Deficits in Smooth-Pursuit Eye Movements After Muscimol Inactivation Within the Primate’s Frontal Eye Field

DEXIU SHI, HARRIET R. FRIEDMAN, AND CHARLES J. BRUCE
Section of Neurobiology, Yale University School of Medicine, New Haven, Connecticut 06520-8001

Shi, Dexiu, Harriet R. Friedman, and Charles J. Bruce. Deficits in smooth-pursuit eye movements after muscimol inactivation within the primate’s frontal eye field. J. Neurophysiol. 80: 458–464, 1998. To evaluate smooth-pursuit (SP) function in the primate frontal eye field (FEF), microinjections of muscimol, a γ-aminobutyric acid (GABA) agonist, were used to reversibly deactivate physiologically characterized sites in FEF. SP was severely impaired by deactivation at sites in the FEF’s smooth eye movement region (FEFsem) located in the fundus and posterior bank of the macaque monkey’s arcuate sulcus. These SP deficits were apparent immediately after the muscimol injection and persisted for several hours but recovered by the next day. SP was most drastically and consistently impaired for directions similar to the injected site’s elicited smooth eye movement direction or to the optimal SP direction for its neuronal responses. Targets moving in these directions, usually ipsilateral to the injected hemisphere, were tracked primarily with saccades after the muscimol injection, the peak SP velocity being only 10–30% of preinjection velocity. SP in other directions, including contralateral, was less strongly affected. Initial SP acceleration in response to target motion onset was also significantly diminished, generally by approximately the same proportion as peak SP velocity. In contrast, saccades were largely unaffected by muscimol injections in FEFsem; nor was there an immediate effect on SP when control sites in the saccadic region of FEF (FEFsac) were deactivated, although a SP deficit often appeared 30–60 min after FEFsac injections, possibly reflecting diffusion of muscimol into neighboring FEFsac. These reversible SP deficits produced by muscimol inactivation within FEFsem are similar to permanent deficits caused by large aspiration lesions of FEF and indicate that inclusion of FEFsem is the critical factor determining whether FEF lesions impair SP. The severity of the reversible deficits found here indicates how extremely critical FEFsem is for normal high-gain SP.

INTRODUCTION

In addition to its saccade-related functions (for review see Bruce 1990), the frontal eye field (FEF) of the monkey also has a smooth-pursuit (SP) region, buried in the depths of the arcuate sulcus, where neurons selectively respond during SP and electrical stimulation elicits smooth eye movements (Gottlieb et al. 1993, 1994; MacAvoy et al. 1991; see also Bruce et al. 1985). To further substantiate the role of the FEF in SP, we examined the monkey’s ability to track moving targets with SP eye movements after cortical deactivation at physiologically characterized sites within this smooth eye movement region of FEF (FEFsem) using muscimol, a γ-aminobutyric acid (GABA) agonist. The data presented here show that muscimol deactivation in FEFsem profoundly impairs SP eye movements. These reversible deficits in visually guided pursuit are similar in many aspects to the chronic SP deficits caused by large aspiration lesions targeting the entire FEF (Keating 1991, 1993; Keating et al. 1996; Lynch 1987; MacAvoy et al. 1991). The severity of pursuit deficits obtained from these discrete inactivations by muscimol injection indicates that, even though FEFsem is smaller than its saccadic counterpart (FEFsac), the integrity of FEFsem is critical for achieving high-gain SP that matches visual target velocity. Parts of these data were published earlier in abstract form (Shi et al. 1997).

METHODS

All surgical and behavioral protocols were approved by the Institutional Animal Care and Use Committee and complied with U.S. Public Health Service policy on the humane care and use of laboratory animals. Our general methods have been described in detail previously (e.g., Gottlieb et al. 1993, 1994). Briefly, two adult female rhesus monkeys (Macaca mulatta) were prepared for chronic single-neuron recording by using aseptic surgical procedures. During experimental sessions they sat in a primate chair with their head held stationary. Eye position was obtained from a search coil implanted in one eye. Microelectrodes, either glass-coated Elgiloy wire or epoxy-coated tungsten wire, were advanced through intact dura. To enhance the accuracy and reproducibility of electrode penetrations and subsequent injections, a plastic grid with 1-mm spacing between adjacent holes (Crist Instrument) (see Crist et al. 1988) was secured inside the recording well. The electrodes and injection needles traveled inside 23-gauge guide tubes secured within this grid.

