Location of the human frontal eye field as defined by electrical cortical stimulation: anatomical, functional and electrophysiological characteristics

O. Blanke,[1,2,CA] L. Spinelli,[1,2] G. Thut,[2,3] C. M. Michel,[2,3] S. Perrig,[1] T. Landis[1] and M. Seeck[1]

[1]Laboratory of Presurgical Epilepsy Evaluation, [2]Human Brain Mapping Laboratory and [3]Plurifaculty Program of Cognitive Neurosciences, Department of Neurology, Department of Neurology, University Hospital, 24 rue Micheli-du-Crest, 1211 Geneva, Switzerland

[CA]Corresponding Author

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Electrical cortical stimulation of the human frontal gyri and the precentral gyrus has been shown to induce eye movements and it has classically been assumed that these stimulation-induced eye movements result from electrical interference with the human homologue of the monkey frontal eye field (FEF). However, amplitude of electrical current and induced type of eye movement, which are essential for the determination of eye fields in the monkey. have not been investigated systematically in man. We applied electrical cortical stimulation in the lateral frontal cortex in six epileptic patients. Sites whose stimulation resulted in eye movements were determined with respect to gyral and sulcal patterns, Talairach coordinates and neighboring functions as found by electrical cortical stimulation. Based on this approach, a restricted location of the electrically defined FEF is proposed within a larger oculomotor region on the posterior part of the middle frontal gyrus. *NeuroReport* 11:1907–1913 © 2000 Lippincott Williams & Wilkins.

Key words: Electrical stimulation; Epilepsy; Frontal eye field; Man; Saccades; Smooth eye movements

INTRODUCTION

Eye movements (EMs) can be electrically induced from a large area of the dorsolateral frontal cortex of the monkey ranging from the rostral end of the principal sulcus to the arcuate sulcus and dorsomedially beyond it (Fig. 1a) [1]. In combining microstimulation with precise EM recordings different eye fields have been defined within this large frontal EM region. These consist of the frontal eye field (FEF) in the rostral bank of the arcuate sulcus (Fig. 1a) [2,3], the supplementary eye field in the dorsomedial premotor cortex [4] and a region posterior to the arcuate sulcus in the ventral premotor cortex [5].

In the human dorsolateral frontal cortex, electrically induced EMs have been investigated in epileptic patients undergoing presurgical evaluation. Whereas Foerster [6] induced EMs only from the posterior part of the middle frontal gyrus, Rasmussen and Penfield [7] observed oculomotor responses on all frontal gyri and the precentral gyrus (Fig. 1b). Both studies stimulated intraoperatively under important time constraints, making it difficult to precisely observe induced behavior. A more recent study [8] stimulated outside the operational unit via chronically implanted subdural electrodes with the patient fully awake and more relaxed. Combined with modern video equipment and without the pressure to complete stimulation within a few hours as is the case when stimulating during surgery, Godoy *et al.* [8] confirmed the functional location of EM sites anterior to the motor representation of arm and face as suggested by previous studies. However, they did not localize the EM sites with respect to underlying gyral and sulcal patterns. It has been assumed that these stimulation-induced EMs result from electrical interference with the human homologue of the monkey FEF. However, current amplitude and induced type of EM, which are essential for the determination of the FEF in the monkey, have not been investigated in man. Systematic analysis of the induced oculomotor behavior at each current amplitude and electrode in humans might lead to a more restricted location of the human FEF and allow a better comparison with the monkey data.

Recently a more restricted location of the human FEF has been suggested by results from studies using fMRI [9–11] or PET [12,13] (Fig. 1b). Some neuroimaging studies have supported the location as found by ECS, but most studies have suggested a more posterior location along the dorsoventral extent of the precentral sulcus extending largely onto the precentral gyrus. This precentral location is very robust across numerous studies involving the

