeys were run for 5 days a week with daily training sessions lasting until the animal completed 750–1000 correct trials (1–3 h).

2.3. Behavioral tasks and testing

2.3.1. Visual saccade task

After the monkey maintained fixation on the fixation point for 1000 ms, a target stimulus in 1 of 8 randomly chosen locations turned on simultaneously with the offset of the fixation point. Target stimuli appeared at 8 degrees above or below the fixation point and at 8, 15 or 22 degrees to the right or left of the fixation point.

Following the offset of the fixation point and onset of the target, the monkey had 1000 ms to fixate within either 2 degrees of the target (for those targets 8 and 15 degrees from the fixation point) or 3 degrees of the target (for those targets 22 degrees from the target). The animal was then required to maintain fixation for the remainder of the 1000 ms interval to receive 1.3 ml of apple juice or water as reward. Breaking fixation or failing to make a saccade to the target and fixate it resulted in termination of the trial and imposition of a 1-s time out in addition to the normal 1-s inter-trial interval. A noncorrecting procedure was used (i.e., the next stimulus after an incorrect trial was randomly chosen).

2.3.2. Pursuit task

There were three pursuit tasks: pursuit of stimuli moving 5 deg/s, pursuit of stimuli moving 13 deg/s, and pursuit of stimuli moving 20 deg/s. Following a 1 second fixation period, the fixation point began moving and the animal subsequently was required to maintain eye position within either 4 degrees (5 deg/s and 13 deg/s tasks) or 5 degrees (20 deg/s task) of the stimulus. Either breaking fixation or failing to pursue the target stimulus within these limits resulted in termination of the trial and imposition of a 1 second time out. As in the saccade task a noncorrecting procedure was used. The targets moved to a final eccentricity of either 8 degrees (5 deg/s) or 10 degrees (13-deg/s and 20-deg/s tasks) to the left, right, up or down. When the stimulus reached its final eccentricity it shut off and the animal received apple juice or water. In the 20-deg/s task stimuli moving along the horizontal meridian to a final eccentricity of 20 degrees were also presented. Data for the latter trials were similar to the results for targets traveling to an eccentricity of 10 degrees and will not be considered further in this report.

2.3.3. Baseline testing

Each day during the baseline period the monkeys were tested until they achieved 300 trials correct on the saccade task. The monkeys were also tested until they achieved 150 trials correct on the 5-deg/s, 13-deg/s and 20-deg/s pursuit tasks. After a criterion of 85% correct was met for 2 consecutive days on a task, the animal was run on the task for 2 more days and the data for these 4 days was used for post-lesion comparisons. During this period eye movement records were saved for all correct and incorrect trials. Fixation latency (the time between fixation stimulus onset and achievement of fixation), saccade latency (the time between saccade target onset and fixation of the target) and percent correct to each saccade target for all tasks were also saved during this period as was done during the training phase of the experiment. Following completion of baseline testing, the animal was given free water for a period of not less than 6 weeks prior to cortical surgery.

2.3.4. Postoperative testing and data analysis

When the monkeys began postoperative testing (7–10 days after the FEF removal) they were initially unable to fixate the central fixation point (see Section 3: Results). During the early testing we discovered that the monkeys were able to fixate if a dim light was turned on in the testing room. This enabled us to calibrate the eye coil by having the monkey fixate spots of light in various positions with the room dimly illuminated. As the animals regained the ability to fixate in the dark they fixated at the same point that they did in the dimly lit room suggesting that this was a valid way of calibrating the eye coil. The monkeys were initially run on a fixation task requiring the animals to fixate for 500 ms for blocks of ten trials in darkness mixed with blocks of ten trials in dim illumination. Once the animals regained the ability to fixate the central fixation point in darkness they were tested on all tasks as in the baseline testing period for 5 days per week. If a monkey was unable to track the stimulus within the standard windows on the pursuit tasks the windows were expanded to allow the collection of enough eye movement data to do a quantitative comparison with the preoperative results. The animals were tested on the saccade task until the mean postoperative saccade latencies over a week of testing either were no longer significantly increased over preoperative performance ($P<0.05$, two tailed t-test) for all targets or until the mean postoperative saccade latencies to the most peripheral targets were within 7.5% of the mean preoperative level. If the monkey failed to make a saccade to the target within 1s, the saccade latency was given a value of 1000 ms for that trial. They were also tested on the pursuit tasks until the percent correct over a week of testing was no longer below 85%. One monkey with combined STP and FEF damage (monkey 1) did not recover to the baseline level of performance on the saccade task; testing of this animal was terminated after 20 weeks.

For all lesions, preoperative and postoperative fixation latency, percent correct and saccade latency over each week of postoperative testing were compared to baseline performance on the saccade task. Differences that reached a level of $P<0.05$ (two tailed t-test for unpaired observations) were considered statistically significant. The mean saccade latency and percent correct of all preoperative trials to a given target ((300 trials per day/8 randomly selected targets) × 4 days = approx. 150 trials per target) was compared to the mean value of all postoperative trials to the same target ((300 trials per day/8 randomly selected targets) × 5 days = approx. 188 trials per target). For each lesion the mean preoperative fixation latency (300 trials per day × 4 days = 1200 trials)

was compared to the postoperative fixation latency (300 trials per day × 5 = 1500 trials).

To analyze the pursuit data, the digitally recorded eye position signal on the pursuit task was differenced (i.e., the mean slope was determined using a method similar to differentiating a continuous function) to yield eye speed, any saccades made were excluded from each record, and the mean eye speed was calculated for each trial. Similar to the analysis of the saccade data, for each lesion the mean preoperative and postoperative eye speeds for each week of testing were compared using a two-tailed *t*-test for unpaired observations and differences that reached a level of $P < 0.05$ were considered statistically significant. Thus, for each lesion and target speed the mean eye speed of all preoperative trials to a given target ((150 trials per day/4 randomly selected directions) × 4 days = approx. 150 trials per direction) was compared to the mean eye speed of all postoperative trials to the same target ((150 trials per day/4 randomly selected directions) × 5 = approx. 188 trials per direction).

2.4. Cortical surgery

For surgery the monkey was first given an intramuscular injection of atropine sulfate (0.4 mg) followed by a restraining dose of ketamine (11 mg/kg). Animals were then anesthetized with intravenous sodium pentobarbitol (15 mg/kg, supplemented as necessary). Body temperature and heart rate were monitored throughout surgery. After the skin and muscle were retracted, the bone overlying the frontal lobe was removed. The dura mater was then opened and the FEF was removed by aspiration with the aid of an operating microscope. When the lesion was complete, the overlying tissue was sewn up and the animal was allowed to recover from anesthesia. Following surgery, the animal was given a prophylactic course of penicillin (Bicillin).

2.5. Histology

Following all postoperative testing, the monkeys were overdosed with sodium pentobarbitol and perfused through the heart with saline followed by either (a) 10% buffered formalin or (b) first, 10% buffered formalin; second, 10% buffered formalin with 10% sucrose; third, 10% buffered formalin with 20% sucrose; and finally, 10% buffered formalin with 30% sucrose. The brain was then placed in 30% sucrose formalin until it was sectioned. The area of interest was sectioned in 50-μm slices in the coronal plane. Every tenth section through the frontal lobe was mounted on a glass slide and stained with cresyl violet.

The lesions of STP and IT have been described in detail in a previous report [42]. Monkeys 1, 2, 3 and 4 in this paper correspond to monkeys 1, 2, 5 and 6 in the previous paper. The STP lesions, with the exception of the right side lesion in monkey 2 which largely involved the posterior half of STP, were as intended with the exception of varying amounts of damage to IT cortex in the lower bank of the superior temporal sulcus. The IT lesion removed IT cortex lying in the lower bank of the superior temporal sulcus and the adjacent dorsal portion of the inferior temporal gyrus as a control for unintentional IT damage in monkeys 1 and 3.