We located sites in the FEFsem both by studying the responses of isolated neurons during SP eye movements and also by examining eye movements evoked by electrical stimulation through the tip of the recording electrodes. Parameters of microstimulation and methods of testing pursuit neurons were described in detail by Gottlieb et al. (1993, 1994). Sites were found where SP-like eye movements were electrically elicited and/or where neurons specifically responded during SP and did not respond in conjunction with saccades. Control sites in the FEFsac were selected on the basis of electrically eliciting saccades and recording neurons that responded principally in conjunction with saccades and not pursuit.

Once a suitable site was located, the exact electrode depth was noted and the electrode was removed from the guide tube and replaced with a 27-gauge beveled needle connected to a 10-μl Hamilton syringe filled with muscimol solution (5.0 μg/μl muscimol in saline). The needle was lowered into the brain through a guide tube to the desired depth by using the top of the guide tube as a reference point. The volume injected was 1.0–1.4 μl at different sites and was delivered slowly (~5 min) in steps of ~0.2 μl/min.
Immediately after the injection the monkeys began a battery of SP (including sinusoidal and step-ramp target motion) and saccade tasks. Control data came from the same tests conducted earlier that day, before or during the microelectrode penetrations. After 3–5 h of postinjection testing the monkey was returned to its home cage. Tests were then repeated the following day, ~20 h after the injection.

Our principal SP statistic was computed by finding for each trial the 100-ms interval without saccades that had the largest smooth eye movement excursion. Each trial’s peak SP velocity was defined as this excursion divided by 0.1 s. The mean of this peak SP velocity across all appropriate trials is reported with the SE of the mean (σM) appended (e.g., 100 ± 1°/s). To compare pairs of such mean peak velocity statistics (e.g., before and after the injection) two-sample Student’s t significance tests (two-tail) were used.

We conducted complete experiments at one FEFsem site and five FEF sac sites in *monkey JM* and at two FEFsem sites and one FEF sac site in *monkey SS*. *Monkey JM*’s sites were in the anterior bank and fundus of the arcuate sulcus, although particular sites studied here were not marked. One of *monkey SS*’s FEFsem sites was later injected with Fast Blue and was found to lie in the fundus of the arcuate sulcus, similar to the FEFsem location reported by Gottlieb et al. (1993, 1994). The other FEFsem site was estimated to also lie in the fundus, 2-mm away. The saccadic control site was estimated by its coordinates to be in the anterior bank of the arcuate, that is in FEF sac as previously described (Bruce et al. 1985; Stanton et al. 1989).

RESULTS

Injections of muscimol at sites in FEFsem produced immediate and dramatic SP deficits. SP was impaired most drastically for directions ipsilateral to the injection sites that approximately corresponded to the electrically elicited smooth movement’s direction or to the optimal direction of the neural SP responses; however, SP in all directions was usually significantly affected. Overall, the most apparent deficit was a substantial decrease in asymptotic SP gain, but acceleration at the initiation of SP was substantially diminished as well. These SP deficits occurred immediately after the injections, worsened over the initial hour, and remained for at least several hours but recovered completely by the next day. In contrast, saccadic performance and stationary fixation were largely unaffected and, consequently, the monkeys accurately tracked moving targets by using saccades.

Effects on SP velocity

Figure 1 summarizes a right hemisphere injection site in *monkey JM* where SP-like eye movements directed rightward were elicited at low current (threshold <40 µA). As shown in Fig. 1A, the elicited movement profile was entirely smooth and the movement direction was almost perfectly horizontal, being directed ipsilateral to the electrode site as elicited smooth movements usually are (Gottlieb et al. 1993). After testing microstimulation at this site, control data were obtained and 1.2 µl of muscimol was injected at this site. Figure 1B shows that 40°/s target motion to the right was tracked with an SP gain of ~1 before the injection, but that in the very first trial after the injection the monkey achieved only minimal smooth eye velocity and consequently tracked the target primarily with saccadic eye movements. Figure 1C shows velocity profiles for the full set of 40°/s rightward trials, both pre- and postinjection. Mean peak SP was 35.4 ± 1.6°/s preinjection, but only 9.0 ± 1.1°/s in the five trials immediately after the injection. A similar result (not shown) was obtained with 25°/s targets; peak rightward SP averaged 25.4 ± 1.9°/s before the injection, but only 6.8 ± 1.6°/s after. Thus rightward SP, although not abolished, was reduced to only 25% of its normal value by this muscimol injection.