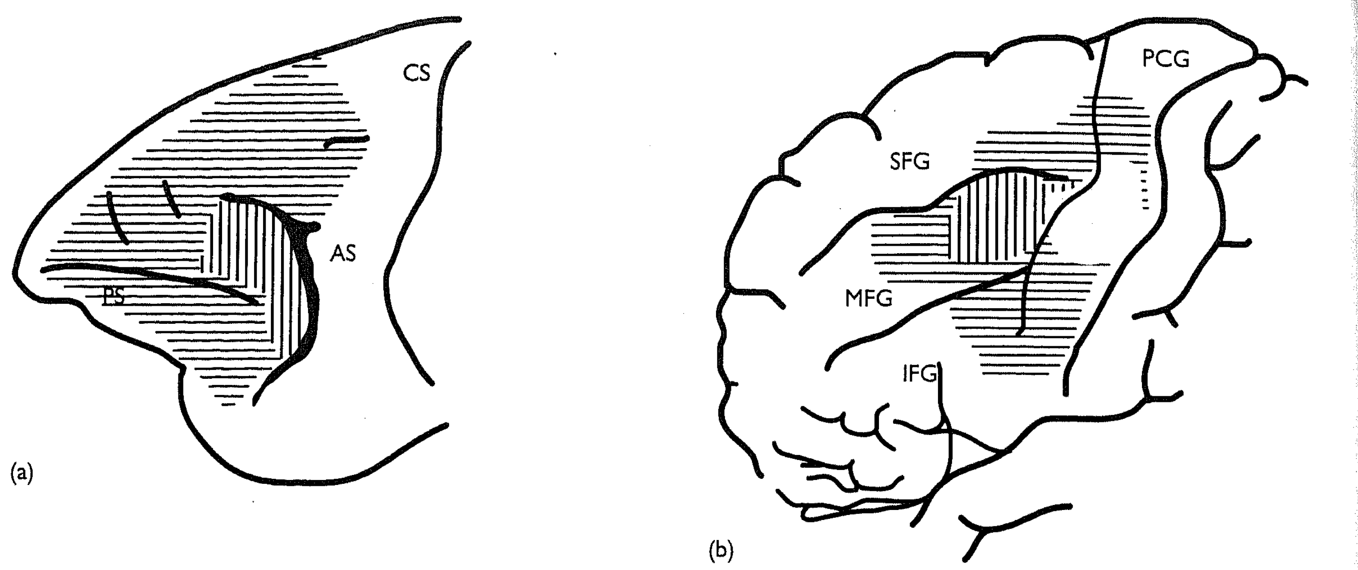

Fig. 1. Location of frontal sites from which eye movements can be induced by electrical cortical stimulation in monkey (**a**) and man (**b**). (a) Eye movement region as determined by Wagman *et al.* [1] stimulating via surface electrodes and using large currents (area indicated by horizontal lines). The area indicated by vertical lines between the posterior end of the principal sulcus (indicated as PS) and the arcuate sulcus (AS) shows the location of the FEF as proposed by Robinson and Fuchs [2] using microstimulation and precise eye movement recordings. Bruce *et al.* [3] confined the FEF to the anterior bank of the arcuate sulcus (indicated by the curved thick black line in front of the AS) by only accepting sites as the FEF which induced eye movements at currents < 100 µV. CS: central sulcus. (b) Rasmussen and Penfield [7] induced eye movements from all frontal gyri and the precentral gyrus (shown by horizontal lines). Foerster [6] only induced eye movements from the posterior part of the middle frontal gyrus (MFG) and proposed this area as the site of the human FEF (area indicated by vertical lines). The white area with black dots, mainly localized on the precentral gyrus (PCG), shows the FEF as proposed by neuroimaging studies [13]. IFG: inferior frontal gyrus, SFG: superior frontal gyrus.

subjects in various saccade paradigms, raising the question as to whether the human FEF is localized within area 6 rather than area 8 of Brodmann. Systematically investigating stimulus parameters of ECS and evoked oculomoter responses to locate the human FEF might help resolve the question of whether differences in FEF-localization by ECS or fMRI/PET are due to methodological differences inherent to the two brain mapping techniques, or instead to differences in examined oculomotor behavior in which the subjects are engaged during both techniques.

