NeuroReport 10, 925–930 (1999)

Visual activity in the human frontal eye field

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ALTHOUGH visual information processing in the monkey frontal eye field (FEF) has been well demonstrated, the contribution of its human homologue to vision is still unknown. Here we report a study of intracranial visual evoked potentials (VEPs) recorded from the human FEF which was identified by electrical cortical stimulation. Electrical stimulations and EEG recordings were carried out via subdural grid electrodes placed over the frontal cortex in three epileptic patients. Evoked eye movements were mainly horizontal and always directed to the hemispace contralateral to the stimulation site. Intracranial VEPs showed responses predominately to stimuli in the contralateral visual field. Our findings demonstrate a close relationship between the direction of the electrically elicited eye movements and the visual stimulus location which predominantly leads to neural responses in the FEF. These findings provide evidence for the functional role of the human FEF in the analysis of visual stimuli from the contralateral visual field as well as in the generation of eye movements towards these conspicuous targets. *NeuroReport* 10:925–930 © 1999 Lippincott Williams & Wilkins.

Key words: Epilepsy; Frontal eye fields; Human; Intracranial event-related potentials; Vision

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Introduction

In order to explore a visual scene, rapid shifts of the eyes successively bring images on the fovea. This visually guided behavior can be characterized by periods of fixation interrupted by eye movements which guide the eyes to novel stimuli [1,2]. The primate frontal eye field (FEF) is one of the cortical key structures involved in visually guided behavior and is classically defined as an area of the lateral frontal lobe where microstimulation produces contralateral saccadic eye movements [3–5]. Wurtz and Mohler [4], and later Bruce and Goldberg [5], demonstrated the existence of FEF neurons with contralateral visual receptive fields. In humans, results from cerebral blood flow studies [6,7], from electrical stimulation in epileptic patients [8–10] and from patients with circumscribed cerebral lesions [11] demonstrated that the FEF is engaged in the generation of purposeful visually guided eye movements and attentional shifts. These studies have allowed the localization of the FEF in man in an area including the anterior and posterior bank of the precentral sulcus and the posterior part of the middle frontal gyrus. The functional organization inside the human FEF, in particular with respect to visual information processing is, however, poorly understood. Even though its implication in overt and covert orienting is well established, recent reviews on human vision do not include the FEF [12,13].

The present study investigated cortical visual responses in the human FEF. We recorded intracranial VEPs from the FEF, determined by extraoperative cortical stimulation, in response to different visual stimuli delivered to either the contralateral or ipsilateral visual field.

Materials and Methods

Patients: All three patients were women (NB, 41 years; DK, 18 years; AM, 26 years). Magnetic resonance imaging (MRI) of NB showed an atrophy of the frontal part of the insula. The neurological exam of this right-handed patient was normal. DK was also right-handed, with a normal MRI and without neurological deficits. In AM, the MRI scan showed atrophy of the left cerebral hemisphere with hippocampal dysplasia and aplasia of the splenium. This ambidextrous patient showed incomplete right homonymous hemianopia (eccentricities $>20°$), facial asymmetry, hypoesthesia of right leg and right-sided dysdiadococinesia. Prolonged invasive EEG recordings in these patients identified the epilepto-

genic focus of NB in the left occipitotemporal lobe, of DK in the left frontal lobe, and of AM in the left temporal lobe.

Intracranial electrode placement: Subdural grid electrodes were implanted as part of diagnostic investigations and were 3 mm diameter stainless steel electrodes with a center-to-center distance of 0.8 cm. Subdural electrodes were MRI compatible and embedded in a clear silastic sheet (Ad-Tech Corp., Racine, WI, USA). Electrode location (Fig. 1) was determined by intraoperative photographs and 3-D MRI of the brain with the implanted electrodes. A total of 94–102 electrodes was placed over the lateral and mesial surface of the left hemisphere, partly covering the frontal, parietal, temporal and occipital lobes.

