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Cortical inhibitory circuits in eye-movement generation

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Abstract

The role inhibitory circuits play in target selection with saccadic eye movements was examined in area V1, the frontal eye fields (FEF) and the lateral intraparietal sulcus (LIP) of the Rhesus Macaque monkey by making local infusions of the GABA agonist muscimol and antagonist bicuculline. In V1, both agents greatly interfered with target selection and visual discrimination of stimuli placed into the receptive field of the affected neurons. In the FEF, bicuculline facilitated target selection without affecting visual discrimination and generated many spontaneous saccades. Muscimol in the FEF interfered with saccadic eye-movement generation. In the LIP, bicuculline was ineffective and muscimol had only a small effect. These findings suggest that in the FEF GABAergic inhibitory circuits play a central role in eye-movement generation whereas in V1 these circuits are essential for visual analysis. Inhibitory circuits in the LIP do not appear to play a central role in target selection and in visual discrimination.

Introduction

We explore the visual scene by making repeated saccadic eye movements at the rate of about three saccades per second, resulting in more than 150 000 saccades a day (Schiller, 1998). Each shift in gaze requires a decision to be made as to where to look next and the computation of the spatial location of the desired target which enables us to generate an accurate saccadic eye movement to it. We examined the role inhibitory circuits play in this process in three cortical structures: striate cortex (area V1), the lateral intraparietal sulcus (LIP) and the frontal eye fields (FEF). Recent work has established that electrical stimulation, when applied at levels subthreshold to those at which saccadic eye movements can be elicited in these areas can significantly influence target selection (Schiller & Tehovnik, 2001). Such stimulation in the lower layers of V1, in the FEF and in some regions of the LIP increases the probability with which a target presented in the receptive and/or motor field of the stimulated neurons is chosen. On the other hand, stimulation in the upper and middle layers of V1 and in selected regions of the LIP interferes with target selection by decreasing the probability with which targets in the receptive or motor fields of the stimulated neurons are chosen. These findings, taken together with other lines of investigation, suggest that these areas play an important role in target selection (Schiller & Chou, 1998; Schall & Thompson, 1999; Tehovnik *et al*., 2002; Tehovnik & Slocum, 2003). At the subcortical level a seminal study by Hikosaka & Wurtz (1985) has shown that the application of the GABA (gamma-amino butyric acid) antagonist bicuculline in the superior colliculus greatly facilitates saccade production, whereas application of the GABA agonist muscimol inhibits saccade generation. To examine the role of inhibitory circuits in target selection with saccadic eye movements in the cortex, we infused these agents in small quantities into V1, the LIP and the FEF through a microelectrode assembly that enabled us to record neuronal activity, to administer electrical stimulation and to infuse the pharmacological agents.

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Materials and methods

Experimental subjects

Three monkeys were used in these experiments. For all surgery, animals were first given a pre-anesthetic dose of Ketamine (10 mg/kg i.m.) or Telazol (5 mg/kg i.m.). They were also given atropine prior to and during surgery (0.05 mg/kg i.m. every 45–60 min). Anesthesia was induced and maintained with Pentobarbitol (8 mg/kg i.v. for induction; 4 mg/kg i.v., as needed, for maintenance). In two monkeys, wells were implanted over area V1. One of these animals also had a well implanted over the LIP. The third monkey had a well placed over the FEF. The eye movements were recorded using the scleral search coil technique (Robinson, 1963; Schiller *et al*., 1987). During the experimental sessions, awake, behaving monkeys were placed into a monkey chair. They faced a colour monitor at a distance of 57 cm. All animal experimentation follows the guidelines laid down by the NIH in the US regarding the care and use of animals for experimental procedures and has been approved by the MIT Committee on Animal Care.

Single-cell recordings, microstimulation and delivery of pharmacological agents

Neuronal recordings, electrical stimulation and pharmacological injections were made with a newly designed assembly that consisted of a stainless steel 31-gauge hypodermic needle to which a glass-coated platinum–iridium microelectrode was affixed with medical epoxy. A 5-μL Hamilton syringe driven by a micrometer was used to inject the pharmacological agents via a PE-20 nylon tube.

Behavioural methods

Fixation task for receptive field mapping

Background illumination on the colour monitor the animals faced was 23 cd/m^2; circular targets of 0.25–0.75° and luminances of

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90–110 cd/m^2 were used. Monkeys were trained to maintain fixation on a red fixation spot for 2–4 s after which time a red target appeared in one of four locations. Monkeys were rewarded with a drop of apple juice for making a saccadic eye movement to this target. While maintaining fixation on the fixation spot a white bar was swept across that portion of the visual field where the receptive field was located. On each trial a single sweep was made. The orientation and size of the bar, its velocity and the amplitude of the sweep were systematically varied. Using this procedure the receptive field can be mapped with high accuracy. Subsequent to mapping, a small, stationary spot was flashed in the receptive field while fixation was maintained (depicted in Fig. 1). Accurate placement of this spot in the receptive field resulted in a vigorous burst of spikes in virtually all cells studied in V1.