The FEF has traditionally been defined as that portion of the frontal cortex which when electrically stimulated results in eye movements. The definition of the FEF has been refined by Bruce and colleagues [7] by using low current stimulation (see [48] for a brief review of the history of the FEF). The FEF as redefined by Bruce et al. lies in the anterior bank of the arcuate sulcus and on the cortical surface immediately anterior to the junction of the upper and lower limbs of the arcuate sulcus. We intended to remove this cortex and the cortex immediately anterior to it (to allow removal of cortex in the depths of the arcuate sulcus) in our FEF lesions. As can be seen in Fig. 1, all of the lesions except that of monkey 1 were as intended. In this animal, there was additional damage to the dorsal posterior bank of the arcuate sulcus and to the underlying white matter on the right side.

3. Results

3.1. Visual fixation

After addition of FEF lesions to the STP lesions, the monkeys had a great deal of difficulty in visually fixating the central fixation point. Fixation latency was increased by over 400% (Fig. 2). This impairment precluded testing on the saccade and smooth pursuit tasks for the first 3 to 5 days of testing. Typically the animals made a saccade to within approx. 10 degrees of the fixation point and then made a number of small saccades until fixation was achieved. We did not see the tendency of animals with unilateral FEF lesions to deviate their eyes ipsilateral to the lesion that was seen by Latto and Cowey [27], perhaps due to our greater experimental control of eye position. The monkey with a combined FEF and inferior temporal cortex lesion (4) had an identical deficit.

It was found that if a dim light was turned on in the testing room, the fixation latency decreased markedly. The animals were then tested on a task that simply required them to foveate the central fixation point for 500 ms in darkness and dim light. This was done both to quantify the effects of dim illumination on fixation latency and to give the monkeys practice foveating the fixation point, as the monkeys sometimes stopped trying to visually fixate altogether after a number of consecutive trials of fixation in darkness. Fig. 3 shows monkey 2's

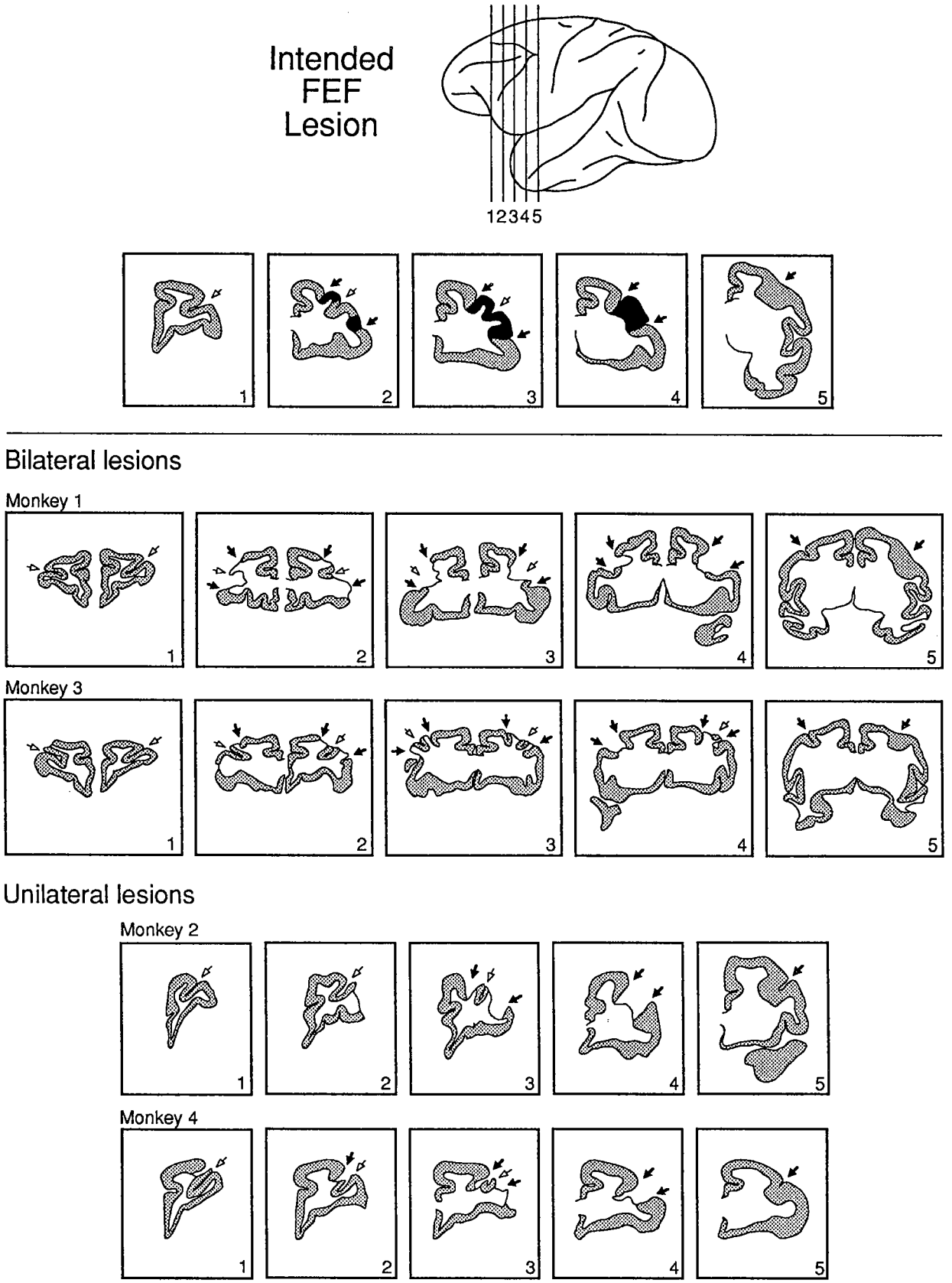


Fig. 1. The intended FEF lesion and the actual lesions in monkeys 1, 2, 3 and 4. The lateral view of the left hemisphere shows the location of the five coronal sections immediately below it. The intended lesion is the blackened region of the cortex in the top row of sections. The arcuate sulcus and principal sulcus are indicated by solid and open arrows, respectively. Note that the lesions are approximately as intended except for monkey 1's lesion which on the right side includes the posterior bank of arcuate sulcus and the underlying white matter.

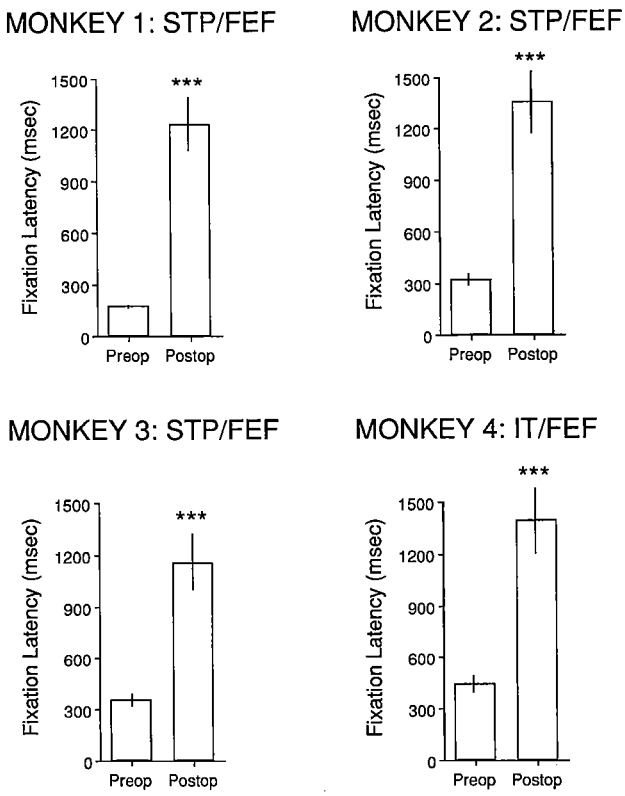


Fig. 2. Mean fixation latency before and after combined STP and FEF lesions (monkeys 1, 2 and 3) and a combined IT and FEF lesion (monkey 4). In this and subsequent figures, error bars indicate 95% confidence intervals and asterisks denote statistically significant differences (*$P<0.05$, **$P<0.01$, ***$P<.001$) for two-tailed t-tests for unpaired observations).