Figure 2 summarizes a left FEFsem site in *monkey SS* that was identified principally by the robust and specific responses of pursuit neurons recorded there. Figure 2A shows the responses during sinusoidal pursuit of a neuron recorded at the exact depth where we later injected muscimol. This neuron responded tonically during leftward SP, but was silent during rightward SP. Other tests showed very little response to visual motion in the absence of pursuit and no response in conjunction with saccades to stationary targets. The optimal SP direction for this neuron was ipsilateral (leftward) and slightly downward. Pursuit cells with other preferred directions and response patterns were recorded above and below this cell.

*Monkey SS* pursued well in formal testing with 1.0-Hz sinusoidal motion conducted just before the injection. *Figure 2B*, with rightward SP slightly faster than leftward. After muscimol (1.4 µl) was injected, SP was severely impaired (Fig. 2C), especially SP to the left. For example, the mean peak leftward pursuit across six trials (such as the one in Fig. 2C) was only 24.5 ± 1.0°/s after muscimol, whereas before the injection it was 55.0 ± 1.5°/s (peak target velocity was 65°/s). As is also evident in Fig. 2C, pursuit of the initial motion to the left was especially poor, peak leftward velocity on the initial cycle being ~10°/s on such trials. Rightward SP was much less severely affected. Peak rightward pursuit velocities were 74.3 ± 0.9°/s before the injection versus 64.1 ± 4.0°/s after; however, this 14% reduction is significant (*t* = 2.861, *P* < 0.025). Similar deficits in leftward SP were obtained immediately after another muscimol injection into another FEFsem site in this monkey’s left hemisphere located ~2-mm lateral to the injection site of Fig. 2.

Directionality of SP impairments

As indicated in the sinusoidal tracking records in Fig. 2C, rightward (contralateral) pursuit was much less impaired than leftward (ipsilateral) pursuit. To further address this issue, the directionality of SP deficits was quantitatively assessed for all sites injected by having the monkeys track constant-velocity target motion in eight different directions. Figure 3 shows SP deficits as a function of tracking direction, target velocity, and time since the muscimol injection for both monkeys. With respect to *monkey SS*, immediately after the injection SP was significantly diminished in every direction except strictly contralateral (Fig. 3A) and was most drastically reduced for ipsilateral pursuit, both horizontal and oblique. The deficit worsened over the first 30 min of testing (Fig. 3B), especially for SP directed down and left, but completely recovered by the next day (Fig. 3C). This overall pattern of deficits was very similar for 25 and 50°/s testing.

In contrast, *monkey JM*’s site yielded an omnidirectional SP deficit (Fig. 3, D and E). Although the most profound impairments were for ipsilateral pursuit, which was illus-
FIG. 1. Deficits in smooth-pursuit (SP) after muscimol injection at a right frontal eye field smooth eye movement (FEFsem) site of monkey JM. A: smooth eye movements to the right evoked by electrical stimulation at the FEFsem site. The monkey was fixating a stationary spot near the center of the screen. Stimulation was a 200-ms train of biphasic pulses (−0.2+/+0.2 ms) at 300 Hz. Negative current was 50 mA. Left: 10 consecutive trials superimposed. The scatter in starting locations is largely because the fixation spot location was varied slightly between trials. Note that most trials have a voluntary return saccade back to the fixation spot 70 ± 110 ms after the end of stimulation. Right: average of the 10 trials. A flat reference line is added to the eye position (H and V) and horizontal eye velocity (dH/dt) traces. B, top: single trial of step-ramp tracking just before injection (dark line) superimposed on the 1st trial (broken line) tested after muscimol was injected at the location of elicited pursuit shown in A. At time 0 on the traces the target instantaneously jumped 4° to the left ("step"), then moved to the right at 40°/s ("ramp") for ~0.9 s (only 0.8 s are shown). Notice that in the preinjection trial the eye trajectory approximately matched the target trajectory shortly after the initial saccade was completed, whereas tracking was principally via saccades in the postinjection trial. Bottom: eye velocity profiles for several 40°/s rightward trials, both pre- and postinjection, including the 2 trials shown above. Notice that for all 6 preinjection trials (dark lines) the peak smooth velocity approaches or exceeds target velocity, whereas peak smooth velocity of all 5 postinjection trials (broken lines) are far below target velocity. All postinjection trials have nonzero pursuit, however, with peak smooth velocities of 4.8–11.2°/s.