Systematic variation in the location of the target relative to the receptive field in V1 established that 0.5 μL of 0.5 μg/μL muscimol administered in a region representing the lower visual field 3° from the fovea affected an area in the visual field having a diameter of 0.75° which corresponds to a volume of tissue ranging between 1.5 and 2.5 mm in diameter.

Single-target task

Following fixation of the central fixation spot a single target appeared in one of four locations one of which was the centre of the receptive or motor field of the neurons from which recordings were made and which were subsequently infused. The single targets appeared interspersed randomly with paired targets as described below.

Paired-target task

Following fixation, two targets appeared that were presented with various temporal asynchronies (base condition shown in Fig. 1, panel 4). The two targets were identical. The probability with which one of the other targets was chosen was plotted as a function of the temporal asynchrony between the targets (Schiller & Chou, 1998, 2000; Schiller & Tehovnik, 2001).

Data for the single- and paired-target conditions were collected concurrently with the order of presentations randomized within blocks. A block most commonly consisted of 13 or 15 conditions. Of these eight were single targets presented at four locations and five or seven were paired targets appearing with varied temporal asynchronies. Most commonly a set consisted of 20 blocks (260 or 300 trials per set). Repeated sets were run in each session to assess the time course of the effects of the infusions. Monkeys performed 2000–4000 trials per day.

Discrimination task

The discrimination task uses the oddity paradigm in which several stimuli are presented, one of which is different from the others. The