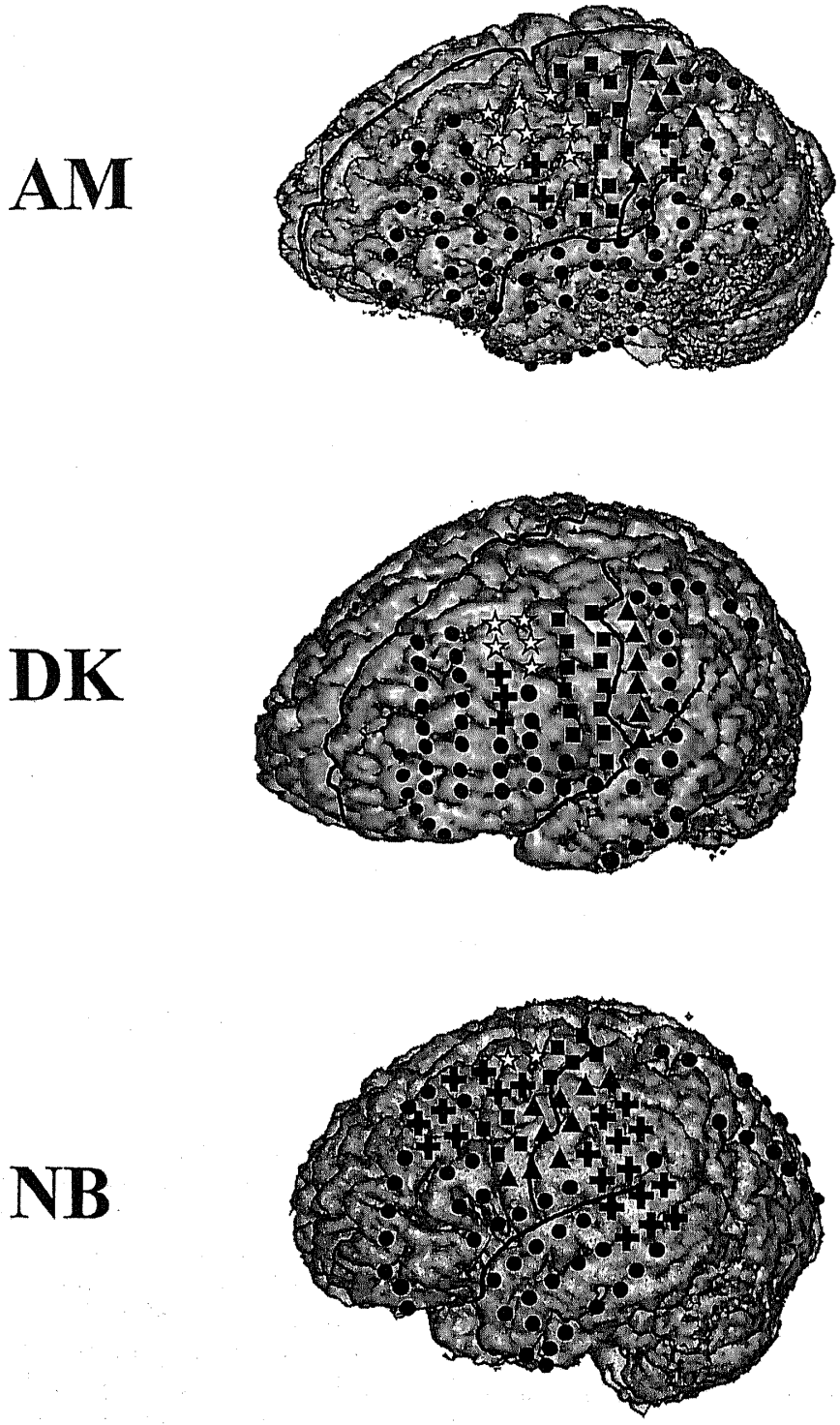

FIG. 1. Localization of grid and strips over the lateral left frontal lobe of the three patients of the study. Responses induced by electrical cortical stimulation (eye and head movements: ☆; face, tongue or hand movements: ■; somatosensory: ▲; language: ✚) are indicated. Circles represent those sites at which in the majority of stimulations no overt responses were evoked. Temporal electrodes where complex experiential or auditory responses were evoked are also indicated by circles. The central sulcus and the sylvian sulcus, as well as the interhemispheric fissure are outlined (black lines).

Electrical stimulation: Stimulations were performed with a Grass Stimulator S12 (Grass Instruments, Quincy, MA, USA). Trains of 2–5 s with increasing currents (0.1–13 mA) and 0.3 s alternating polarity square-wave stimuli were delivered at a repetition rate of 50 Hz on continuous sets of bipolar electrodes, as described elsewhere [14].