In the present study we applied ECS in the lateral frontal cortex in six epileptic patients, to determine the cortical location and the current thresholds necessary to induce unilateral EMs. These sites were determined with respect to gyral and sulcal patterns, Talairach coordinates and neighboring functions as found by ECS and compared with the FEF-location as proposed by neuroimaging studies.

MATERIALS AND METHODS

Patients: Subdural grid electrodes were implanted over the cortical surface in six patients suffering from drug resistant epilepsy in order to localize the epileptic focus, primary motor and somatosensory cortex as well as the language cortex [14,15]. Sex, age, handedness, and lesions as defined by MRI are described in Table 1. The recording and stimulation procedure was carried out, outside the operational unit, with the patient sitting comfortably in bed, head unrestrained. The patient was asked to precisely indicate any sensory and motor percept elicited by ECS. Once an oculomotor response was obtained, subsequent stimulation was applied while the patient fixated an object in the central position with eyes and head aligned.

Intracranial electrodes and electrical cortical stimulation: ECS was performed via 538 subdural electrodes (range: 72–100) placed over the lateral and mesial surface of the left hemisphere, covering partly the lateral and mesial frontal ($n=6$ patients), lateral parietal ($n=6$ patients), lateral and basal temporal ($n=6$ patients) and temporo-occipital lobe ($n=2$ patients). Electrode location was determined by intraoperative photographs and 3D MRI (Fig. 2). Subsequently, MR images with the implanted electrodes were transformed into Talairach space [16] using a 12

Table 1. Clinical data of all patients. Age, sex, handedness, MRI findings, and location of the epileptic focus are given.

Patient	Age	Sex	Handedness	MRI abnormality	EEG localization (ictal)
DK[a]	18	F	R	None	Left mesial and lateral prefrontal
AM[a]	27	F	A	Atrophy of left cerebral hemisphere, left hippocampal dysplasia, aplasia of splenium	Left temporal lobe and left hippocampus
NB[a]	43	F	R(A)	Atrophy of frontal insula	Left occipitotemporal
JG	44	M	R	none	Left temporal
SG	26	M	R	Discrete atrophy of the left lateral frontal cortex	Left prefrontal
NT	23	M	R	Atrophy of frontal insula	Left temporal lobe and left hippocampus

[a]Patients in whom the FEF could be localized.
F: female, M: male, R: right-handed, A: ambidextrous.

Fig. 2. Anatomical location of frontal electrodes. The 3D MR images with the implanted electrodes are shown for the 3 patients in which eye movements could be induced. The MRI of patient AM is shown on the left of the figure, patient DK's MRI in the middle and the MRI of patient NB on the right. The behavioral responses as found by stimulation mapping are indicated as follows. Eye movements: yellow; other motor responses: red; somatosensory responses: blue; language responses: green. Black circles localized over the frontal cortex represent sites at which no overt responses were evoked. Temporal electrodes where complex experiential or auditory responses were evoked are not indicated (also black circles). The central sulcus and the lateral sulcus are outlined (black lines).

parameter linear transformation of the T1-weighted image. Stimulations consisted of increasing currents from 0.5 to 10 mA. Alternating polarity square-wave stimuli of 0.3 ms were delivered at a repetition rate of 50 Hz, as described elsewhere [14]. Trains of stimulation were of 2 s duration (GRASS Stimulator S12, Grass Instruments, Quincy, MA, USA). At each electrode site ECS was started with an amplitude of 0.5 mA and increased in 0.5 mA steps until a response, sensory or motor was obtained. Subdural grid electrodes and EEG recordings have been described previously [17].

Eye movement recording and analysis: EMs were recorded by high-resolution videography (S-VHS) which allowed off-line analysis. The temporal resolution of the videotape was 20 Hz. Data were analyzed offline (in slow-motion) time frame by time frame and searched for saccades and smooth eye movements. Saccades were defined as a rapid single step or multi-step eye deviation. A smooth non-saccadic EM response was noted if a continuous eye deviation which was not separated by fixation periods > 50 ms was encountered. Since precise EM recordings were not performed, the principle direction for saccades (contralateral–ipsilateral) was determined for the saccade sequence as a whole and not for every single saccade. For the same reason vertical components which have been described previously [7,8] were not analyzed.