Effects on SP acceleration and latency

In conditions where peak SP velocity was reduced, SP acceleration was substantially diminished as well. In the premuscimol step-ramp trials shown in Fig. 1C, the mean rightward SP acceleration immediately before the saccade was 88.5 ± 10.2°/s², whereas after muscimol presaccadic mean acceleration was 22.2 ± 2.1°/s². Thus SP acceleration after this injection diminished to ~25% of its normal value, approximately the same proportion by which peak SP velocity was diminished. Initial SP acceleration in other directions also declined roughly in proportion to the decline in peak SP velocity; for example, for leftward SP at 40°/s, peak velocity postinjection was ~35% of preinjection velocity and initial acceleration was ~29%.

Latency to initiate SP was only slightly increased by muscimol deactivation. Because it was difficult to judge the exact start of pursuit in every individual trial after the injections, we made a mean smooth velocity trace for each condition and then estimated the latency to initiate SP by the initial inflection point on these mean velocity records. For 40°/s target motion, the latency to initiate rightward SP was 143-ms preinjection.
A FEF Pursuit Neuron

B Preinjection Pursuit

C Postinjection Pursuit

Saccadic effects from injections in FEFsem and SP effects from injections in FEFsac

Saccade latency was affected little by FEFsem injections. At the Fig. 1 site, for example, the mean latency to the first saccade before inactivation was 297 ± 8 ms for rightward trials and 286 ± 6 ms for leftward trials. After muscimol, these mean latencies were 292 ± 13 and 291 ± 5 ms, respectively, neither change being statistically significant. Likewise, saccadic size and accuracy were not affected by the muscimol injections into FEFsem, neither for saccades made during SP testing nor for saccades made to stationary visual targets.

Control sites in FEFsac were also injected (5 sites in monkey JM, 1 in monkey SS). There was little or no disturbance of SP immediately after these injections; however, 30–60 min after most of these FEFsac injections a significant decrement of SP velocity occurred. Table 1 shows this delayed effect for monkey JM: at 9- to 13-min postinjection there was still little effect on SP, but by 55- to 60-min postinjection peak pursuit velocities declined to approximately one-half of their preinjection values for most directions; the peak deficits at the FEFsac sites were much less severe than the immediate deficits at the FEFsem sites. A similar delayed SP effect followed the FEFsac injection of monkey SS. This could reflect diffusion of muscimol into nearby FEFsem.

Only small impairments in visually guided saccades were evident after FEFsac injections; however, monkey SS had
hypermetric contraversive memory saccades and hypometric ipsiversive memory saccades, both of which worsened with longer delays. *Monkey SS* also had difficulty maintaining fixation and suppressing optokinetic (OK) movements when the fixation target background was a large drifting pattern of stripes. Dysmetric memory saccades and poor eccentric fixation after deactivation in FEFsac were reported in detail since whether FEF lesions result in significant SP deficits is the fixation target background was a large drifting pattern of stripes. These data are consistent with the known neurophysiology of TABLE 1.