Intracranial VEPs: Subjects volunteered to participate and understood the experimental nature of the task. Informed consent was obtained. Subjects were seated comfortably in bed in front of a computer screen, head unrestrained, in a darkened room. The task consisted of fixating a central cross, shown on the screen, while different stimuli were presented randomly in either the right or left visual field. Subjects were instructed to precisely fixate the central cross and to restrain from moving the eyes. We carried out two experiments in order to examine the visual activity in the human FEF in response to extrafoveal stimuli (experiment 1) and foveal stimuli (experiment 2). Furthermore, we presented the stimuli separately in both visual fields.

In the first experiment, stimuli (black dots) appeared at a fixed eccentricity of 5°. The stimuli were 2° of visual angle (Fig. 2, top) and shown on the screen for 500 ms at a rate of 0.4/s. A total of 120 visual stimuli was presented per visual field.

For the second experiment, stimuli consisted of black and white checkerboards (0.5° of visual angle) presented in the central 11° of the left and right visual field (Fig. 2, bottom). A block of 100 pattern reversals was presented in both visual fields at a rate of 2/s.

The intracranial EEG was recorded continuously with a sampling rate of 200 Hz, bandpass 0.1–70 Hz, in a bipolar montage. EOG recordings were carried out simultaneously to monitor eye movements. EEG was analyzed off-line. Only those EEG epochs in which central fixation was maintained were averaged (100 ms before to 500 ms after stimulus onset). VEPs were calculated for the left and the right visual field for both experiments and for all patients separately. The VEPs of adjacent bipolar recordings in FEF were compared and searched for inversion of polarity or difference in amplitude (> 1 s.e. of the individual average) in order to localize the cortical sites which responded to the visual stimulation.

Results

Electrical stimulation: Eye movements could be elicited from 15 electrodes (mean: 5, range: 2–8) in all patients and were always directed contralaterally. Eye movements could be evoked from a cortical area in front of the motor representation of face, tongue or hand (Fig. 1). This cortical region was located anatomically at the posterior part of the middle frontal gyrus, anterior to the precentral sulcus and lateral of the superior frontal sulcus, as shown previously in other studies [6,8,10,11] (Fig. 1).

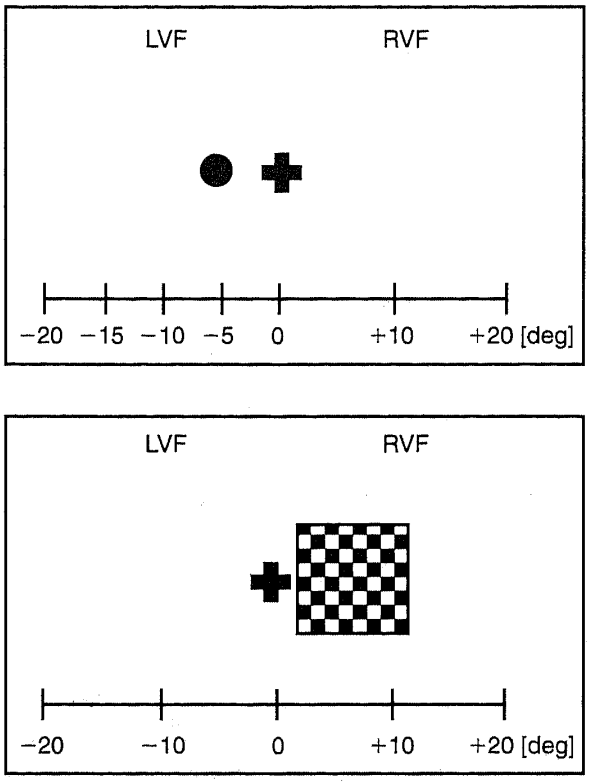

FIG. 2. Upper figure, experiment 1: A peripheral stimulus appeared randomly in the left or the right visual field (circle). Stimulus position was chosen at 5°. Stimulus size was 2° of visual angle. The stimulus appeared on the screen for 500 ms and subjects were instructed to maintain fixation of the central cross. Lower figure, experiment 2: Visual stimuli consisted of black and white checks (0.5° visual angle) presented in the central 11° of the visual field. Reversal Checkerboards were presented in the right and the left visual field and alternated every 500 ms.