RESULTS

A total of 251 electrodes (mean: 42/patient, range: 18–54) was positioned over the frontal lobe of six epileptic patients. Oculomotor responses were evoked in three patients at 15 frontal electrodes (range: 2–8) in 40 trials and were always conjugate and directed contralaterally. Saccadic EMs were induced at 8% of all frontal electrodes in patients AM, DK and NB. Smooth EMs were rare and induced in patient AM and DK at 3% of all frontally positioned electrodes.

Saccadic eye movements: ECS at 11 electrodes (seven bipolar stimulation sites) resulted in saccadic EMs in a total of 33 trials. The current threshold, i.e. the least current required to evoke a saccadic EM was 4.3 mA (mean) and varied between 3.5 and 5.5 mA. Only at one EM site was a higher current (8.5 mA) observed. The large majority of saccadic responses were composed of a sequence of saccades or a staircase of saccades which consisted of 2–4 contralateral EMs driving the eyes into their mechanical limits (85% of all stimulations). In the remaining cases at four saccade sites a single-step saccade was noted at the current threshold. However, stepwise increase of applied current amplitude at each of these latter sites eventually led to the induction of a sequence of contralateral saccades as observed at the other electrode sites in our patients and in monkeys [2]. The maximal increase of current amplitude was 0.5–1.5 mA at these four sites. Mean current threshold to evoke other skelettal motor responses, posterior to the sites which induced EMs, was 3.0 mA (range: 2.0–4.5 mA).

Smooth eye movements: ECS at four electrodes (two bipolar EM sites) elicited smooth EMs in seven trials. The thresholds to evoke a smooth EM were at 1.5 and at

4.5 mA. Stimulation-induced smooth EMs always lasted for the entire period of stimulation, in contrast to the discontinuous saccadic responses. In patient DK, currents 1.0 mA higher than the threshold altered neither the direction nor the amplitude of the elicited movement. However, higher currents were associated with an unpleasant, more prominent sensation induced with the EM. In patient AM currents were not modified during testing.

Anatomical and functional location: Electrodes positioned on the posterior part of the middle frontal gyrus ($n=13$) and the neighboring part of the superior frontal gyrus ($n=2$) induced unilateral EMs in three patients (Fig. 2). The extent of the area from which EMs could be induced varied between patients (Fig. 2, Fig. 3a) with a maximal length of 16 mm along the anteroposterior and the dorsoventral axis (patient AM, Fig. 2, Fig. 3a). The smallest region (patient NB) consisted of two electrodes only. Functionally, the oculomotor region was found immediately anterior to electrodes from which contralateral motor responses of face ($n=4$), mouth and tongue ($n=4$) or hand ($n=2$, Fig. 3a) could be induced. At the electrodes, located infero-lateral of the EM-sites, speech arrest ($n=3$), tongue movements ($n=1$) and hand movements ($n=1$) were found. Two stimulations provoked no responses. Anterior contacts were mainly silent but evoked speech arrest in one patient. The other three patients had more inferior and posterior positioned frontal electrode contacts and no oculomotor response was evoked. In these patients the most mesial electrode contacts were over the inferior frontal gyrus or the lower part of the middle frontal gyrus in front of motor cortex involved in the generation of mouth and tongue movements.

In patients AM and DK smooth EMs were induced from a small area in the posterior and mesial corner of the EM region. This area was located in both patients on the cortex immediately anterior to the junction of the superior frontal sulcus with the precentral sulcus (Fig. 2, Fig. 3a). Saccades were represented laterally and rostrally to the smooth EM sites. Electrodes where constant saccadic and smooth ocular responses (at and above the EM threshold) could be evoked were localized in the posterior part of all EM sites.