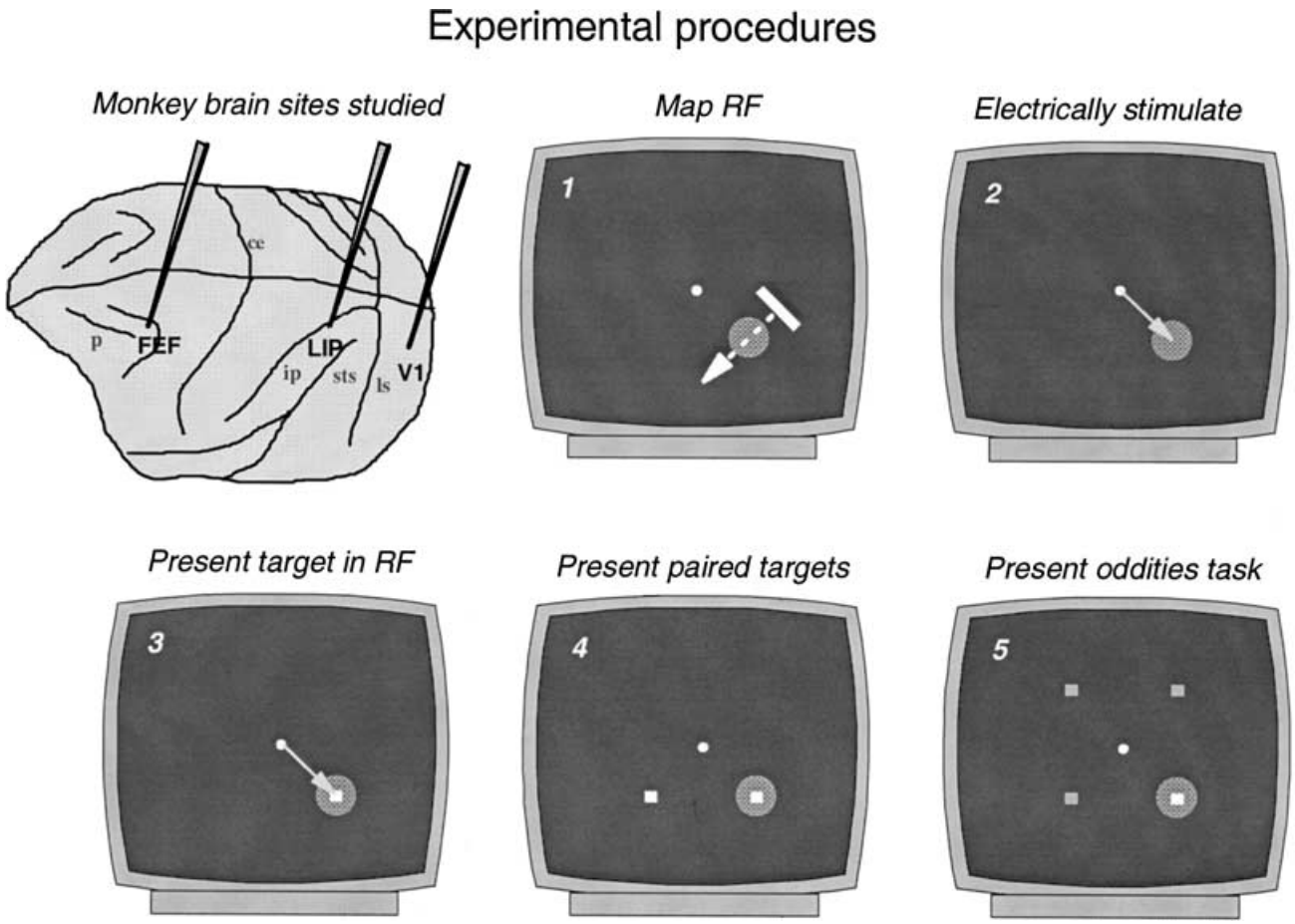

FIG. 1. Experimental methods: top left figure shows monkey brain and the three areas studied, striate cortex (V1), the lateral intraparietal sulcus (LIP) and the frontal eye fields (FEF). p, principal sulcus; ce, central sulcus; ip, intraparietal sulcus; sts, superior temporal sulcus; ls, lunate sulcus. The steps taken in experimental sessions were: (1) the receptive field (RF) of the neuron recorded from was mapped; (2) the motor field (MF) was established by eliciting saccadic eye movements with electrical stimulation; (3) one target was then placed into the RF/MF and elicited saccades with the same vector; (4) two targets were presented with varied temporal asynchronies with one of them placed into the RF/MF; (5) four targets were presented, one of which was different from the others in luminance. The luminance of the three identical distracters was systematically varied and the luminance of the target was kept constant. Data were collected before, during and after the infusion of pharmacological agents.

basic form of this paradigm is the following: after the animal fixates a central fixation spot several stimuli appear (4–8), one of which is different from the others. The animal is rewarded only when he makes a saccade to the odd stimulus which is the target. Psychometric functions can be generated by systematically varying the difference between the target and the other stimuli (the distracters). The luminance levels used for the target in the discrimination task were the same as in the paired-target task and were kept constant; the luminance of the three identical distracters was varied between 25 and 70 cd/m^2. Conditions of presentation were randomized during data collection.

Conduct of the experiment

The conduct of the experiment is described in Fig. 1. Five steps were involved. (1) First, the animals performed on the fixation task. This enabled us to map out the receptive field of the neurons from which we were recording. (2) Second, electrical stimulation was delivered after the monkey fixated on the fixation spot. This elicited a saccadic eye movement which established the motor field of the neurons at the tip of the electrode. The receptive and motor fields, when accurately mapped, were always in correspondence. (3) Third, single targets were presented with one of the locations in the receptive and/or motor field of the neurons. Proper placement meant that the saccadic vector elicited by this visual stimulus was identical to the one elicited by the electrical stimulation for the second step above. (4) Fourth, monkeys performed on the paired-target task with one of the targets placed into the receptive and/or motor field of the neurons. The targets were presented with varied temporal asynchronies. The presentation of paired targets was intermingled with the presentation of single targets which appeared at the same locations. (5) Fifth, monkeys performed on the discrimination task. One of the stimulus locations was in the receptive and/or motor field of the neurons.

After the collection of normative data the pharmacological agent of choice was infused after which data were collected repeatedly over an extended time and then again the following day. Neuronal activity was closely monitored following each infusion.

As can be seen in Figs 2 and 4, there was some variation in the time at which animals were tested after injections of bicuculline and muscimol. These two agents act quite differently. Bicuculline administered in the dosages indicated becomes effective in a relative short time (5–10 min) and also recovers quite rapidly (30–60 min). By contrast, muscimol takes much longer to become effective (30–120 min) and can remain effective for many hours (Hikosaka & Wurtz, 1985; Schiller *et al*., 1987). Animals were always tested subsequent to the change in single-cell activity induced by the infusion. Testing was first done on the paired-target task and was followed by the oddities task.

Results

Prior to the injections of pharmacological agents into areas V1, LIP and FEF, these areas were examined in the animals with single-cell recordings and microstimulation. In 295 penetrations (V1, 47; LIP, 156; and FEF, 92) we established their layout and the effectiveness of stimulation on target choice. Subthreshold stimulation in conjunction with the paired-target task in V1 produced facilitation in the lower layers and interference in the upper layers. In the LIP some sites yielded facilitation, some sites interference and, at some sites where neurons discharged vigorously while fixation was maintained, increased fixation times. In the FEF, subthreshold stimulation consistently produced facilitation. The results of this work have been published (Schiller & Tehovnik, 2001; Tehovnik *et al*., 2002). In this study, penetrations were made at sites where these previously reported effects had been observed.

The effects of muscimol infusion

The effects of infusions were first monitored by the single-cell recordings. Muscimol greatly decreased neuronal activity. The effects of the muscimol injections lasted several hours.