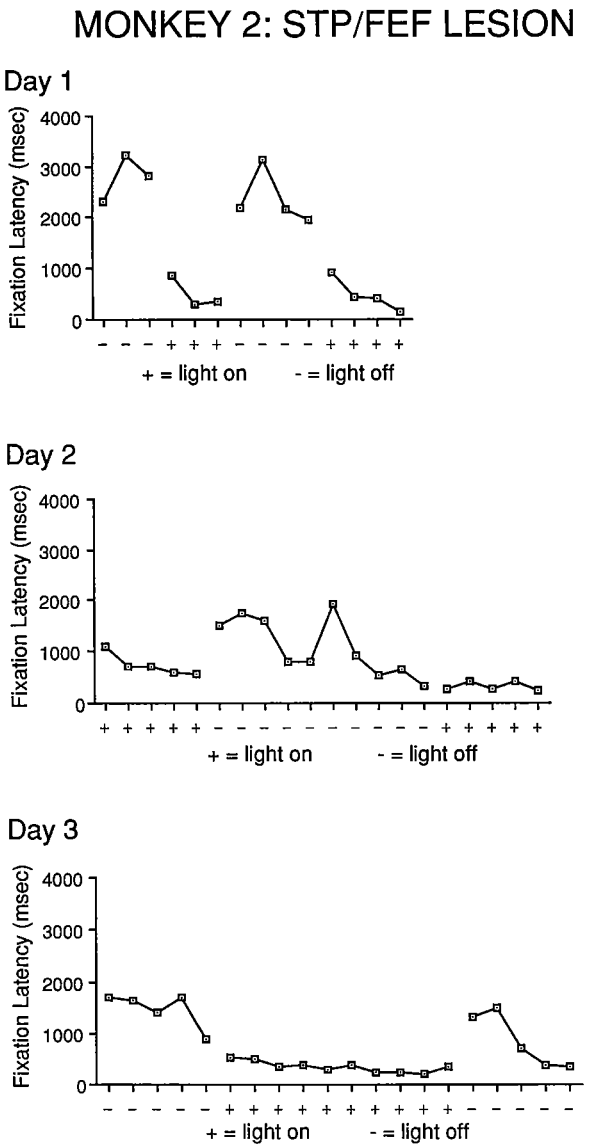


Fig. 3. Fixation latency in darkness and dim illumination for monkey 2 on the: first, second and third day of testing after a combined STP and FEF lesion. Each data point represents the mean fixation latency from a block of 10 trials.

fixation latency in darkness and in dim illumination 10 days, 11 days and 12 days after a combined bilateral STP lesion and unilateral FEF lesion (i.e., the first 3 days of postoperative testing). It is evident that the fixation latency was much greater in darkness and that the fixation latency tended to decrease throughout the testing session and across testing days. Fig. 4 shows monkey 4's fixation latency in darkness and dim illumination 10, 11 and 12 days after a combined bilateral IT lesion and unilateral FEF lesion. As after combined STP and FEF lesions, the fixation latency was much higher in darkness than in dim illumination and decreases over testing days. Fig. 5 shows the mean fixation latency in darkness and dim illumination for all animals with combined STP and FEF lesions, and for the animal with a combined IT and FEF lesion. Fixation latency was not only decreased in dim illumination but was decreased to the preoperative level. Within a week of postoperative testing the monkeys' ability to fixate improved to the point where they could be tested on the saccade task and the smooth pursuit task although their fixation remained both less accurate and of longer latency than it had been preoperatively.

The effects of addition of FEF lesions to bilateral removal of STP or IT on the monkeys' ability to fixate recovered to a large extent during the time that they were tested for the effects of the lesions on eye movements (Fig. 6). The mean fixation latency across monkeys is shown for the first 3 weeks of testing on the saccade task. Although most animals did not recover completely to preoperative performance within this time, the mean deficit was decreased by 50% within 3 weeks of testing. Linear, exponential and logarithmic functions were fitted to the data, and the logarithmic function Fixation Latency = 1259.1 − 1459.6log(postoperative week) was found to give the best fit to the data ($r^2 = 0.98$). Extrapolating from the data using this function, it would be expected that the mean fixation latency over all

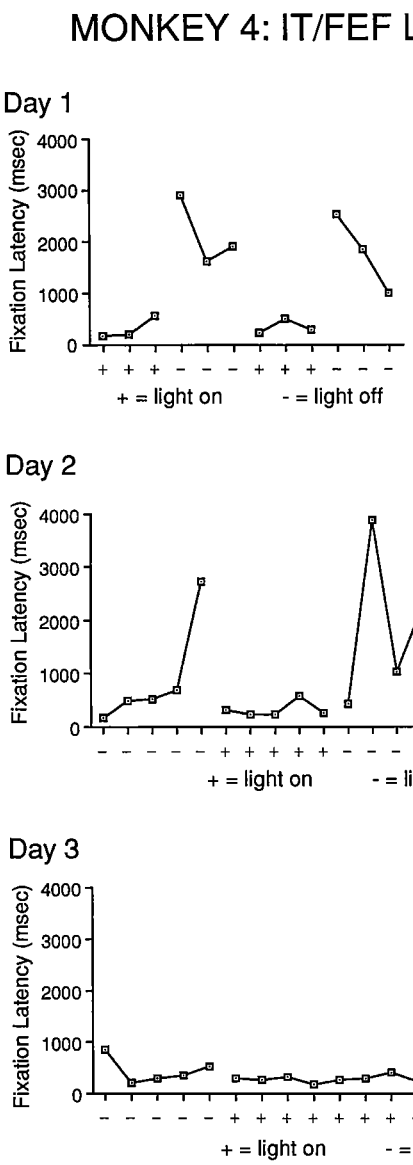


Fig. 4. Fixation latency in darkness and dim illumination for monkey 4 on the first, second and third day of testing after a combined IT and FEF lesion. Each data point represents the mean fixation latency from a block of 10 trials.

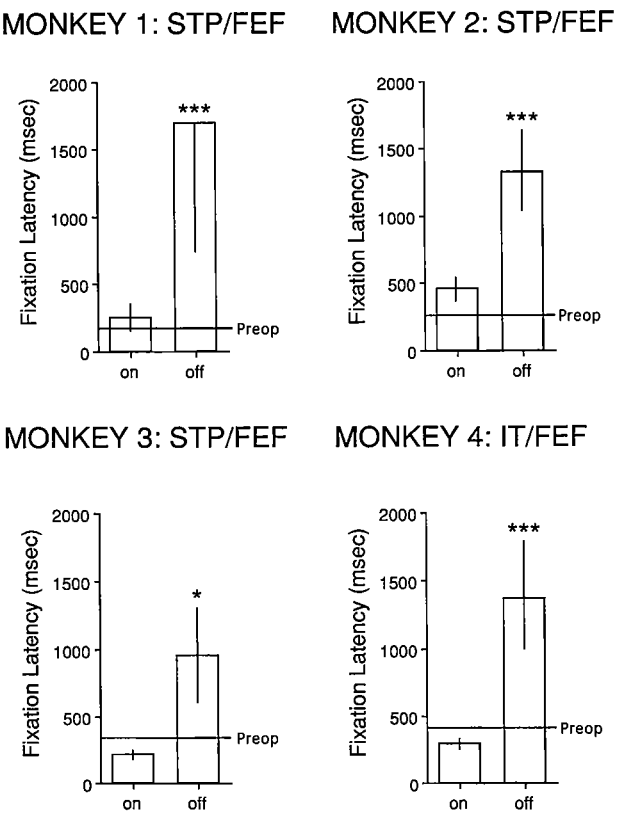


Fig. 5. Fixation latency in darkness and dim illumination after combined STP and FEF lesions (monkeys 1, 2 and 3) and a combined IT and FEF lesion (monkey 4). Preoperative performance is indicated by a horizontal line. Conventions are as in Fig. 3, with asterisks denoting a significant difference between the trials in darkness and in dim illumination.

