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RESEARCH ARTICLE

Olaf Blanke · Margitta Seeck

Direction of saccadic and smooth eye movements induced by electrical stimulation of the human frontal eye field: effect of orbital position

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Abstract The present study reports on the direction of saccadic and smooth eye movements, which were induced electrically from the human dorsolateral frontal cortex including the human frontal eye field (FEF). The eye position prior to stimulation was varied in order to examine its effect on induced eye movement direction. The five patients of the study underwent invasive presurgical evaluation for pharmacoresistant epilepsy. The present data show that the direction of electrically induced eye movements was always contralateral and either horizontal or oblique upward if the eye started from the primary position. The elicited direction was changed if the eyes started from an eccentric position. The frequency of oblique eye movements was increased and oblique downward responses were induced, which were not observed if the eye started from the primary position. This was found for saccades and, especially, for smooth eye movements. Head movements, which were almost exclusively induced with saccades, did not depend on initial orbital position. Four conclusions can be drawn. Firstly, saccades and smooth eye movements induced from the human dorsolateral cortex including the human FEF have the same directional bias. Secondly, the frequent upward responses and the absence of downward responses induced from the primary position suggests either a more numerous or a more superficial representation of neurons that code for the former direction. Thirdly, at some sites the direction of saccades and smooth eye movements varies depending on the initial orbital position. Since these directional changes were observed without changes in eye-head coordination, our data suggest that stimulation of the FEF might evoke goal-directed saccades or interferes with a resettable saccade integrator. Fourthly, human studies that investigate eye movements induced from the lateral frontal cortex need to control eye position prior to stimulation.

Keywords Saccades · Smooth eye movements · Frontal eye field · Human · Electrical stimulation

O. Blanke (✉) · M. Seeck
Presurgical Epilepsy Unit, Department of Neurology,
University Hospital of Geneva,
24 rue Micheli-du-Crest, 1211 Geneva, Switzerland
e-mail: olaf.blanke@hcuge.ch
Tel.: +41-22-3728355
Fax: +41-22-3728358

Introduction

How is the direction of a saccade coded in one of the cortical key structures of oculomotor control, the frontal eye field (FEF)? Studies using functional magnetic resonance imaging (fMRI) (Darby et al. 1996; Petit et al. 1997; Corbetta et al. 1998; Luna et al. 1998) and electrical cortical stimulation (ECS) (Förster 1931, 1936; Rasmussen and Penfield 1948; Godoy et al. 1990; Blanke et al. 2000; Lobel et al. 2001), and the effects of focal lesions (Rivaud et al. 1994; Gaymard et al. 1999; Ploner et al. 1999) have demonstrated a prominent role of the FEF in the generation of fast and accurate contralateral saccades. However, the anatomical representation of saccade amplitude and especially saccade direction in the human FEF is not known and is largely based on extrapolation from monkey data.

In the monkey the FEF is classically defined by electrical microstimulation. It was found that the saccade amplitude is topographically coded, whereas the direction of the saccade has no global topography but rather a local organization with different directions coded at different tangential depths (Robinson and Fuchs 1969; Bruce et al. 1985). Electrical stimulation of the FEF and surrounding cortex has also been used in humans to examine the direction of electrically elicited eye movements (EMs) (Förster 1931, 1936; Rasmussen and Penfield 1948; Godoy et al. 1990; Lobel et al. 2001). This approach is similar to the one applied in monkeys, and all human studies agreed that electrically induced EMs are mainly contralateral as well as horizontal. However, with respect to oblique EMs, the results between the above-mentioned ECS studies differ substantially and complicate the investigation of the coding of EM direction in the human