Figure 2 shows representative data from two monkeys on the paired-target task before and at various times after muscimol infusion. In one of these monkeys, infusions were made either into V1 or LIP; in the other the infusion was made into the FEF. The top panel demonstrates that in V1 muscimol (0.8 μL of 0.5 μg/μL concentration solution)

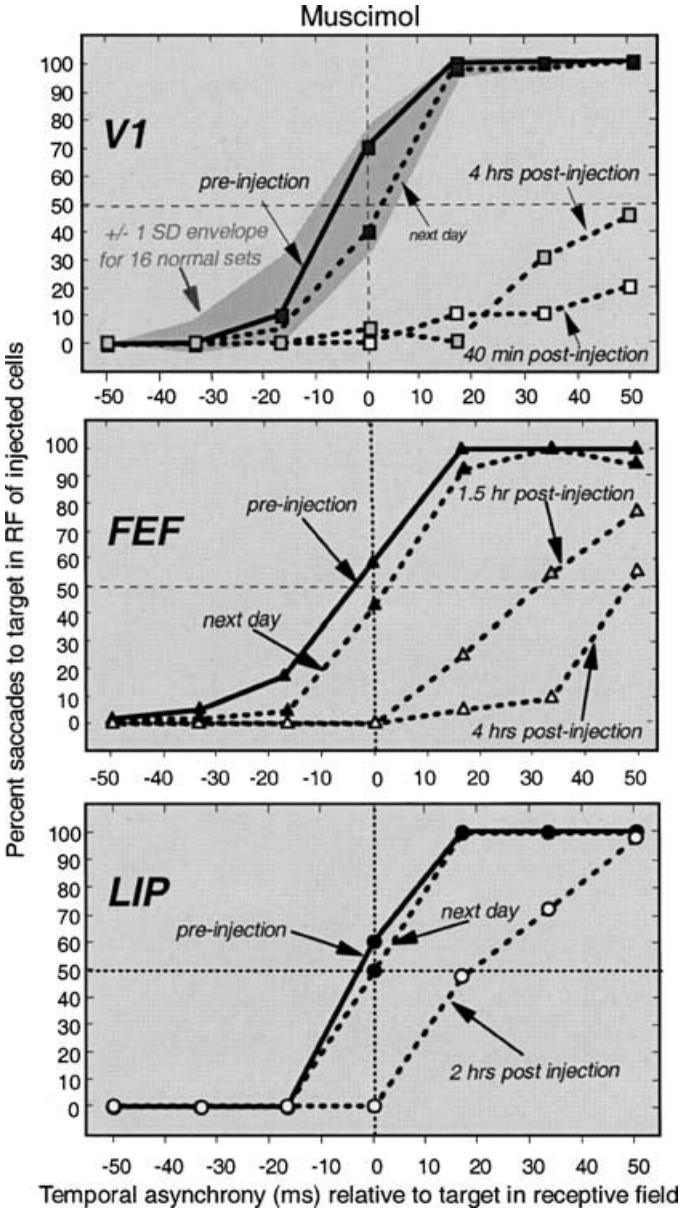

FIG. 2. The effects of infusing muscimol into areas V1, LIP and FEF on the paired-target task. Plotted is the percentage of time the target presented in the receptive and motor fields of the neurons was chosen as a function of the temporal asynchrony between the two targets. Muscimol injections in V1 were 0.8 μL, in the FEF 0.5 μL and in the LIP 1.5 μL of 0.5 μg/μL solution. Each data point shown in the graphs is based on a minimum of 20 and a maximum of 100 trials. The grey regions shown in the top panel denote the ±1 SD envelope collected for 16 normal sets of data (20 blocks each). Each block had 15 conditions consisting of eight single targets presented at four target locations and seven paired targets presented with various temporal asynchronies. Each data point is based on 20–100 trials, in this as well as all the other figures.