Intracranial VEPs, experiment 1: VEP responses in the FEF were observed in all three patients after the presentation of small dots. Differences were obtained 150 ms and 200–300 ms after stimulus onset (Fig. 3, Fig. 4). Within the frontal cortex, these responses were obtained only at FEF electrodes and adjacent frontal electrodes. Sixty-seven percent of all FEF electrodes (10/15) showed responses if stimuli were presented in the contralateral visual field (Fig. 3, Fig. 4). Amplitudes of the VEPs in patient NB (only two electrodes were positioned over the FEF) were smaller than those of the other patients. Twenty-seven percent (4/15) showed responses after ipsilateral stimulus presentation and were always at electrodes that also responded to contralateral visual stimuli. However, VEPs after ipsilateral stimulation were always of lower amplitude than responses to contralateral stimulation at the same electrode con-

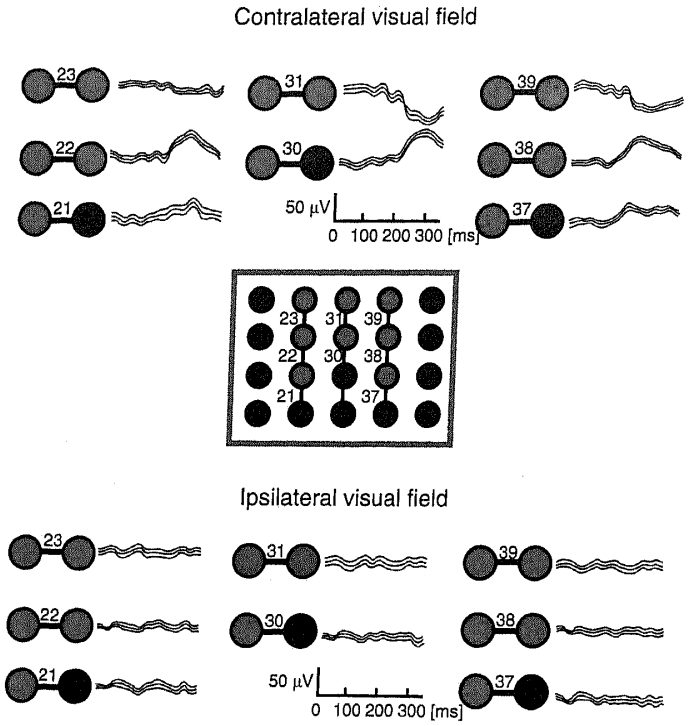

FIG. 3. Mean VEP (thick black line) with s.e. (thin gray lines) for all bipolar FEF recordings in patient AM in experiment 1. Middle figure indicates number and position of bipolar recordings that are shown in the upper and lower graphs). Upper graphs show VEPs to stimuli in the contralateral visual field, lower graphs those to ipsilateral stimuli. Note the presence of a VEP in six of eight FEF recordings, whereas ipsilateral visual stimuli do not lead to responses in the FEF.

tacts (Fig. 3, Fig. 4). At five electrodes neither contralateral nor ipsilateral stimulus presentation led to responses.

Intracranial VEPs, experiment 2: VEP differences were observed for all patients after the presentation of checkerboards in the contralateral hemifield (60%, 9/15 electrodes). The largest differences were obtained 100 ms, 150 ms and 200–300 ms after stimulus onset. In patient AM the differences at 100 ms and at 150 ms were larger than those seen in response to the presentation of the small dot stimuli in experiment 1 (Fig. 4, Fig. 5). No responses were obtained after presentation of checkerboards in the ipsilateral visual field (Fig. 5).

Discussion

The present study permitted to examine a circumscribed cortical area in man by combining methods with high spatial and temporal accuracy: cortical electrical stimulation and intracranial evoked potentials. This approach allowed us to describe VEP components in the human FEF which demonstrate the existence of visual processing in this area which has to our knowledge not yet been described.