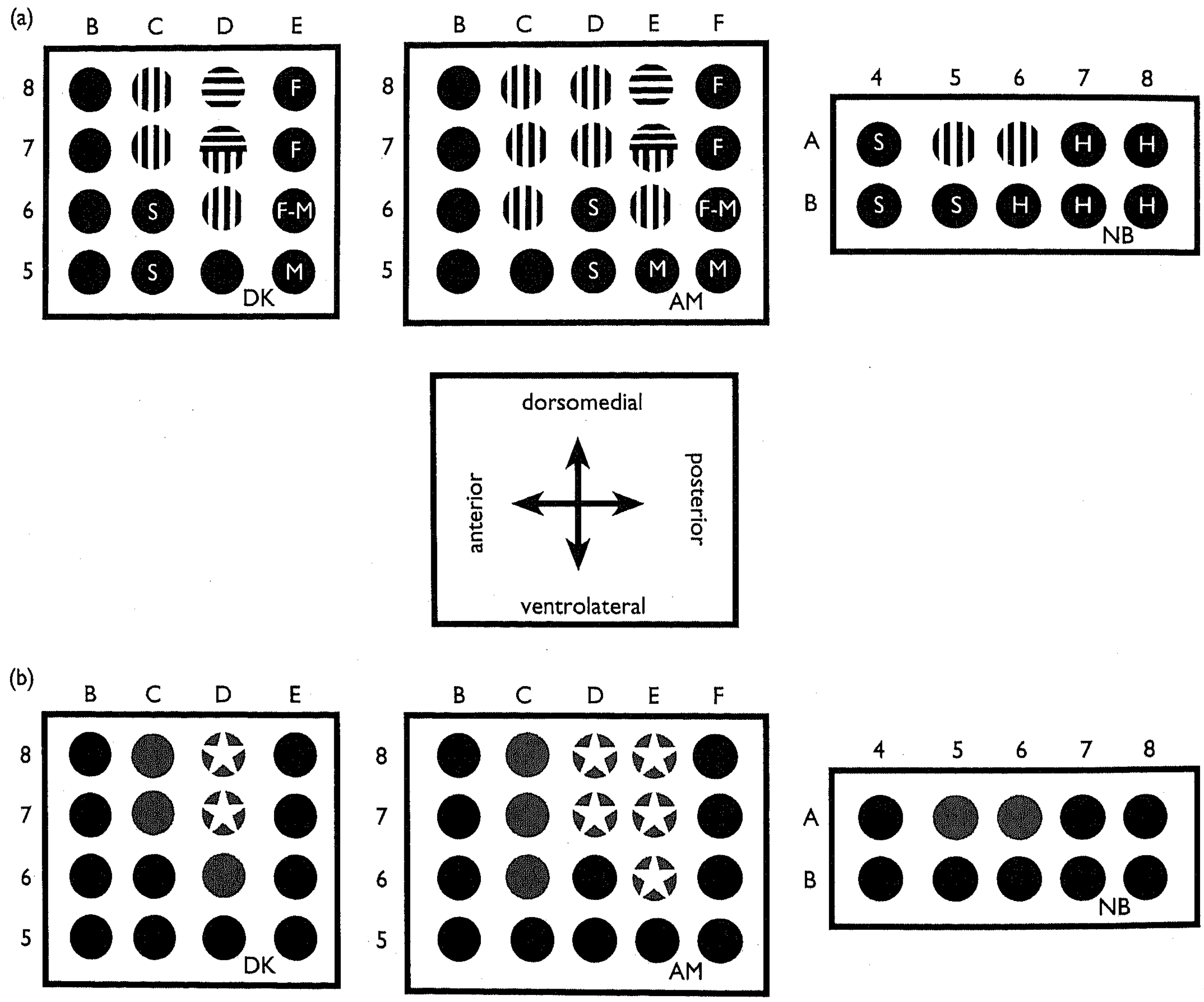

Fig. 3. Oculomotor subregions in the human dorsolateral frontal cortex. (**a**) EM sites and their location with respect to skeletal motor sites and speech sites are shown for patient DK (left), patient AM (middle) and patient NB (right). Electrodes whose stimulation elicited saccades are indicated by vertical lines and smooth eye movements by horizontal lines. Hand movements are indicated by H, face movements by F, mouth movements by M and speech responses by S. Black circles without indication represent sites without motor or speech responses. (**b**) Same electrode arrays as in (a) shown in the same order of patients. EM sites where a single-step saccade was induced at the current threshold or sites characterized by a high saccade threshold are indicated by gray circles. The remaining sites (gray circles with star) are presumed to represent electrodes lying over the human frontal eye field. These sites are characterized by low thresholds, similar to those necessary to evoke skeletal motor responses, and by constant oculomotor responses evoked at and above the EM threshold.