<table>
<thead>
<tr>
<th>Tracking Direction</th>
<th>Preinjection Peak Eye Velocity</th>
<th>9–13 min Postinjection Peak Eye Velocity</th>
<th>55–60 min Postinjection Peak Eye Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Preinjection SP Gain Post + Pre</td>
<td>9–13 min Postinjection SP Gain Post + Pre</td>
</tr>
<tr>
<td>0°</td>
<td>21.6/s</td>
<td>21.0%</td>
<td>10.5%</td>
</tr>
<tr>
<td>45°</td>
<td>13.5%</td>
<td>10.9%</td>
<td>5.2%</td>
</tr>
<tr>
<td>90°</td>
<td>8.0%</td>
<td>6.6%</td>
<td>5.3%</td>
</tr>
<tr>
<td>135°</td>
<td>13.3%</td>
<td>13.4%</td>
<td>7.9%</td>
</tr>
<tr>
<td>180°</td>
<td>14.9%</td>
<td>15.0%</td>
<td>10.3%</td>
</tr>
<tr>
<td>225°</td>
<td>18.7%</td>
<td>15.4%</td>
<td>15.6%</td>
</tr>
<tr>
<td>270°</td>
<td>17.3%</td>
<td>17.1%</td>
<td>14.8%</td>
</tr>
<tr>
<td>315°</td>
<td>22.0%</td>
<td>19.3%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The FEF is an important source of neural signals controlling voluntary saccadic eye movements (e.g., Bruce 1990); however, it is now established that the macaque monkey’s FEF has a representation of FEFsem buried in the arcuate sulcus posterior to its saccade representation (Gottlieb et al. 1993, 1994; Keating 1993; MacAvoy et al. 1991). The immediate and profound affects reported here of muscimol injections at physiologically identified sites within FEFsem directly verify a causal role of this physiologically defined region in generating SP eye movements. By contrast, there was no immediate effect on SP when muscimol was injected into FEFsac sites. These data are consistent with the known neurophysiology of the macaque FEFsem. Furthermore, they support the hypothesis that whether FEF lesions result in significant SP deficits is determined by whether FEFsem tissue is spared (Keating by Dias et al. (1995) and by Sommer and Tehovnik (1997).

*Monkey JM* was tested neither on memory saccades nor on fixation during OK stimulation.

**Possible mechanisms of SP impairment**

Muscimol deactivation had a profound effect on SP acceleration attendant to the reduction in SP gain. These results, coupled with single neuron recordings and electrical stimulation studies, support the idea that the FEF output that contributes most directly to SP is, at least in part, a SP acceleration

![Graph](http://jn.physiology.org/DownloadedFrom//http://jn.physiology.org/DownloadedFrom/922303.3June14,2017)
signal. For example, stimulation at SP sites can continue to accelerate the eye for up to 500 ms when a foveally stabilized target is used (Gottlieb et al. 1993). Furthermore, most pursuit units begin responding before the eye starts to move in response to a step change in target motion (Gottlieb et al. 1994), and during pursuit of sinusoidal motion the spiking rate of some pursuit units follows eye acceleration rather than velocity (Fig. 1 in Gottlieb et al. 1994). Having an eye acceleration signal be the critical signal from FEFsem fits well with the “image motion” class of SP models (e.g., Krauzlis 1995, Fig. 2A; Krauzlis and Lisberger 1994). In these models, the SP eye acceleration signal represents a complex response to the retinal slip (both velocity and acceleration). This acceleration signal informs the “pursuit velocity integrator,” which is located in the pontocerebellar circuitry of the metencephalon and determines smooth eye velocity. This circuit is anatomically plausible because nearby FEFsac sends several specific projections to pontine nuclei (Huerta et al. 1986; Stanton et al. 1988), and our preliminary anterograde tracer data indicate that FEFsem also has a heavy pontine projection. Similar ipsiversive SP deficits, with profound reductions in both SP acceleration during SP initiation and in steady-state SP velocity, follow unilateral lesions or inactivation of the dorsolateral pontine nuclei (DPLN) (May et al. 1988).

Of course, this SP acceleration signal must be gated by the choice of whether to pursue a given moving target, but we know that neurons in FEFsem drastically modulate their responses to visual motion as a function of the monkey’s decision or instruction whether to pursue (e.g., Fig. 2 in Gottlieb et al. 1994). Thus we hypothesize that deactivation in FEFsem effectively eliminates much of the SP acceleration signal to the pontocerebellar pursuit apparatus and consequently substantially impairs the monkey’s ability to accelerate its eye speed to match target velocity, resulting in tracking that is principally saccadic.

A permanent deficit in SP acceleration was also found with large aspiration lesions of FEF (MacAvoy et al. 1991). Furthermore, Keating et al. (1996) found that FEF lesions do not disrupt the smooth following of large visual targets, i.e., the OK response, an involuntary, reflexive smooth eye movement. In contrast, DLPN lesions disrupt OK responses as well as SP (May et al. 1988). We hypothesize in the OK situation (motion over large areas of the visual field), posterior visual motion areas such as middle temporal (MT) and medial superior temporal (MST) send a sufficiently strong signal to the pontocerebellar circuitry such that FEF participation is not necessary, even though FEFsem neurons also respond during OK stimuli. In contrast, FEF participation is critical for pursuit of a single small target that would excite far fewer MT and MST cells than OK stimuli. Interestingly, the SP impairment associated with schizophrenia also does not extend to the OK situation (Levin et al. 1988).