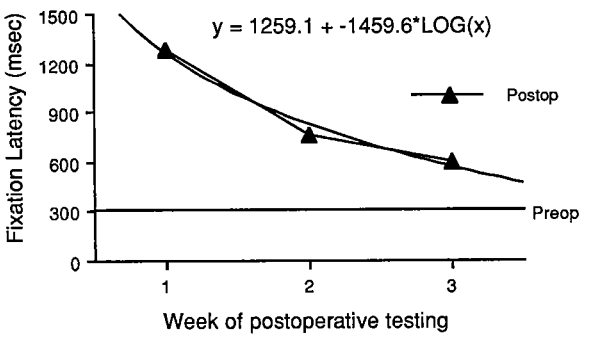


Fig. 6. Mean fixation latency for all lesions for 1, 2 and 3 weeks of postoperative testing above the mean preoperative fixation latency. The formula corresponds to the logarithmic curve fitted to the data.

animals would return to the mean preoperative level (320 ms) within 5 weeks of postoperative testing.

3.2. *Visual saccade task*

Combined STP and FEF lesions produced large effects on saccadic eye movements. Monkey 1 was profoundly impaired in making visually guided saccades, especially to peripheral targets to the left of the fixation point. Postoperatively the monkey made a series of grossly hypometric saccades to these targets. Monkey 2 had an even larger deficit in making eye movements to peripheral targets contralateral to a unilateral FEF lesion that was added to a STP lesion. This animal often failed to make a saccade within 1000 ms of the target's onset (see Fig. 7.). In fact, the monkey made as many saccades away from as toward the target.

After bilateral removal of the FEF from an animal with a bilateral STP lesion (1), we observed an increase in saccade latency to all targets along the horizontal meridian and to the target above the fixation point (Fig. 8). The deficit increased with increasing target eccentricity and was especially large to peripheral targets

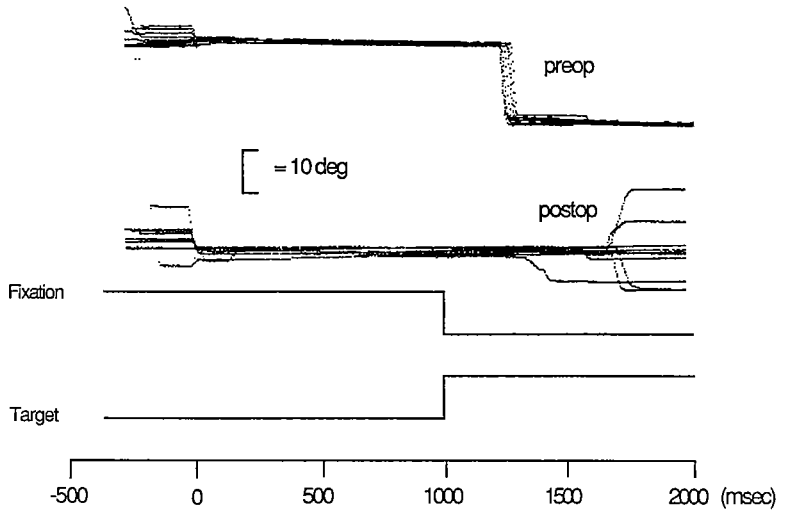


Fig. 7. Horizontal eye movement records on the saccade task before and 13 days (first day of testing on the saccade task) after addition of a unilateral FEF lesion to a bilateral STP lesion (monkey 2). The target is 22 degrees contralateral to the FEF lesion. The eye movement traces are lined up on the time when the animal achieved fixation.

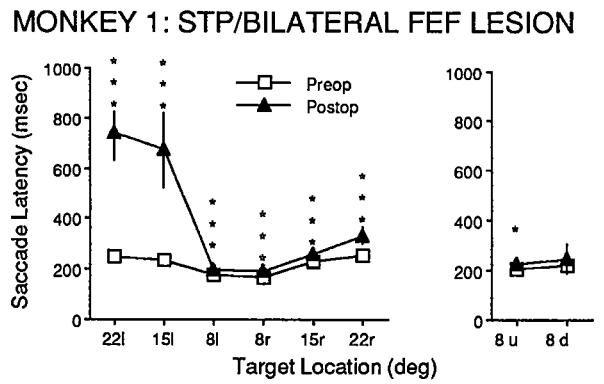
to the left of the fixation point. Consistent with the gross deficits in making saccadic eye movements to leftward targets, this animal had a larger FEF lesion in its right hemisphere. There was also a drastic impairment in making saccades to contralateral targets that increased monotonically with increasing target eccentricity after monkey 2's unilateral FEF lesion. As can be seen from the confidence intervals the variability of the saccade latencies also increased postoperatively. There was a slight decrease in saccade latency to the ipsilateral targets and no change in saccade latency to targets 8 degrees above or below the fixation point. Finally, one combined bilateral STP and FEF lesion (monkey 3) was followed by a small increase in the mean saccade latency to the target above the fixation point and a small decrease in the mean saccade latency to targets 15 degrees to the right of the fixation point. Saccade latency to other target locations was unaffected by this lesion.

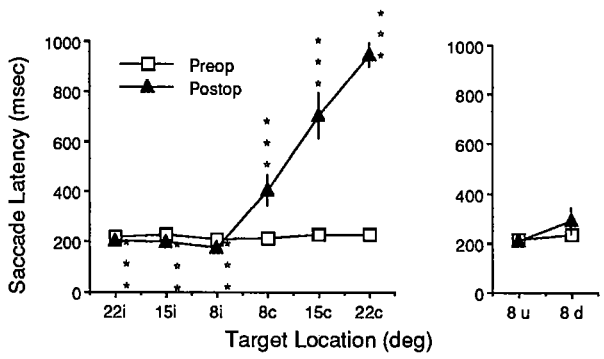
All three monkeys with combined STP and FEF lesions showed a decrease in the percent of trials correct on the saccade task. On-line observation of their behavior revealed that this deficit was the result of two separable impairments. First, there was a nonspecific decrease in percent correct to all targets due to the aforementioned deficit in visual fixation. This resulted in a decrement of 5–20% to all saccade targets. Second, there was an impairment in the accuracy of saccades to peripheral targets contralateral to the lesion (Fig. 9). This appeared to be largely due to the monkeys making hypometric saccades. Monkey 1 showed a large impairment to peripheral targets, especially to those to the targets 15 and 22 degrees to the left of the fixation point. There was an even larger impairment in saccadic accuracy to contralateral targets after a unilateral FEF lesion in monkey 2, with virtually no accurate saccades being generated to the most peripheral target contralateral to the lesion. On subsequent weeks of testing this monkey did generate saccades to the target although they were still not as accurate as they were preoperatively. Monkey 3 had a slightly smaller deficit in saccade accuracy to peripheral targets, especially to rightward targets. In summary, there were gross impairments in saccadic eye movements reflected by the large deficits in saccade latency and accuracy in two of three monkeys.