FEF. Whereas Förster (1936) and Godoy et al. (1990) induced only contralateral oblique upward responses, Rasmussen and Penfield (1948) also induced contralateral downward responses and on a few occasions ipsilateral EMs. In a recent study, the vertical component of the EM was not analyzed and only contralateral EMs were observed (Lobel et al. 2001). However, for a number of reasons the comparison of the different human ECS studies proves difficult. Firstly, Rasmussen and Penfield (1948) did not distinguish between saccades and smooth EMs. Since it is known that in the monkey FEF both types of EMs can be induced and that they are characterized by different predominant directions (Robinson and Fuchs 1969; Bruce et al. 1985; Gottlieb et al. 1993, 1994), the differences in human studies might be related to varying degrees of saccades and smooth EMs included in the analysis. Secondly, whereas eye position was controlled in the monkey, the orbital position prior to ECS was not reported in human studies. Although it is known that the direction of an electrically induced EM from the FEF in the monkey is largely independent of the initial orbital position (vector-code; Robinson and Fuchs 1969; Bruce et al. 1985; see reviews by Schall 1998 and Tehovnik et al. 2000), this need not be the case for the human FEF (especially if eye and head position varies extensively from the primary position prior to stimulation). Thirdly, intra-operative ECS is carried out under important time constraints, which allows neither precise observation of the induced oculomotor behavior nor stimulation of a given site repeatedly.

Here, we investigated the direction of EMs outside the operational unit by ECS of the human FEF and surrounding cortex in five fully awake patients undergoing presurgical epilepsy evaluation. The direction of EMs was assessed with the eyes either in the primary position or in an eccentric orbital position, while the head was always in the primary position. This was done with three questions in mind. Firstly, to examine the effect of the initial orbital position on the direction of the electrically induced EM. Secondly, to investigate whether saccadic and smooth EMs are characterized by different directional biases as suggested for the monkey. Thirdly, to determine if head movements can be induced with saccades and smooth EMs, and if the induction of a combined eye-head movement depends on the initial orbital position. A brief report of these results have appeared previously (Blanke et al. 1999).

Materials and methods

Patients

The five patients of the study suffered from drug-resistant epilepsy and underwent presurgical epilepsy evaluation. For clinical details of the patients please refer to Table 1. Subdural grid electrodes were implanted as part of diagnostic investigations. These were 3-mm diameter stainless steel electrodes with a center-to-center distance of 0.8 cm. Subdural grid electrodes were magnetic resonance imaging (MRI) compatible and were embedded in a clear silastic sheet (Ad-Tech Corp., Racine, WI, USA). Electrode location was determined by 3D-MRI of each patient's individual brain with the implanted electrodes as described previously (Blanke et al. 2000). Thus, in each patient, precise anatomical localization was possible, whereas in other recent studies the electrode position was determined by functional localization (Godoy et al. 1990), by visual inspection during the neurosurgical operation (Förster 1936; Rasmussen and Penfield 1948), or by extrapolation from stereotactic images to the proportional atlas of Talraich and Tournoux (Lobel et al. 2001). In the present study, a total of 88–102 electrodes were placed over the lateral and mesial surface of one hemisphere (left hemisphere n=4, right hemisphere n=1). ECS was performed with a Grass Stimulator S12 (Grass Instruments, Quincy, MA, USA) in order to localize the epileptic focus, primary motor and somatosensory cortex as well as cortical language centers (Lesser et al. 1987; Ojeman et al. 1993; Blanke et al. 2000). Stimulations were 0.3-ms alternating polarity square-wave stimuli that were delivered at a repetition rate of 50 Hz, in conformity with Lesser et al. (1987). Trains of stimulation were of 2-s duration, and thus shorter than previously used stimulation trains (5 or 10 s: Godoy et al. 1990; Lobel et al. 2001). Short stimulation trains are important, since longer ones make current spread more likely and change eye movement parameters, as was shown in the monkey (Robinson and Fuchs 1969). At each electrode site, ECS was started with an amplitude of 0.5 mA and incremented in 0.5-mA steps until a response, sensory or motor, was obtained. The oculomotor threshold (minimal current amplitude to induce an EM) for saccades and smooth eye movements was variable (range 1.5–8.5 mA, mean in condition 1 5.7 mA; see Experimental paradigms section) and somewhat larger than reported by Lobel et al. (2001; 0.5–3.0 mA, mean 1.9 mA). Yet, since latter authors used smaller electrodes (0.8×2.0 mm) than those of the present study