Electrodes where single-step saccades were induced at the current threshold or where higher currents were necessary to induce EMs were localized in the anterior and lateral part of the oculomotor region (Fig. 3b).

The Talairach coordinates of the electrodes which evoked oculomotor responses are given in Table 2. In patients DK and NB, the location of electrodes which induced EMs and other motor responses as well as language responses were compared with the mean location of the FEF, its standard deviation and range in Talairach space as proposed by 17 neuroimaging studies [13] (see Fig. 4). Since patient AM had left hemispheric atrophy as found by MRI we did not compare the normalized location of EM sites with the FEF location as found by neuroimaging studies. Talairach coordinates in this patient, with a predominant left posterior atrophy, suggest a backward shift of the coordinates (Table 2), however gross anatomy and functional cortical organization was very similar in all three patients (see Fig. 2, 3a). Note that in patient NB and DK only one EM site (white circle in Fig. 4) could be found within the range of the FEF as found by neuroimaging studies. Of the other six electrodes located within this range four induced hand movements, one face movements, one speech arrest (Fig. 4).

DISCUSSION

In agreement with Foerster [6], we could only induce EMs from the posterior part of the middle frontal gyrus and the immediately adjacent part of the superior frontal gyrus. We did not induce EMs from the inferior frontal gyrus and the precentral gyrus as suggested by Rasmussen and Penfield [7]. The location of electrodes which induced EMs was largely consistent within and across patients and no silent areas or other responses were found between EM sites. The interindividual variability, with respect to the extent of cortex from which EM could be elicited in our patients, has also been found for the skeletal motor cortex and is thought to be related to the variability of cortical folding patterns [18]. Differences in electrode positioning due to medical reasons also bias the number of electrodes covering the middle frontal gyrus and lead to a variable

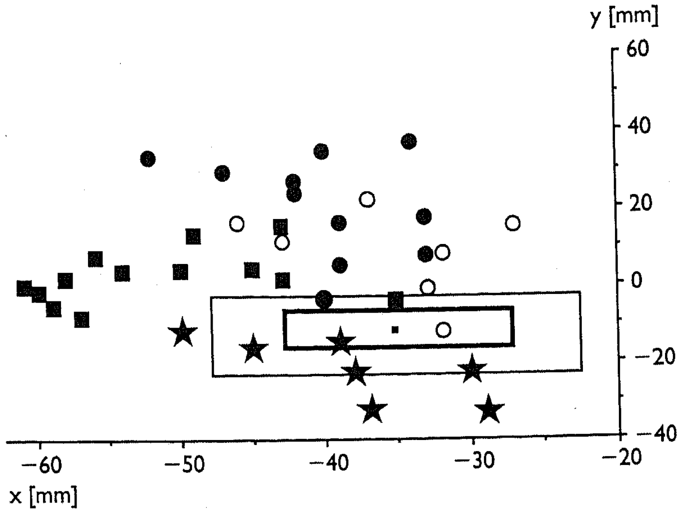

Fig. 4. Talaraich coordinates of electrodes which induced eye movements, skeletal movements and speech responses. The x-values (medial-lateral dimension) and y-values (anterior-posterior dimension) of the Talaraich coordinates of the electrodes which evoked oculomotor responses and other motor responses are drawn for patients NB and DK. Language responses are indicated by black circles, hand motor responses by black stars, face and mouth motor responses by black squares, oculomotor responses by white circles. The mean (small square), the standard deviation (thick lines) and the range of the location of the FEF (thin line) as proposed by neuroimaging studies [13] are shown. Note that in patients NB and DK only one EM-site can be found within the range of the FEF as found by neuroimaging studies. Of the other six electrodes located within this range four induced hand movements, one face movements and one speech arrest.

size of the EM region as determined by ECS. The functional localization of EM sites in our patients (Fig. 3a) is congruent with earlier ECS studies in man [7,8] and also very similar to microstimulation results in monkeys which obtained arm, hand and mouth movements posterior to the monkey FEF at the posterior bank of the arcuate sulcus [3].