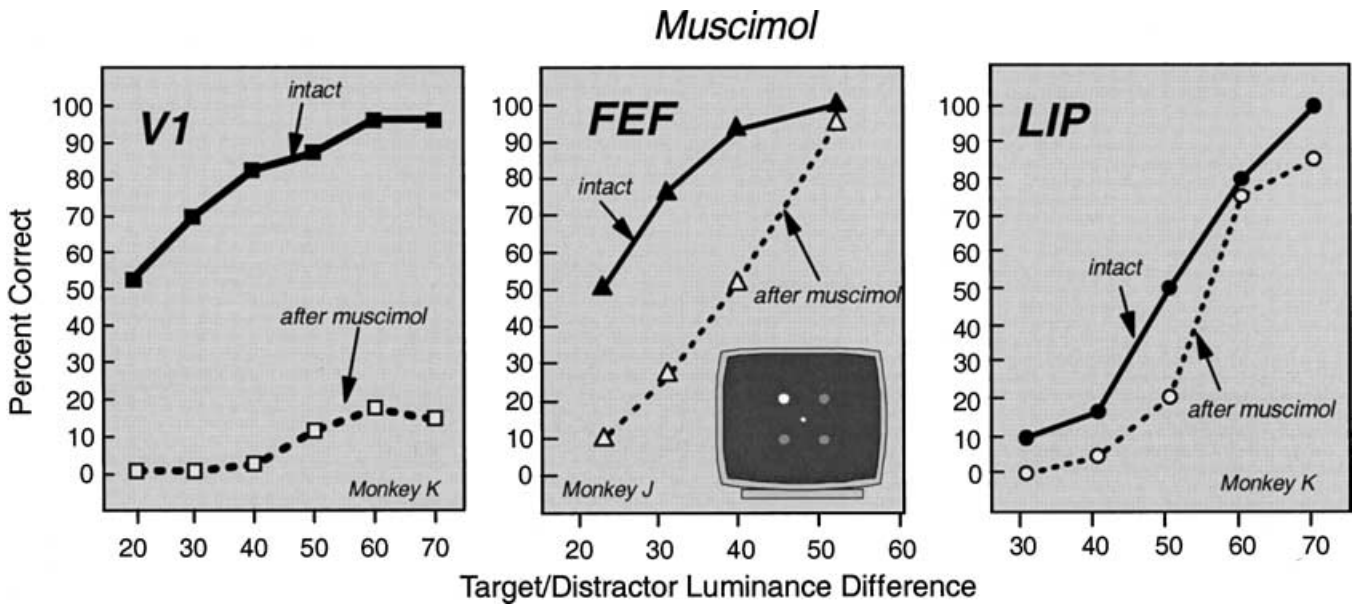

FIG. 3. The effects of muscimol infusion on the brightness discrimination task. Inset in centre panel shows the brightness discrimination task. The percentage contrast difference between the target (bright stimulus) and the distracters was varied in randomized order from trial to trial keeping the luminance of the background and the target constant and varying the luminance of the distracters. In area V1 the muscimol infusion produced a significant loss in the ability to discriminate brightness differences. In the FEF and LIP the infusion produced only a mild deficit. Each data point is based on 20–100 trials.

significantly and prominently decreased the probability with which the target in the receptive field of the infused neurons was chosen. Infusion of 0.5 μL of 0.5 μg/μL into the FEF (centre panel) also produced a major deficit. In the LIP (bottom panel) infusion of 1.5 μL of 0.5 μg/μL produced only a small although significant effect. This volume was three times that shown for the FEF and nearly twice that for V1 in Fig. 2.

The LIP data, shown in Fig. 2, bottom panel, were analysed using a test for the difference of two proportions. The curve obtained 2 h postinjection is significantly different from the (pooled) pre- and postinjection results for temporal asynchronies of 0 ms ($z = 5.5$, $P < 0.001$), +16.7 ms ($z = 5.3$, $P < 0.001$), and +33.3 ms ($z = 3.5$, $P < 0.01$). Smaller injections of muscimol, comparable to those administered in V1 and the FEF, were ineffective in the LIP.

The shaded area in the top panel of Fig. 2 shows ±1 SD in performance which was obtained when the intact animal was tested repeatedly over a period of several days on the paired-target task. Sixteen such sets were collected with each set having 15 conditions and with each condition repeated in randomized order 20 times per set, yielding thereby 4800 trials. These data are provided to show two things: (i) that performance over time is quite consistent and (ii) that performance after lowering the electrode into the region of neurons into whose receptive fields the visual stimuli were presented did not significantly alter performance prior to the infusion of the pharmacological agents. This is indicated by the fact that the preinjection curve (solid line), obtained just prior to the first infusion, fell within the ±1 SD of the data collected on preceding or subsequent days. Demonstration of this is desirable as just the lowering of a recording or injection electrode could conceivably affect the neurons, thereby altering performance when stimuli were presented in their receptive fields. The SEMs for the 16 sets of normative data were 0.15, 1.50, 4.18, 5.63, 0.85, 0.63 and 0 starting with the point at −34 ms and ending at +34 ms as indicated in the top panel.

Concurrently collected data on the brightness discrimination task appear in Fig. 3. These data show that in area V1 muscimol caused a major deficit in performance, indicating that the ability to make brightness discriminations was devastated. In the FEF, muscimol produced a mild deficit. Only a very small, statistically insignificant, effect was found in the LIP. Smaller injections into the LIP did not have any effect on visual discrimination. In some experiments similar effects were also obtained when colour and shape discrimination were examined. Each data point is based on 20–100 trials.

The effects of bicuculline infusion

Bicuculline infusions increased neuronal activity, generally yielding high-frequency bursts of action potentials; neuronal activity typically recovered within 30–60 min after bicuculline infusion. Figure 4 shows representative data from two monkeys on the paired-target task before and at various times after bicuculline infusion. The animals were the same as those whose data are shown in Figs 2 and 3.