Delayed SP impairment from muscimol injections in saccadic FEF

SP deficits after muscimol injections into FEFsac only appeared after ~30-min postinjection. This delayed deficit could simply be caused by diffusion of the muscimol from the vicinity of the injected saccade sites into the adjacent pursuit region. Similarly, although SP deficits were immediate after muscimol injections at verified SP sites, these deficits worsened significantly over the first half hour or so after the injection; this could likewise reflect a larger portion of the FEFsem being deactivated by muscimol spread. Another possibility is that the FEFsem has an important input from the nearby FEFsac, such that as the muscimol spreads to deactivate a large area of FEFsac, that input is more completely silenced, which in turn would impair FEFsem. Our recordings indicate that some cells in FEFsac are indeed sensitive to visual motion (Shi et al. 1996). This motion sensitivity could help guide saccades to moving targets (Shi et al. 1995), but it might also constitute a useful input to the FEFsem.

Laterality of FEF SP representation

These results also address the issue of whether SP deficits from unilateral FEF lesions are bidirectional (e.g., Keating 1991) or principally ipsidirectional (e.g., MacAvoy et al. 1991). Monkey JM had substantial SP deficits in all directions from each FEFsem site tested, although its ipsilateral deficits were larger. For monkey SS, however, deficits for perfectly horizontal contralateral SP were quite small or absent. We propose that the directionality of SP deficits from FEF lesions (reversible or permanent) reflects different combinations of the following two factors: 1) losses of FEFsem representations of particular SP directions and 2) shifts in the overall balance between the left and right hemispheres and/or between left and right pursuit. Gottlieb et al. (1993, 1994) found that although ipsilateral sites predominate, all directions are represented in FEFsem; thus some deficit in contralateral SP is expected after unilateral lesions. However, the left–right imbalance created by a unilateral lesion might effectively obscure contralateral deficits, especially if a preexisting SP asymmetry is exacerbated by the lesion. In fact before these experiments monkey SS pursued less well to the left (Fig. 2, A and B). Thus even if left FEFsem inactivation included some tissue representing contralateral (rightward) SP, it also increased the overall balance even more in favor of rightward SP. Unfortunately, we could only test this monkey with left FEFsem injections. Monkey JM also pursued less well to the left (gain 0.86 at 0° vs. 0.59 at 180°; see Table 1) and right FEFsem inactivation caused an omnidirectional SP deficit, although the ipsilateral (rightward) SP loss was more profound. Individual differences in normal pursuit were similarly suggested as a critical factor in determining the strength and laterality of SP deficits following inactivation in the caudal fastigial nucleus of the cerebellum (Robinson et al. 1997).

Clinical relevance

The present study in monkeys predicts that the effects of frontal lobe damage in humans on SP depend critically on lesion location. Indeed, recent functional magnetic resonance imaging studies show that in humans the FEFsem lies immediately posterior to the saccade-activated FEF (Petit et al. 1997; Sweeney et al. 1997). In contrast, the effects of frontal lesions on saccades are manifest principally in higher-order tasks like memory saccades wherein not only FEFsac, but
also prefrontal cortex anterior to FEFsac have a role. Likewise, the dramatic effects of muscimol inactivation in the monkey FEFsac is consistent with the hypothesis that the SP deficit associated with schizophrenia (e.g., Levy et al. 1994; MacAvoy and Bruce 1995) could be a very specific manifestation of a pervasive frontal lobe dysfunction responsible for schizophrenia (Goldman-Rakic and Selemon 1997; Levin 1984; Weinberger and Berman 1996).

We thank E. C. Dias for valuable methodological information pertaining to preparing and injecting the muscimol and also G. B. Stanton for valuable assistance with the anatomic location of injection sites.

This work was supported by National Institutes of Health Grants EY04740 and MH-44866.

Address for reprint requests: C. J. Bruce, Section of Neurobiology, Yale University School of Medicine, 333 Cedar St., Room C303 SHM, PO Box 208001, New Haven, CT 06520-8001.

Received 7 January 1998; accepted in final form 6 March 1998.

REFERENCES