The present results show that within this rather large oculomotor region, sites can be determined which are characterized by low thresholds, similar to those necessary to evoke skeletal motor responses [15], and by constant oculomotor responses evoked at and above the EM thresh-

Table 2. Talairach coordinates (x, y, z) of EM-sites. The Talairach coordinates and the respective evoked oculomotor response are given for all electrodes in the three patients in whom EMs could be induced.

Patient	Electrode	x	y	z	Oculomotor response
DK	C7	−30	19	47	Saccadic
DK	C8	−33	16	58	Saccadic
DK	D6	−50	15	40	Saccadic
DK	D7	−43	10	50	Saccadic, smooth
DK	D8	−36	7	55	Smooth
NB	A5	−34	20	45	Saccadic
NB	A6	−33	11	52	Saccadic
AM	C6	−49	−3	43	Saccadic
AM	C7	−44	−9	53	Saccadic
AM	C8	−29	−14	59	Saccadic
AM	D7	−45	−21	50	Saccadic
AM	D8	−37	−28	59	Saccadic
AM	E6	−51	−33	37	Saccadic
AM	E7	−46	−38	46	Saccadic, smooth
AM	E8	−36	−40	54	Smooth

old. These latter sites are localized at the posterior end of the middle frontal gyrus immediately anterior to the precentral sulcus and in proximity of the superior frontal sulcus: in the postero-mesial part of this large oculomotor region (Fig. 5). This anatomico-functional location of the EM sites is very similar to the location of the monkey FEF proposed by Robinson and Fuchs [2] presenting evidence in favor of a homologous representation of the FEF in monkey and man at the posterior part of Brodmann area 8 (Fig. 1a, Fig. 5). More precisely, the electrically defined human FEF might be confined to the posterior part of area 8A as defined recently [19] in man and monkey. Since Bruce *et al.* [3], based on microstimulation, have further limited the monkey FEF to a smaller and more posterior site at the anterior bank of the arcuate sulcus, it seems reasonable to suggest that the use of smaller electrode arrays and shorter stimulus trains might lead to an even more precise definition of the FEF in humans. It can be argued that our results cannot be applied to normal brain function since stimulations have been carried out in epileptic patients. However, the epileptic focus in all patients was found outside the FEF: in two patients outside the frontal lobe and in patient DK at mesial and more anterior prefrontal sites. Furthermore, the usual somatotopic mapping of motor and language functions in all patients does not suggest deviant brain pathology with respect to anatomical representations of cortical functions.

The location of the electrically defined human FEF is not in accordance with the localization of EM-related activation patterns in recent neuroimaging studies. These studies which used fMRI [9–11] and PET [12,13] have suggested a more posterior site on the precentral gyrus with only limited extensions onto the middle frontal gyrus. This area