The results demonstrate that in V1 (top panel) bicuculline significantly decreased the probability with which the target in the receptive field of the infused neurons was chosen. As in Fig. 2, the shaded area in the top panel represents ±1 SD in performance under intact conditions which were collected over several days using 16 sets in which 13 conditions were used and each set consisted of 20 presentations of each condition in randomized order ($n = 4160$). The solid line shows data obtained just prior to injection after the electrode had been lowered into the brain. The SEMs for these data from left to right were 2.86, 5.54, 7.38, 4.50 and 0.92.

In contrast to the results obtained in V1, in the FEF (centre panel) bicuculline produced facilitation; not only did the frequency with which the target appearing in the motor field of the infused neurons increase, but the animal also had a disposition to make numerous spontaneous eye movements with the saccadic vectors represented by the infused neurons. This is demonstrated in the inset of the middle panel of Fig. 4. These eye-movement data were obtained while the monkey made saccades to single targets which appeared at one of three locations. The animal was able to perform this task after the infusion of bicuculline, but right after making a saccadic eye movement to the target in many cases a subsequent saccade or staircase of saccades was made spontaneously. Considerable recovery occurred within

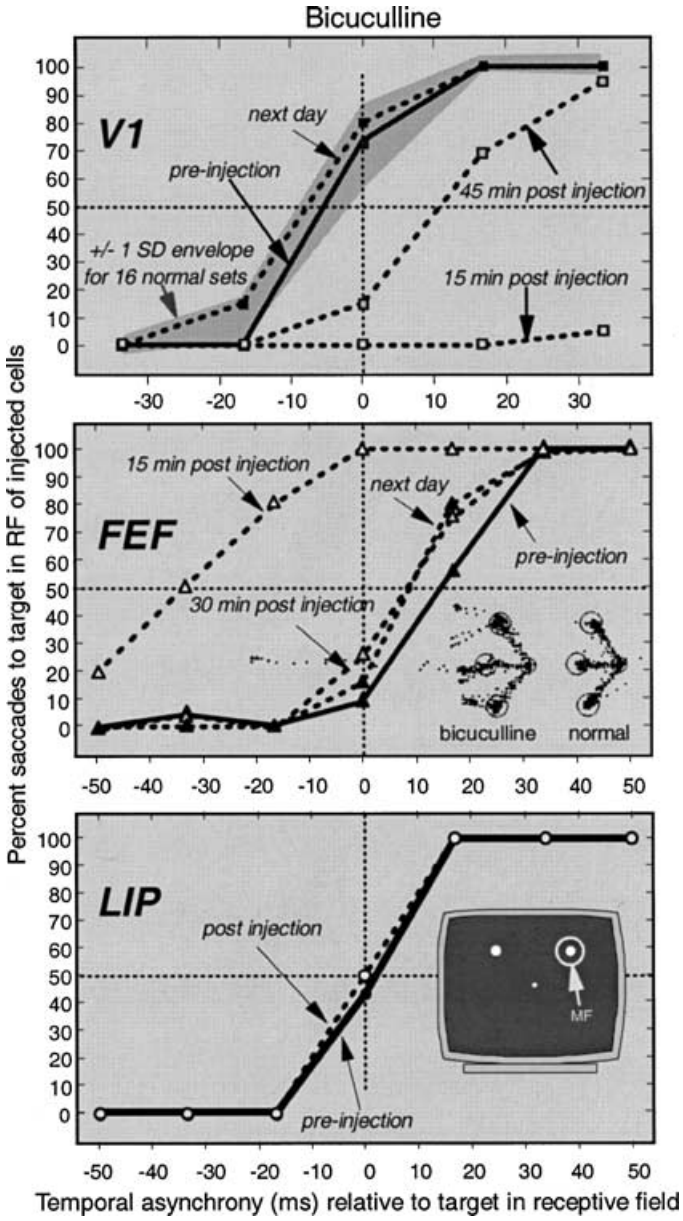

FIG. 4. The effects of infusing bicuculline into areas V1, LIP and FEF on the paired-target task. Plotted is the percentage of time the target presented in the receptive and motor fields of the neurons was chosen as a function of the temporal asynchrony between the two targets. Bicuculline injections in V1 were 0.5 μL, in the FEF 0.3 μL and in the LIP 0.4 μL of 1 μg/μL solution. In V1 the bicuculline infusion produced a major deficit. In the FEF the infusion produced facilitation and irrepressible saccades. In the LIP the infusion was ineffective.

30–45 min after the infusion which correlated with the recovery of neuronal activity. Bicuculline did not have a significant effect on target choice when infused into the LIP (bottom panel).

Concurrently collected data on brightness discrimination after bicuculline infusion appear in Fig. 5. The left panel shows that after bicuculline injection into V1 the animal had a major deficit on the brightness discrimination task. We had also found similar deficits when animals were tested on colour and shape discrimination. All four bicuculline injections we made into V1 produced similar deficits. By contrast, bicuculline infusions into the FEF and LIP did not affect visual discrimination. Each data point is based on 20–100 trials.