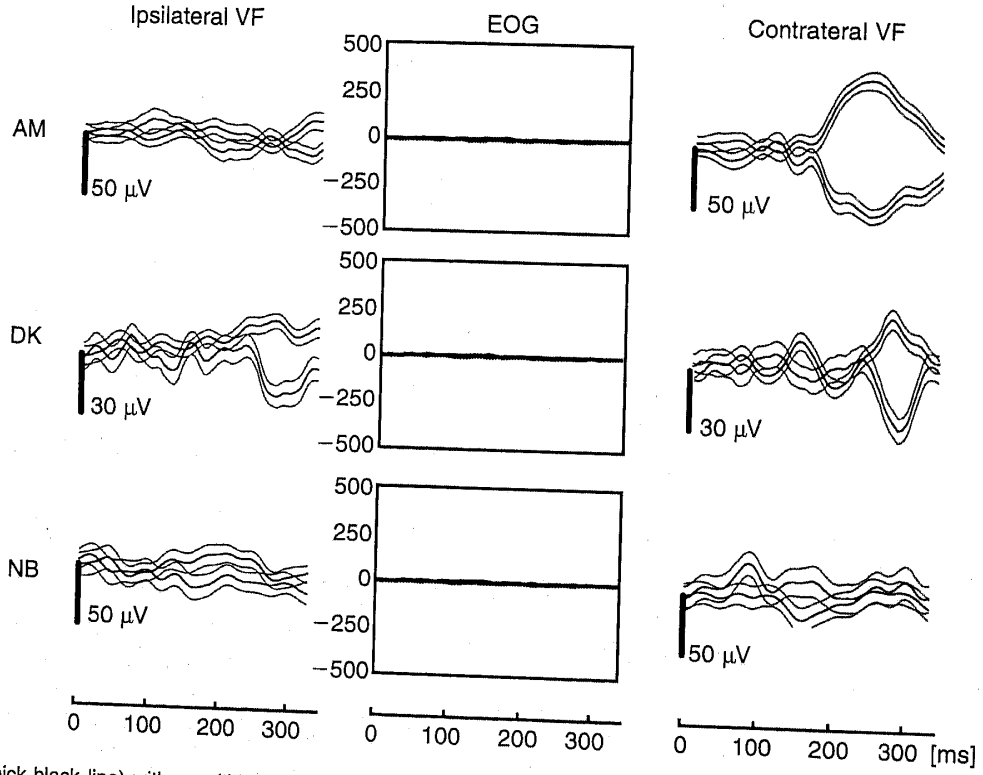

FIG. 4. Mean VEP (thick black line) with s.e. (thin gray lines) for two adjacent bipolar recordings in experiment 1. Figures on the right show VEPs to stimuli in the contralateral visual field. The VEP of two adjacent bipolar EEG recordings is plotted, showing amplitude differences with polarity inversion at 150 and 200–300 ms after visual stimulus onset. Figures on the left show the VEP for ipsilateral visual stimuli. Note the disappearance or diminished amplitude of the VEP at the same electrode pairs as compared with contralateral visual stimulation in all patients. EOGs in the middle column confirm fixation without eye movements in all patients during the ipsilateral and contralateral VEPs.