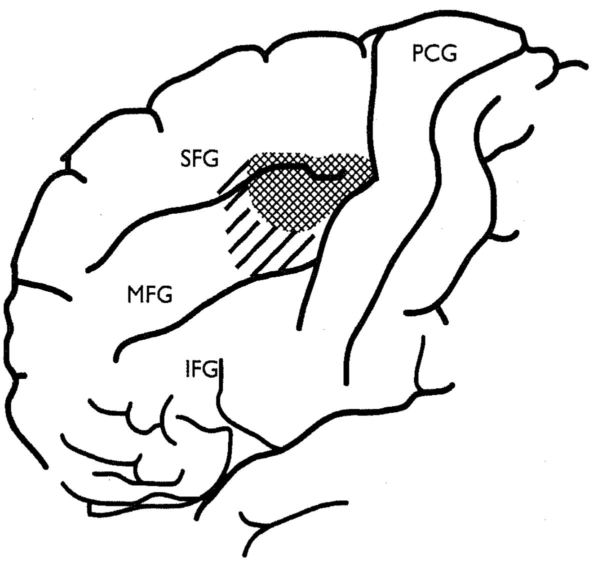

Fig. 5. Proposed location of the electrically defined human frontal eye field. The area represented by the diagonal lines and the checkerboard pattern indicates all sites in the present study from which eye movements could be induced. Within this oculomotor region, sites can be determined which are characterized by low thresholds and constant oculomotor responses (area indicated by the checkerboard pattern). These latter sites are localized at the posterior end of the middle frontal gyrus (MFG) immediately anterior to the precentral sulcus and in proximity to the superior frontal sulcus. This location is very similar to the location of the human FEF as proposed by Foerster [6]. IFG: inferior frontal gyrus, SFG: superior frontal gyrus, PCG: precentral gyrus.

is localized within the ventral premotor cortex in area 6. Several methodological differences might account for the anatomical divergence between neuroimaging and ECS studies. First during neuroimaging studies, subjects were engaged in bilateral and repetitive EMs which may lead to differences in location and strength of activation if compared with unilateral two-to-four step EMs as induced in our study or monkeys. Moreover, subjects were tracking a constantly moving visual stimulus or generating saccades towards repetitively jumping visual targets [9,10,12,13]. These visual targets activate visual and visuomovement neurons which have been defined in the FEF [17,20] but also in adjacent ventral premotor cortex [21]. Visual activity evoked during bilateral and repetitive EMs can thus be assumed to interfere with oculomotor activity in previous neuroimaging studies. A further issue concerns the subtractive nature of the latter studies, in which the amount of activation is relative and calculated between the task (i.e. visually guided EMs) and a comparison condition (i.e. visual fixation). As a result, a region which is involved in both conditions might be missed or shifted. It is therefore conceivable that the activation patterns on the precentral gyrus, as found in neuroimaging studies during bilateral and repetitive EMs, might not relate to the classical FEF. Instead, they may represent the human homologue of a premotor oculomotor region such as the recently described oculomotor region in area 6 posterior to the site of the classical FEF and distinct from it [5].

Finally our results show that saccades and smooth EMs can be elicited from distinct subregions with a small smooth EM region and a larger saccadic region. Smooth and saccadic EMs have also been observed by Godoy *et al.* [8], who induced saccades in the large majority of stimulations and smooth EMs in 10%. However, they did not report if the two EM types were induced within single patients and they did not compare the two EM types with respect to underlying anatomy. Recently, Petit *et al.* [9], using fMRI, found a small pursuit-related and a large saccade-related activation in the FEF and noted that the activity patterns for both eye movement types overlapped extensively. Based on our results we confirm that smooth EMs are localized in a smaller subregion of the FEF. However, we found stimulation-induced lateralized smooth EMs in the posterior and mesial portion of the FEF, rather than at its infero-lateral part as suggested by Petit *et al.* [9]. Our data are thus again in accordance if compared with the functional topography in the monkey FEF [22]. Stimulation-induced smooth-pursuit EMs in the monkey have been confined to the fundus at the posterior part of the arcuate sulcus and to the posterior bank of the arcuate sulcus [22] with saccades lateral and mesial from these former sites. Therefore, these data seem to suggest an anatomical homology between the superior part of the precentral sulcus and the posterior part of the superior frontal sulcus in man and the arcuate sulcus in monkey.

CONCLUSION

Based on the eye movement pattern induced at different currents by electrical stimulation of the human dorsal frontal cortex, we propose the location of the human FEF at the posterior end of the middle frontal gyrus immediately anterior to the precentral sulcus. This approach, which is similar to the technique used to determine the FEF in monkey, leads to a remarkably similar location in both species with respect to the underlying anatomy, neighboring function and internal oculomotor topography. These data suggest a homologous representation of the FEF in human and non-human primates in area 8.

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