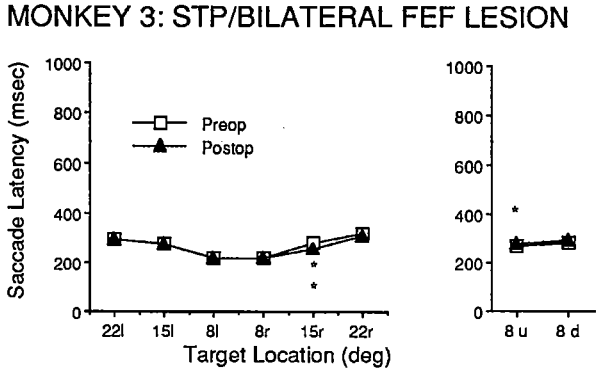
We added a unilateral FEF lesion to one animal's bilateral inferior temporal cortex lesion both as a control for IT damage in the animals with STP lesions and to ensure that our testing procedures were not more sensitive to oculomotor impairment than those of other laboratories that have studied the effects of FEF damage. There was a small increase in saccade latency to targets 8 degrees contralateral to lesion and a decrease in saccade latency to all ipsilateral targets (Fig. 8). This lesion resulted in a nonspecific decrement in percent correct due to fixation problems similar to that seen after combined STP and FEF lesions (Fig. 9). The dissociation between visual fixation and saccade deficits (see Section 4: Discussion) was particularly striking when observing the real time behavior of this monkey; who (like all of the monkeys postoperatively) often took well over a thousand ms to fixate, only to make a normal saccade of under 300 ms latency in response to the proximal saccade targets. There was also a similar but smaller decrease in saccadic accuracy, as reflected by the decrease in percent correct to the two most peripheral targets contralateral to the lesion.

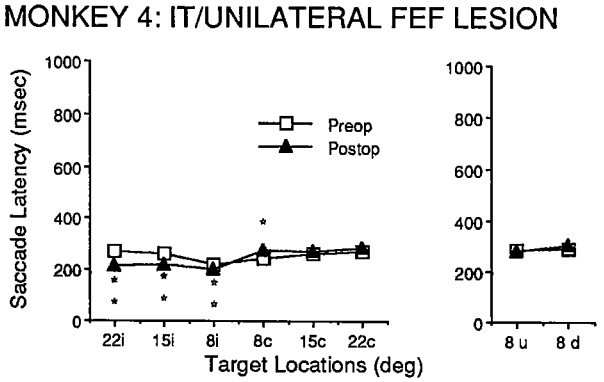
3.3. *Smooth pursuit task*

Following a combined bilateral FEF and STP lesion monkey 1 showed a large decrease in smooth pursuit









speed to all targets. Pursuit became almost entirely saccadic with very slow pursuit movements interposed between the saccades (Fig. 10). Fig. 11 shows that the smooth pursuit deficit in monkey 1 occurred to all target directions and speeds. A combined unilateral FEF and bilateral STP lesion in animal 2 had a relatively small effect on smooth pursuit. Eye speed was decreased for targets moving upward and for targets moving toward the side of the lesion for all target speeds. There was also a decrease in eye speed to targets moving 13 deg/s in a downward direction. Finally, monkey 3 had a combined bilateral FEF and STP lesion and showed a deficit in making rightward and upward smooth pursuit eye movements to targets of all speeds. There was also a decrease in eye speed to downward moving targets moving 13 deg/s and 20 deg/s. Eye speed was increased to targets moving leftward at 5 deg/s and 13 deg/s.

A combined unilateral FEF and bilateral IT lesion in monkey 4 decreased eye speed to targets moving 13 deg/s upward, away from, and toward the side of the FEF lesion. There was also a decrease in eye speed to targets moving upward and toward the lesion when the targets moved 20 deg/s (Fig. 11).

In summary, combined STP and FEF lesions produced a deficit in making smooth pursuit eye movements which varied from a nearly complete loss of pursuit to a relatively mild decrease in eye speed.

4. Discussion

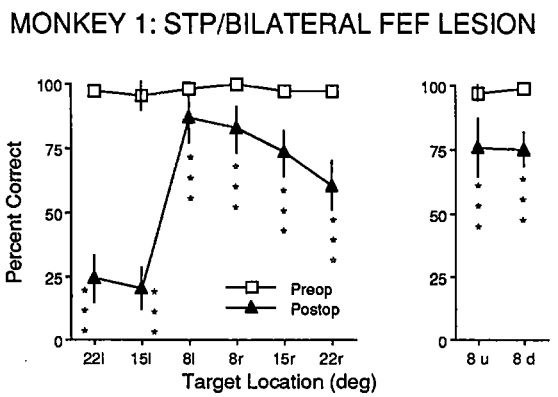
4.1. General

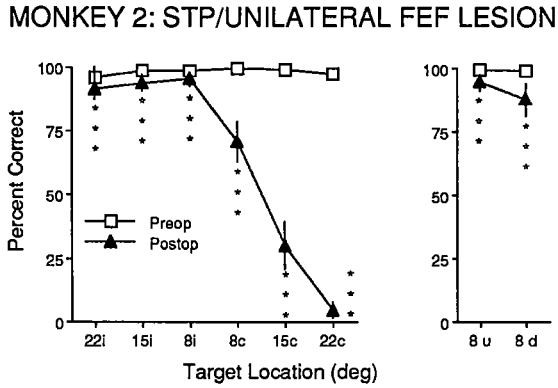
The most striking result of this study is the large impairment in visual fixation in the dark, but not in dim illumination, after either combined STP and FEF lesions or a combined IT and FEF lesion. Two out of three monkeys with removal of STP and the FEF also had a gross impairment in making saccades to visual targets and all three had an impairment in making pursuit eye movements. A combined IT and FEF lesion produced similar deficits in making smooth pursuit eye movements and a relatively small impairment in making saccades.

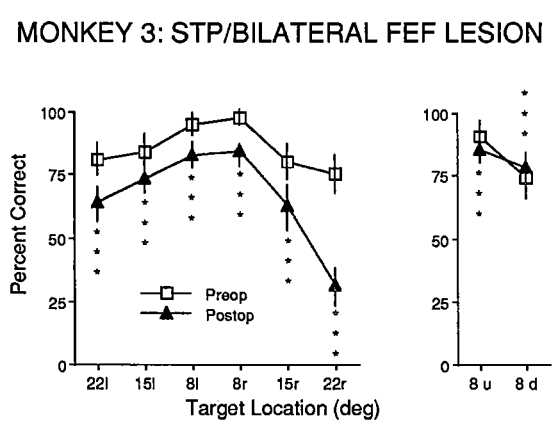
4.2. Visual fixation

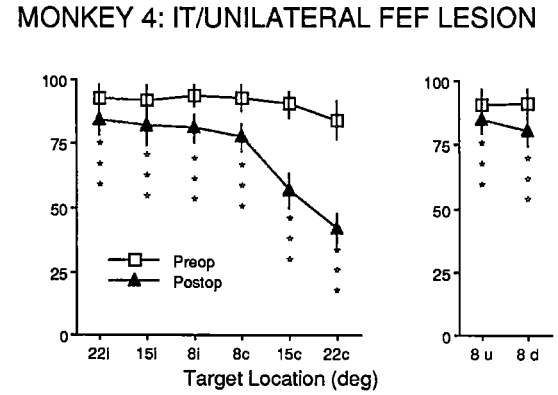
Visual fixation latency is sensitive to the monkeys' motivation. Nevertheless, there are a number of reasons why the increase in fixation latency after combined FEF

Fig. 8. Mean preoperative and postoperative saccade latencies for each combined STP and FEF lesion (monkeys 1, 2 and 3) and combined IT and FEF lesion (monkey 4). Conventions are as in Fig. 3, with asterisks above the data points for increases in saccade latency and below the data points for decreases in saccade latency (often the error bars are smaller than the symbols).









and STP and combined FEF and IT lesions cannot be attributed to a change in the monkeys' motivation or to a nonspecific effect of the surgical procedure. First, the animals were on a drinking schedule identical to one which failed to produce a fixation latency increase after STP or IT lesions alone [42]. Second, the animals made saccades toward the fixation point and typically their eye position stayed near it until fixation was achieved. This contrasts with the behavior of unmotivated animals who either make saccades that have no relation to the fixation point or make slow drifting eye movements indicative of sleep. Third, unmotivated animals show rapidly increasing fixation latencies, unlike the animals with FEF lesions which did not have such an increase in fixation latencies; in fact, their fixation latency remained stable or decreased throughout the testing period. Finally, the increase in fixation latency could be reliably eliminated by turning a dim light on in the testing room, strongly implying that something other than lack of motivation is responsible for the fixation latency increase.