Table 1 Clinical characteristics of patients. Age, sex, handedness, magnetic resonance imaging (MRI) and electroencephalography (EEG) results are shown

Patient	Age (years)	Sex	Handedness	MRI abnormality	EEG localization (ictal)
DK	18	Female	Right	Normal	Left mesial and lateral prefrontal region
AM	27	Female	Ambidextrous	Atrophy of left cerebral hemisphere, left hippocampal dysplasia, aplasia of splenium	Left temporal region and left hippocampus
NB	43	Female	Right (ambidextrous)	Atrophy of frontal insula	Left occipito-temporal region
FM	43	Female	Right	Normal	Right anterior temporal region
CR	41	Female	Left	Normal	Left basal temporal and temporo-parietal region

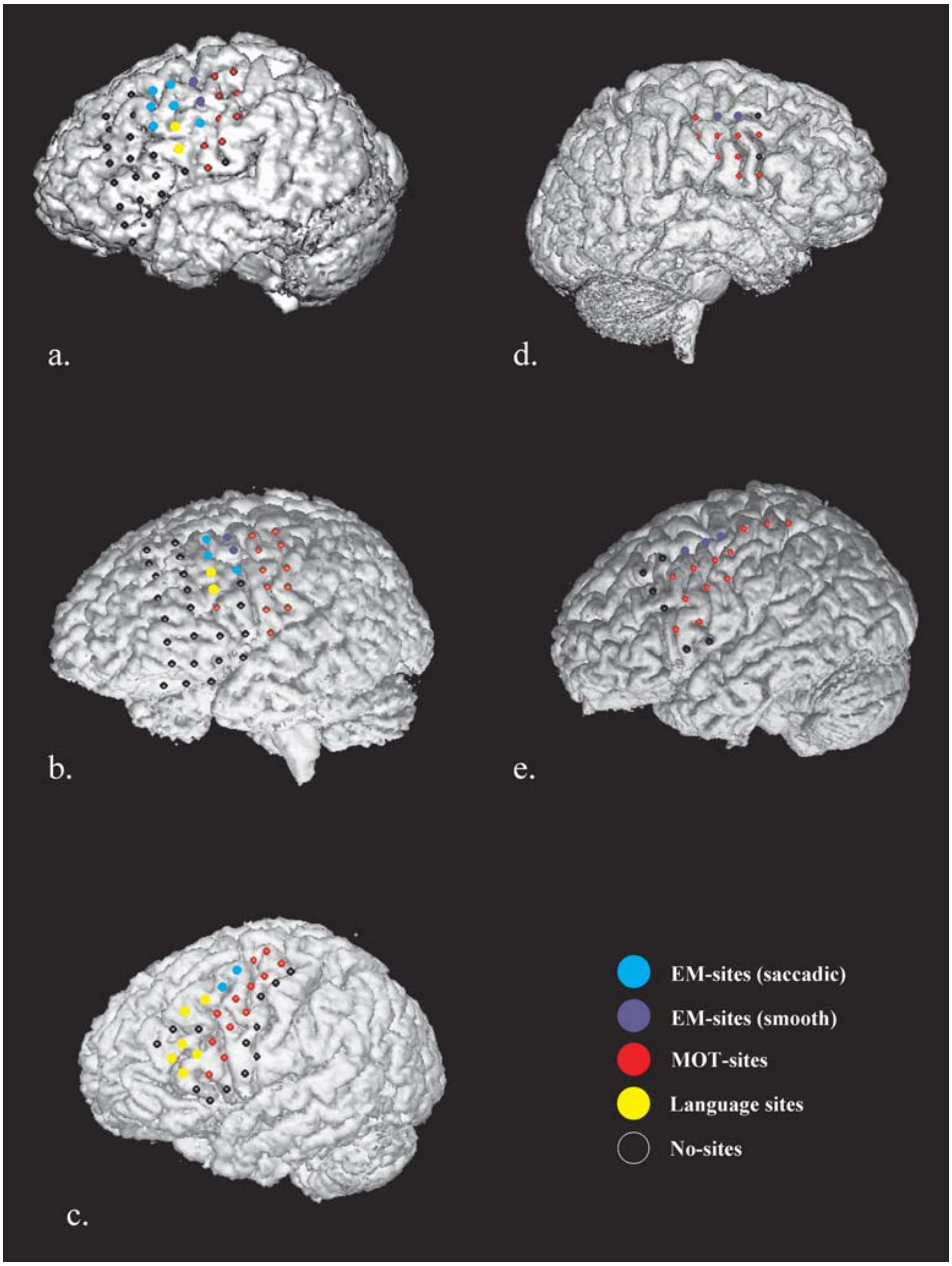

Fig. 1 Anatomical location of all frontal electrodes in the five patients. The 20 electrodes whose stimulation resulted in eye movements (EM-sites) are depicted in *blue* (smooth EMs) and *turquoise* (saccades). Electrodes where skeletal motor responses (MOT-sites, *red dots*) and language responses (*yellow dots*) were obtained are also shown. Since bipolar stimulations were carried out, electrical cortical stimulation (ECS) of a given electrode might lead to different responses with its two adjacent electrodes. The 20 electrodes whose stimulation led to EMs were thus determined by ECS at 12 bipolar stimulation sites and are indicated: five in patient AM (**a**), three in patient DK (**b**), one in patient NB (**c**), one in patient FM (**d**), and two in patient CR (**e**). Only frontal electrodes are shown. Electrodes indicated in *black* did not induced any overt responses