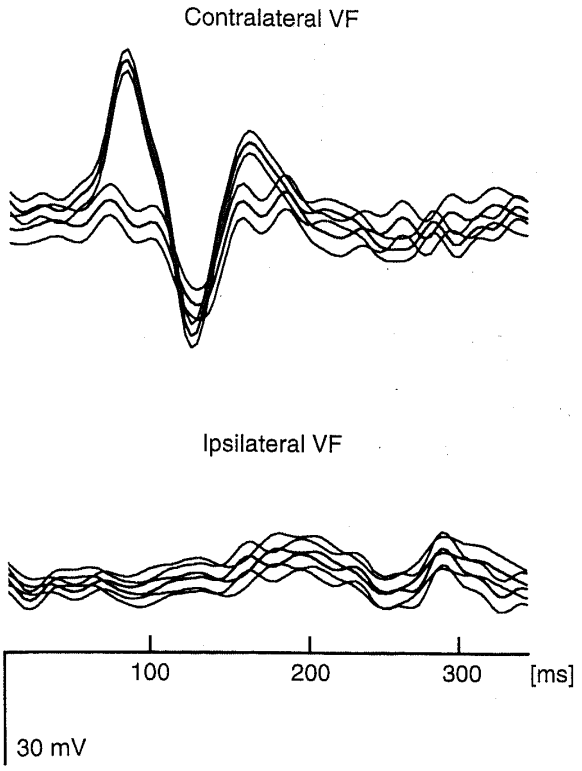

FIG. 5. Mean VEP (thick black line) with s.e. (thin gray lines) for two adjacent bipolar recordings in experiment 2 in patient AM. Upper figure shows VEP to stimuli in the contralateral visual field. The VEP of two adjacent bipolar EEG recordings is plotted, showing main responses at 100 and at 150 ms after visual stimulus onset. Lower figure shows the VEP for ipsilateral visual stimuli. Note the dissociation between contralateral and ipsilateral visual field stimulation in patient AM as in experiment 1.

The importance of the monkey FEF for the control of saccadic eye movements, and the maintenance of fixation, has been proven in several studies [3,5]. A high number of FEF neurons with visual receptive fields were initially described by Wurtz and Mohler [4]. Later, Bruce *et al.* [15] were able to demonstrate a spatial correlation between the contralateral location of the visual receptive field and the contralateral direction and endpoint of the stimulation-induced saccade. These findings, and the existence of extensive cortico-cortical connections between the FEF and higher-order visual cortices [16,17], demonstrate the key role of the primate FEF in visuo-motor processing. Moreover, while early studies using intracranial stimulation techniques in the human FEF did not describe visual phenomena [8–10], a recent case report indicates that complex visuo-spatial phenomena can be evoked by electrical stimulation of this cortical area [18]. Our data showed maximal visual responses at different latencies in experiments 1 and 2. Whereas extrafoveal visual stimuli (small dots, experiment 1) led to maximal responses 200–300 ms after stimulus onset, stimuli which covered foveal and extrafoveal parts of the visual field (checkerboards, experiment 2) evoked large responses at 100 ms. We might, therefore, suggest that the observed different VEP components reflect different stages of visual information processing of foveal and peripheral stimuli during visual target selection as described in the monkey [2,19]. Since eye movements during the experiments were monitored by simultaneous EOG recordings, the observed VEPs cannot be movement potentials related to saccade execution. However, we cannot exclude that saccade inhibition or attentional processing such as covert orienting towards the visual stimuli [8] biased our findings.

It can be argued that our results cannot be applied to normal brain function since stimulations have been carried out in epileptic patients. However, it should be pointed out that the epileptic focus in all patients was found outside the FEF. Moreover, the usual somatotopic mapping of motor functions and the location of language functions do not suggest grossly deviant brain pathology with respect to anatomical representations of cortical functions.

The second major finding of our study concerns the dissociation in the human FEF between visual stimuli from the ipsilateral and the contralateral hemifield. Visual stimuli from the contralateral hemifield evoked strong responses whereas ipsilateral stimuli elicited fewer and weaker responses. Moreover there seems to be a close relationship between the direction of the eye movement which can be electrically evoked from the FEF and the visual stimulus location which leads to maximal VEPs: all stimulation-induced eye movements were directed contralaterally and evoked responses to contralateral visual stimuli were more frequent and of higher amplitude when compared with ipsilateral stimulus presentation. Therefore, the maximal visual activity in the human FEF is predictive of the main direction of the eye movement that can be electrically evoked in this cortical area. This result is similar to findings in the monkey FEF, in which the location of visual receptive fields of single neurons corresponds to the location of its movement field [5,19]. The potential of the FEF to analyse visual stimuli from both hemifields is suggested by rare VEP responses to ipsilateral visual stimuli (see Fig. 4, patient DK).

Conclusion

The human FEF, precisely localized by electrical cortical stimulation, is involved in visual processing of foveal and extrafoveal stimuli, as determined by intracranial VEPs. FEF activity was found to dissociate between stimuli from the contralateral and the ipsilateral visual field with more frequent and stronger responses for the former. The close relationship between the direction of the electrically elicited eye movements and the visual halffield

which predominantly leads to neural responses in the human FEF seems to reflect the functional role of the human FEF in the analysis of mainly contralateral visual stimuli, as well as in the generation of an eye movement towards these conspicuous targets.

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ACKNOWLEDGEMENTS: This work was supported by the Swiss National Science Foundation (Grant-No. 31-52933.97 and 4038-044081).

Received 22 December 1998; accepted 28 January 1999