There was a striking dissociation of deficits on visual fixation, which occurred after all FEF lesions, and the gross deficits on the saccade task, which occurred only after combined STP and FEF lesions (2 of 3 monkeys) and not after a combined IT and FEF lesion. Despite most animals having no or little impairment in making saccades to targets 8 degrees from the fixation point they had great difficulty in making a similar or smaller size saccade to fixate the fixation point. Consistent with this, the magnitude of impairment on the saccade task was not correlated with the magnitude of impairment on the fixation task (Bonferroni-adjusted probability for Pearson correlation coefficient, $P=0.304$). These data raise the issue of what the difference is between these superficially similar tasks. Although they both involve making a saccade to a small visual stimulus, in the saccade task the stimulus comes on at one of eight fixed locations on the retina and in the fixation task the retinotopic position of the stimulus depends on the monkey's eye position. The fixation point provides a landmark in the saccade task with the 8 target locations being a constant distance and direction from the fixation point. This is consistent with dim illumination of the testing room decreasing the fixation latency since illumination of the room yields landmarks such as the borders of the screen, the primate chair, and the drive coils for eye coil apparatus, which are a fixed distance from both the fixation point and the monkey's head.

Fig. 9. Mean preoperative and postoperative percent correct for each combined STP and FEF lesion (monkeys 1, 2 and 3) and combined IT and FEF lesion (monkey 4) for all tested locations. Conventions are as in Fig. 3, with asterisks above the data points for increases in percent correct and below the data points for decreases in percent correct (often the error bars are smaller than the symbols).

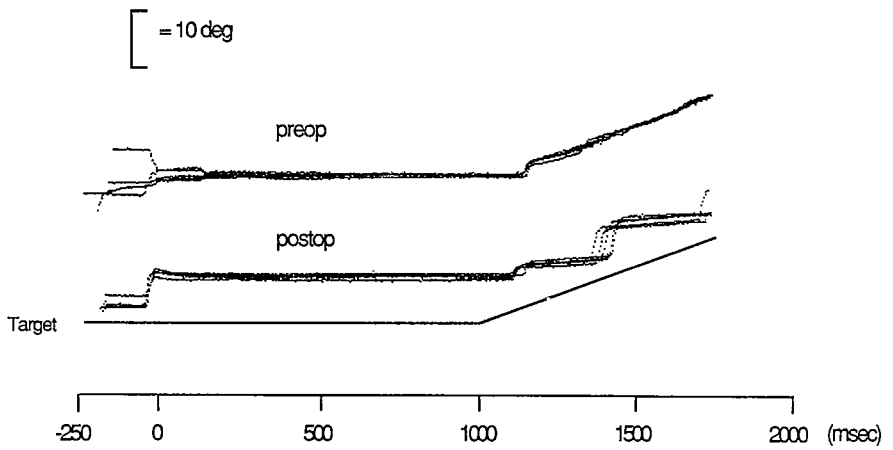


Fig. 10. Five superimposed eye movement records to a target moving 13 deg/s along the horizontal meridian 14 days after monkey 1's combined bilateral STP and FEF lesion.

Generally, the prefrontal cortex seems to be involved in tasks which present a discontiguity (e.g., temporal, spatial or modality) between the stimuli themselves and/or the appropriate response to them [16]. For instance, people with putative FEF lesions have difficulty in performing a task that requires them to make a saccade *away* from a flashed stimulus [18]. Frontal lesions in humans have been shown to impair a task in which a person has to orient a line to vertical when his body is tilted; when his body is vertical, no deficit is found [53]. Although these authors interpreted their results as indicating that prefrontal cortex is largely involved in "the integration of postural with visual functions", it seems that these deficits may also reflect a more general cognitive impairment in responding to stimuli with impoverished context (such as lack of landmarks) or unusual response requirements. The degradation of normal spatial landmarks in the fixation task resembles a spatial stimulus-response discontiguity in the sense that the stimulus present when the animal responds lacks a normal background of spatial landmarks.

4.3. Saccade task

Two combined STP and FEF lesions (monkeys 1 and 2) elevated the mean saccade latency to 280% of the preoperative saccade latency for targets 22 degrees from the fixation point. The saccade deficits seen after these combined STP and FEF lesions are much larger than the deficits seen after FEF lesions alone studied in other labs. Deng et al., [9] found no deficits in saccade amplitude, accuracy, or latency contralateral to unilateral FEF lesions in the 2 monkeys that they tested. Keating [24] found slightly hypometric saccades in 1 of 2 monkeys with FEF lesions and Lynch [33] saw no change in saccade latency after FEF lesions in three monkeys. On the whole, impairments in making saccadic eye movements following FEF lesions are restricted to possibly a slight hypometria with little or no effect on saccade latency. STP lesions [42] increased saccade latency to peripheral targets by 25% and did not affect accuracy. Therefore, neither the effects of FEF lesions nor STP lesions alone can possibly explain the large size of saccade deficits seen in monkeys 1 and 2; instead, the combined loss of both areas is necessary for this magnitude of impairment.

There are two possible reasons why the combined bilateral FEF and STP lesion in monkey 3 did not cause a gross impairment in making saccadic eye movements. First, in this animal the location of the FEF may have differed with respect to sulcal landmarks from other monkeys. This possibility is supported by reports that there is some inter-animal variability in the location of the FEF as defined by low current microstimulation [7]. Second, a particularly interesting possibility is that the deficit in this monkey may have been less severe because its FEF lesion was bilaterally symmetric, unlike those of monkeys 1 and 2. Lynch [33], who used a methodology similar to ours, found that a monkey with a unilateral FEF lesion in combination with a bilateral posterior parietal lesion produced a considerably larger deficit than three bilateral FEF lesions in combination with bilateral posterior parietal lesions. The influence of lesion asymmetry finds support in the fact that unilateral striate cortex and superior colliculus lesions can produce greater neglect than bilateral lesions, even to the point where removing more tissue contralateral to the first lesion can *decrease* the impairment [51].