We made a total of 33 infusions in the three monkeys used in this study, as shown in Table 1. All muscimol solutions had 0.5 μg/μL concentration; the volume of injections ranged between 0.5 and 1.5 μL. The effect of these injections on unit activity and behavioural performance were all long-lasting (4–6 h), as has previously been reported (Hikosaka & Wurtz, 1985; Schiller *et al*., 1987). Bicuculline injections used concentrations between 0.2 and 1.0 μg/μL and volumes of 0.5–2.5 μL. Bicuculline-induced disinhibition was short-lasting (30–60min); to obtain data over a more extended time period bicuculline was often infused several times during each session, typically at 15–30-min intervals with the time determined by the monitoring of single-cell activity. In addition to the muscimol and bicuculline injections we made one 2% lidocaine injection into each of these structures and one saline injection into V1. The results we obtained were highly consistent. All muscimol and bicuculline injections into V1 caused major interference in target selection as well as in visual discrimination, similar to the effects shown in Figs 2–5. Similar interference was obtained with the lidocaine injection into V1. By contrast, the saline injection of 0.5 μL into V1 had no effect at all on either task. In the FEF all bicuculline injections facilitated target choice in the target selection task and produced irrepressible saccades but had no effect on visual discrimination. Muscimol infusions into the FEF decreased target choice consistently but had only a very mild effect on visual discrimination; the strongest effect we obtained on the visual discrimination task is shown for the data presented in Fig. 3. In the LIP, bicuculline and lidocaine infusions were entirely ineffective; muscimol at a high volume (1.5 μL of 0.5 μg/μL), as shown in Figs 2 and 3, did have a mild effect; however, none of the other muscimol injections, whose volumes were 0.6 μL, affected either target choice or visual discrimination. The infusions we made never produced any deficits in the intact hemifield.

Discussion

The findings lead to the following conclusions.

(i) In area V1 infusion of either the GABA agonist muscimol or the GABA antagonist bicuculline produces a major interference in target selection. The effect appears to be due to interference in visual processing. This finding is in agreement with several studies that had shown that bicuculline administration compromises the orientation and direction specificity in V1 neurons (Sillito, 1975). A behavioural study by Newsome *et al*. (1985) had shown previously that administration of muscimol in V1 produces major visual deficits. Our study is the first to show that bicuculline infusion into V1 also produces visual deficits.

(ii) In the FEF, infusion of bicuculline dramatically increases the probability with which targets placed in the motor field of the infused neurons are chosen and also increases the spontaneous generation of such saccades. Muscimol injection has the opposite effect: it greatly reduces the probability with which saccades with vectors represented by the infused neurons are produced. Visual discrimination is unaffected by bicuculline infusion into the FEF and yields only a small deficit with muscimol. These findings suggest that inhibitory circuits play a central role in eye-movement generation in the FEF. These results are similar to what had been reported for the superior colliculus by Hikosaka & Wurtz (1985). Thus infusion of the GABA antagonist bicuculline into both the superior colliculus and the FEF results in the generation of irrepressible saccades with vectors represented by the affected neurons. Previous work has shown that lesions and inactivation of the superior colliculus eliminate short-latency saccadic eye movements and decrease saccadic accuracy and velocity as well as frequency of saccade generation (Schiller *et al*., 1979; Wurtz &