(3.0×3.0 mm), the induced cortical current densities (Nathan et al. 1993) were actually smaller in the present study (1.2 mA/cm^2 in Lobel et al. 2001; 0.6 mA/cm^2 in the present study). During the stimulation procedure, the patients were sitting comfortably in bed, with head unrestrained. At 20 electrodes (12 bipolar stimulation sites) in the dorsolateral frontal cortex, ECS resulted in contralateral stimulation-induced EMs (EM-sites, indicated by *turquoise* and *blue dots* in Fig. 1). These 12 EM-sites on the posterior part of the middle frontal gyrus were found anterior or dorsal to electrodes whose stimulation resulted in contralateral motor responses of the face, mouth or hand as described previously (Godoy et al. 1990; Blanke et al. 2000). The anatomical location of skeletal motor sites (*red dots*) and language sites (*yellow dots*) is shown in Fig. 1. At seven sites, saccades were induced (saccade sites, *turquoise*), and at five sites smooth EMs were induced (smooth EM-sites, *blue*, see Fig. 1).

Experimental paradigms

The influence of the initial orbital position on the direction of EMs was investigated in two experimental conditions. Patients were instructed to fixate the fingertip of one of the investigators at the beginning of all trials. Head position stayed constant during all trials and was central. In condition 1 (C1), ECS was applied while the patient fixated the fingertip at the primary position (no horizontal or vertical eye deviation; Fig. 2). In condition 2 (C2), ECS was applied while the patient fixed a peripheral position (see Fig. 2). Three eccentric eye positions were tested: (1) the patients' eyes were directed contralateral to the EM-direction induced by ECS in C1 at a horizontal eccentricity of ≈30° (no vertical deviation), (2) the patients' eyes were elevated ≈20° (no horizontal deviation), and (3) the patients' eyes were depressed ≈20° (no horizontal deviation). An identical fixation target (fingertip) was