In his 1992 study, Lynch specifically studied the effects of combined FEF and posterior parietal cortex lesions on saccades to targets 10 and 20 degrees from the fixation point. The combined lesions resulted in saccade latencies ranging from 158% of the preoperative saccades latencies to a gross neglect like deficit similar to that seen in monkeys 1 and 2. The similarity of the effects of

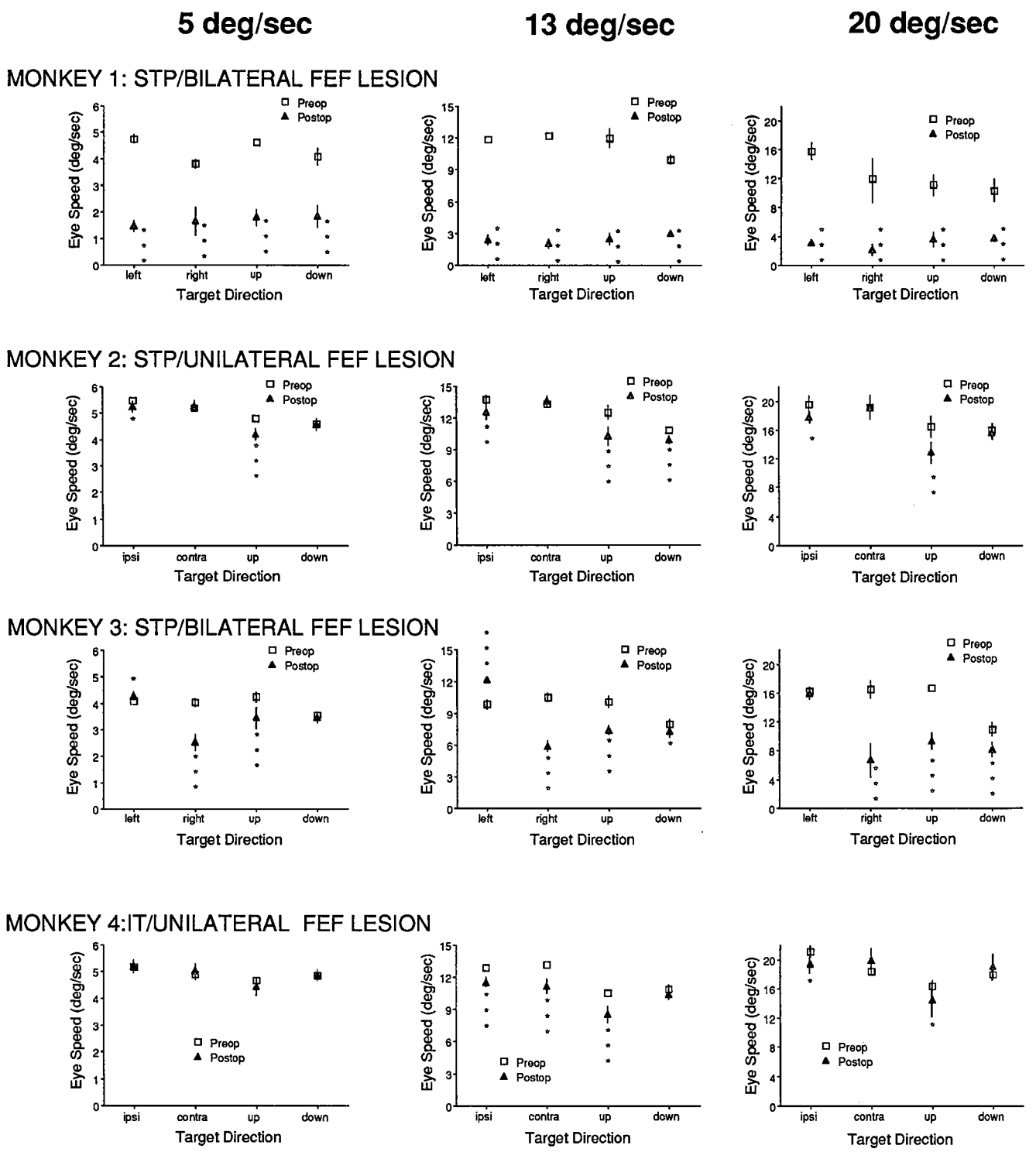


Fig. 11. Mean preoperative and postoperative (first week of testing) eye speed to targets moving 5, 13 and 20 deg/s for each combined STP and FEF lesion (monkeys 1, 2 and 3) and combined IT and FEF lesion (monkey 4). Conventions are as in Fig. 3, with asterisks above the data points for increases in smooth pursuit speed and below the data points for decreases in smooth pursuit speed (sometimes the error bars are smaller than the symbols).

combined STP and FEF lesions and combined posterior parietal cortex and FEF lesions on visually guided saccades provides further evidence that STP and posterior parietal cortex play a similar role in visuospatial and visuomotor behavior. That the size of the deficit after combined STP and FEF lesions is not merely an effect of the amount of tissue removed is supported by the fact that a combined IT and FEF lesion had smaller

effects on saccadic eye movements. This lesion also provides evidence that the large size of the eye movement deficits after combined STP and FEF lesions are not due to our techniques being more sensitive than those in use in other labs, since a combined IT and FEF lesion should be at least as effective as a FEF lesion alone in causing eye movement deficits. Finally, unlike the deficits after the STP lesions, which always recovered to preoperative performance, the deficits after the combined STP and FEF lesions did not recover completely in monkey 1.

4.4. Pursuit task

The effects of combined STP and FEF lesions on pursuit were variable and ranged from a profound deficit in monkey 1 to relatively moderate effects in the other two animals. This variability is consistent with the literature on the effects of FEF lesions on smooth pursuit eye movements. Lynch [32] reported that bilateral FEF lesions produce a deficit similar to the largest deficit that we saw after a combined STP and FEF lesion. Schiller and Logothetis [45], however, did not see an effect on smooth pursuit eye movements after FEF lesions. In 1991, Keating and colleagues found a large deficit in making smooth pursuit eye movements after FEF lesions. Finally, MacAvoy et al. [36] reported that FEF lesions sometimes produced a dramatic decrease in smooth pursuit velocity and sometimes had no effect. To explain this they suggested that the crucial area for the smooth pursuit deficit lies in the fundus of the arcuate sulcus including cortex on the posterior bank of the sulcus not previously considered part of the FEF, consistent with the single unit response properties and effects of electrical stimulation [17] in the arcuate sulcus. This suggestion is consistent with our results, because the animal that showed a large pursuit deficit (1) had the largest FEF lesion, which included invasion of the fundus of the arcuate sulcus and underlying white matter. Similar to the effects of combined STP and FEF lesions, combined posterior parietal cortex and FEF lesions produce a decrease in eye velocity to both horizontal and vertical targets similar to the effects of FEF lesions alone [34]. In summary, the effects of combined FEF and STP lesions on eye movements are consistent with the FEF playing a larger role in the control of pursuit eye movements than STP and with a specific sub-localization within the FEF for the control of pursuit.

4.5. Dual cortical control pathways for both saccadic and smooth pursuit eye movements

If 'higher order' cortical areas are involved in the production of eye movements, why are the oculomotor deficits produced by lesions of single areas typically small? In agreement with Schiller and colleagues [47], we suggest that there are two dissociable sets of pathways from the cortex to the brainstem that are capable of controlling saccadic eye movements (Fig. 12a). One flows from the frontal eye fields and perhaps other prefrontal areas (such as the supplementary eye fields) to the brainstem para-oculomotor regions [19,28–30,52], both directly and via the superior colliculus. The second one flows from the posterior parietal cortex (most likely LIP; see Ref. [2]), STP, and possibly other posterior visual areas to the superior colliculus and subsequently to the brainstem oculomotor regions. In support of this notion, combined lesions or cooling of the FEF and the superior colliculus (which would interrupt both pathways) produce a deficit in the production of saccadic eye movements that approaches paralysis of the eyes [25,47]. The finding that superior colliculus lesions abolish eye movements evoked by electrical stimulation of striate cortex [43] or of parietal cortex but not of the FEF [26,44] is consistent with the visual areas' control of saccades flowing through the colliculus while the FEF can control eye movements more directly.