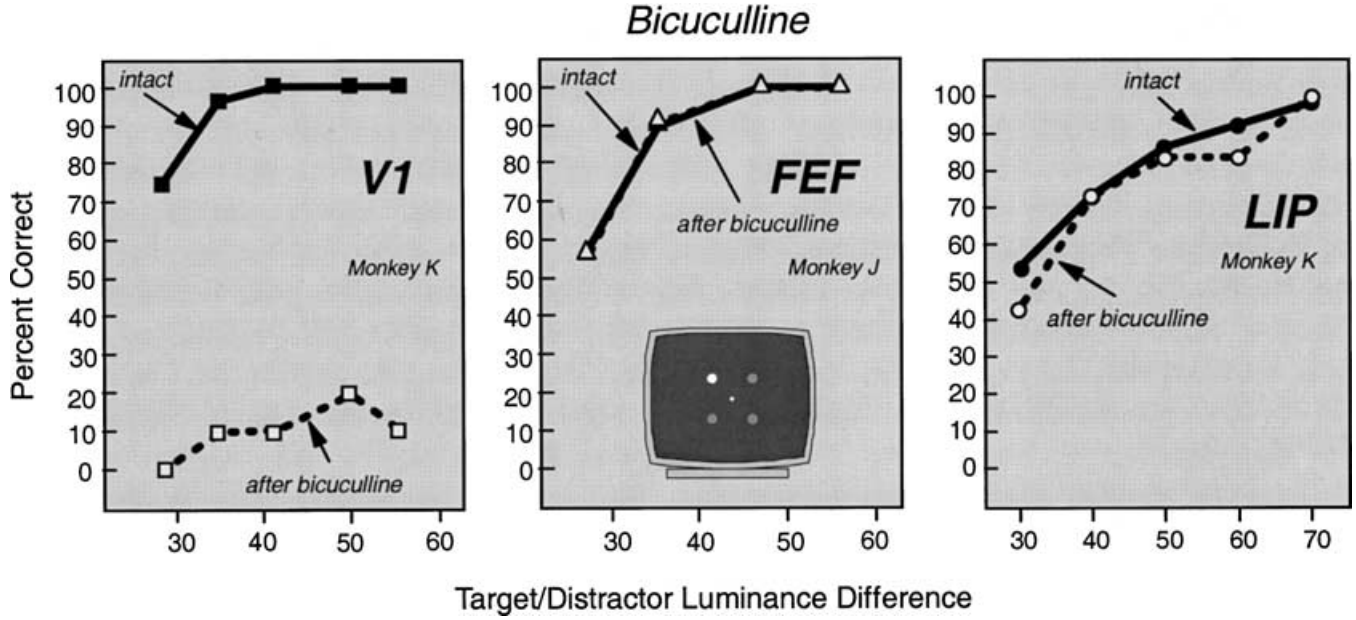

FIG. 5. The effects of bicuculline infusion on the brightness discrimination task. In V1 the infusion caused a major deficit in visual discrimination whereas in the FEF and LIP the infusion had no effect on this task. Each data point is based on 20–100 trials.

TABLE 1. Numbers of infusions

Area	Muscimol	Bicuculline	Lidocaine	Saline
Striate cortex (V1)	8	4	1	1
Frontal eye field (FEF)	5	4	1	0
Lateral intraparietal sulcus (LIP)	4	4	1	0

Albano, 1980; Hikosaka & Wurtz, 1986; Schiller & Chou, 1998). Ablation or inactivation of the FEF interferes with target selection but does not have significant long-term effects on saccadic latencies, accuracies and velocities (Sommer & Tehovnik, 1997; Schiller & Chou, 1998; Dias & Segraves, 1999).

(iii) As several studies have shown, the LIP plays a significant role in eye-movement generation (Andersen, 1987; Thier & Andersen, 1996; Schiller & Tehovnik, 2001). Injection of muscimol in previous studies had limited effects on saccade generation to normally appearing targets but did have a strong effect on memory-guided saccades and attentional processes (Li *et al*., 1999; Wardak *et al*., 2002). The muscimol injections used in these studies were much larger than in the present one. In our study, when muscimol and bicuculline were infused into the LIP at doses comparable to those infused into V1 and the FEF and which produced major deficits in visual processing and target selection, we obtained no deficits. A small but significant deficit was observed when muscimol was injected in larger doses into the LIP (Fig. 2). By contrast, as noted in the introduction, electrical stimulation in the LIP was effective in influencing target choice at current levels comparable to those administered in V1, V2, the FEF and the medial eye fields (MEF). Taken together, these findings suggest that GABAergic inhibitory circuits play a less central role in the LIP in visual target selection with saccadic eye movements than in V1 and the FEF.

(iv) Numerous clinical studies have used paired targets in assessing various brain injuries (Bisiach & Vallar, 1988). Patients with unilateral parietal infarcts are often capable of perceiving single targets in both the intact and affected visual hemifields. However, when two targets are presented simultaneously, they report perceiving only the one that had been placed in the field of the intact hemisphere. Hence this has been referred to as the extinction effect. Work on monkeys has shown that right after unilateral FEF lesions it is necessary to present the target in the affected hemifield >100 ms before the target in the intact hemifield in order to obtain equal probability choices for the two targets (Schiller & Chou, 1998, 2000). This suggests that one effect of unilateral brain damage is a slowing down of processing. A similar situation seems to arise with muscimol injection into the FEF (Fig. 2).

The seemingly simple task of making repeated saccadic eye movements in exploration of the visual scene necessitates many computations and involves many brain structures. The structures involved include the brainstem oculomotor centres, the superior colliculus, areas V1, V2, regions of the inferotemporal cortex, the parietal cortex and, in the frontal lobe, the frontal and medial eye fields (Sparks, 1986; Schiller, 1998; Tehovnik *et al*., 2000; Scudder *et al*., 2002). Each eye movement generated requires a decision to be made not only where to look but also where not to look, an analysis of the objects in the visual scene, a decision about when to initiate the saccade, and the generation of signals for producing accurate saccadic vectors (Schiller & Tehovnik, 2001). Our results indicate that the inhibitory circuits in posterior cortex contribute centrally to visual analysis whereas release from inhibition is a pivotal process for the generation of the desired saccadic eye movements in the frontal eye fields as well as in the superior colliculus, as had been shown by Hikosaka & Wurtz (1985).

Acknowledgements

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Abbreviations

FEF, frontal eye fields; GABA, gamma-amino butyric acid; LIP, lateral intraparietal sulcus; MEF, medial eye fields; V1, striate cortex.

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