One way to explore the notion of separate and specialized cortical output pathways for the control of saccadic eye movements would be to determine if they subserve different functions. A large body of evidence exists which indicates that the prefrontal cortex in general is involved in the completion of a variety tasks with a discontiguity between the stimuli used to respond and the response that is made [9,14,18], see [16]. For example, working memory tasks (such as delayed response and delayed alternation) involve a temporal discontiguity between the stimulus presentation and the monkey's response and the antisaccade task involves a spatial discontiguity between where the stimulus is presented and where the saccade is made. By contrast, the posterior pathway seems to be involved in the production of more stimulus-driven behavior. There is evidence that this general organizational scheme also applies to saccadic eye movements. Schiller and colleagues [46] reported a study of the effects of superior colliculus and frontal eye fields lesions on an express saccade task. Because it is difficult to reliably obtain reflexive orienting saccades, the express saccade task is a useful way of experimentally investigating highly stimulus driven eye movements [11]. Superior colliculus lesions eliminated express saccades to targets contralateral to the lesions, while FEF lesions produced only a small and transient effect on saccade latency. The loss of express saccades after superior colliculus lesions suggests that some of the cortical areas that project only to the superior colliculus and not directly to the brainstem oculomotor areas, such as STP and the posterior parietal cortex, control stimulus driven saccades. The lack of FEF involvement in this task is even more striking given that FEF lesions abolish anticipatory saccades to predictably moving targets [6,24]. The difference between these two tasks is that in the express saccade task the animal makes a saccade to a visual

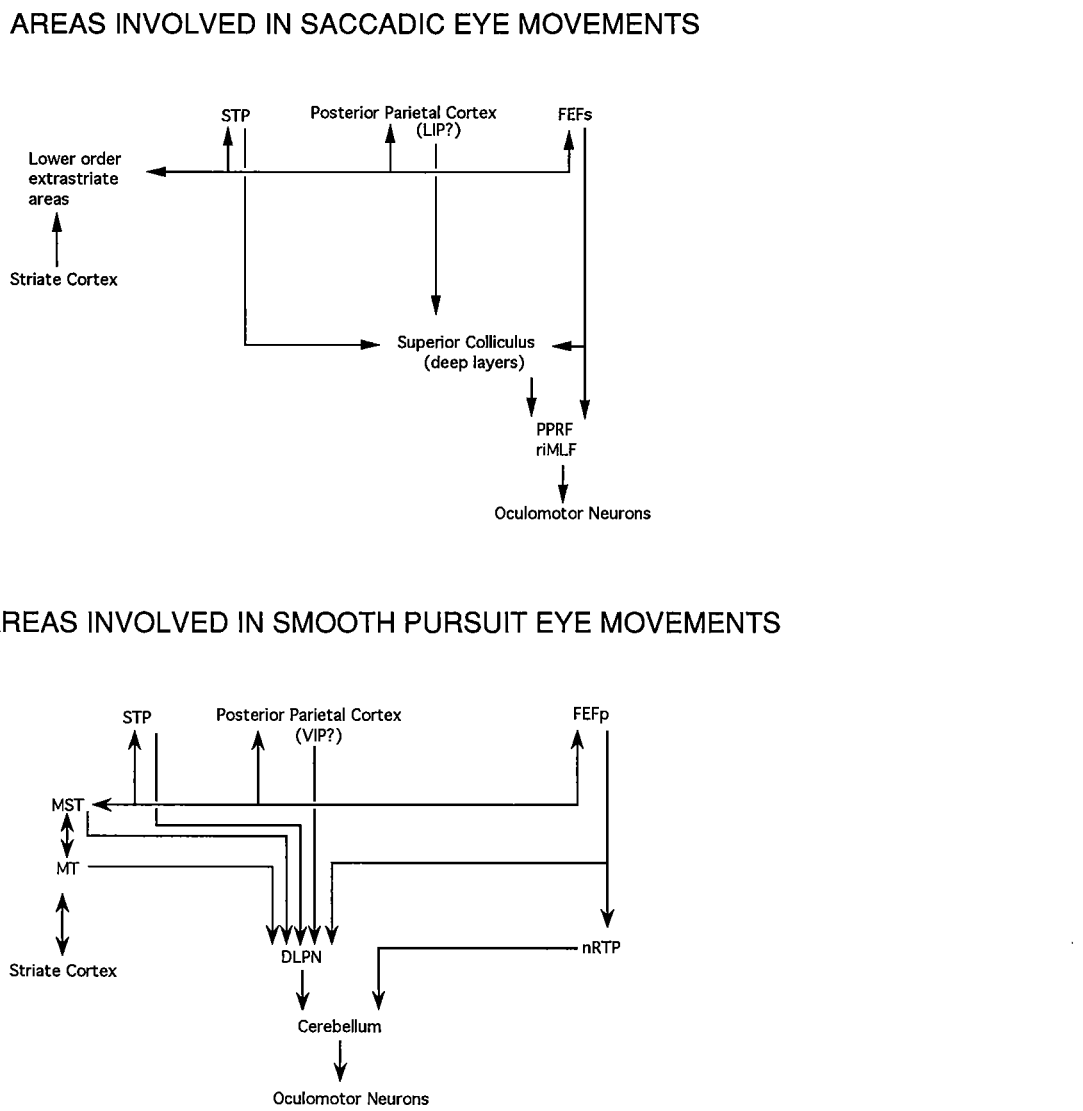


Fig. 12. Schematic diagram of the areas and pathways known to be involved in saccadic eye movements (A) and smooth pursuit eye movements (B). Abbreviations: STP, superior temporal polysensory area; VIP, ventral intraparietal visual area; LIP, lateral intraparietal visual area; FEFsac, saccade related region of the FEF; FEFpur, pursuit related region of the FEF; PPRF, paramedian pontine reticular formation; riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; LGN, lateral geniculate nucleus; MT, medial temporal visual area; MST medial superior temporal sulcus visual area; STP, superior temporal polysensory area; DLPN, dorsolateral pontine nucleus; nRTP, nucleus reticularis tegmenti pontis.

stimulus, and in the predictive saccade task the animal makes a saccade to where a target will appear; one task is highly stimulus driven and the other has a temporal discontiguity between the stimulus and the monkey's response. A direct test of the hypothesis that the output of posterior cortical areas to the superior colliculus is specifically responsible for stimulus driven eye movements would be to examine the effects of a combined lesion of STP and the posterior parietal cortex on express saccades.

The pursuit eye movement system may be organized in a way similar to that suggested for saccadic eye movements, with posterior parietal cortex (most likely VIP; see [8,39], STP, MST and MT and their projection to the dorsolateral pontine nucleus (DLPN) playing a role analogous to the role of the cortical projection to the superior colliculus in saccadic eye movements (Fig. 12b). Consistent with this hypothesis, FEF lesions impair predictive pursuit [24,37]. The pontine outputs of areas MT and MST (see [55]) also suggest that more stimulus-driven smooth eye movements may not necessarily involve the FEF. The projection to the DLPN resembles the projection to the superior colliculus in that all of extrastriate visual areas involved in pursuit project to this nucleus. Stimulation of the DLPN only affects ongoing smooth pursuit [40]. By contrast, stimulation of the nucleus reticularis tegmenti pontis (nRTP), the pontine output of the FEF, can produce pursuit from stationary eye positions [57].

In summary, the results of this report support the

hypothesis that the FEF plays a role in the production of eye movements that is complementary to and distinct from that of STP. The profound impairment in fixation in darkness seen only after FEF lesions is consistent with this region playing a role in eye movements in impoverished visual environments or under unusual response requirements. The FEF also seems to be more critical for making smooth pursuit eye movements than is STP. Finally, the effects of FEF and STP lesions on visually guided saccades suggest that loss of both the FEF and STP has a synergistic effect on saccades to visual targets although the deficit appears to be primarily one of saccade latency after loss of STP and saccade accuracy after loss of the FEF. Further dissociation of the roles of the multiple cortical areas involved in oculomotor control will require the use of tasks specifically designed to separate out their roles.

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