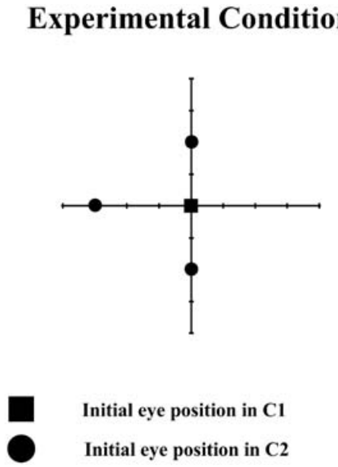

Fig. 2 Experimental paradigms. The influence of the initial orbital position on the direction of the eye movements induced by electrical cortical stimulation (ECS) was investigated in two experimental conditions. Fixation points were always given by the fingertip of one of the experimenters positioned at different locations. In condition 1 (C1), ECS was applied while the patient fixated the fingertip at the primary orbital position (*square*). For condition 2 (C2) the varying fixation points are indicated by *circles*. Three eccentric positions were tested. (1) the patients' eyes were directed contralateral to the EM-direction induced by ECS in C1 at a horizontal eccentricity of ≈30° (no vertical deviation). (2) The patients' eyes were elevated ≈20° (no horizontal deviation) or (3) depressed ≈20° (no horizontal deviation). Head position stayed constant during all trials and was central. Positive values on the *x*-axis indicate contralateral eye positions and negative values ipsilateral ones. Positive values on the ordinate depict eye positions above and negative values orbital positions below the horizontal meridian

presented during all trials since it is known that the current threshold as well as the metrics of induced EMs depend on the behavioral state of the subject (Goldberg et al. 1986).

EM recording and analysis

EMs were recorded by videography (S-VHS) which allowed offline analysis. The temporal resolution of the videotape was low (20 Hz) and did not allow quantification of EM amplitude. Because of patient comfort considerations and time limitations during the stimulation procedure we did not quantify EMs by electro-oculography or infrared-oculography. However, direct visual inspection during ECS and offline analysis (in slow-motion, time-frame by time-frame) permitted us to distinguish saccades from smooth EMs as described previously (Blanke et al. 2000), and to determine their principal direction. Saccades were discontinuous rapid single-step or multi-step eye deviations. In the case of multi-step saccades, fixation periods of generally three time-frames (150 ms) were noted between the saccade steps. A smooth non-saccadic EM response was noted if a continuous eye deviation that was not separated by fixation periods >50 ms was encountered. In contrast to saccades, smooth EMs always lasted for the whole period of stimulation. However, based on the low temporal resolution, we cannot exclude the possibility that EMs classified as smooth EMs actually consisted of many small amplitude multi-step saccades. The principal direction of the first electrically induced EM (in the case of a multi-step EM) was determined and classified into the following groups: contralateral or ipsilateral; horizontal, vertical, oblique upward, or oblique downward. We also determined the presence of a head movement (HM) and its direction (contralateral–ipsilateral). Finally, we determined whether the HM was encountered before, during or after the EM onset.

Results

EMs were induced in a total of 84 stimulation trials. Six trials were excluded from analysis because the eye position prior to ECS could not be determined clearly on video recordings. All EMs evoked during the stimulation were conjugate and directed contralaterally. In agreement with Godoy et al. (1990), no skeletal or language responses were induced at the EM-sites. [In comparison, in five of the eight patients of Lobel et al. (2001), ECS at EM-sites not only induced eye-head movements, but also contralateral hand motor responses and language responses suggesting current spread to adjacent cortical areas or pathways.] In the present study, pure eye movements, only rarely accompanied by a head movement, were induced in each of the five subjects. Of all EMs, 58% were horizontal, the remainder being oblique (29% oblique upward and 13% oblique downward). No electrically induced EM was purely vertical. Forty-four trials (mean of 3.7 trials per site, range 2–7) were carried out in C1 and 34 trials in C2 (mean of 2.8 trials per site, range 1–4). Mean current amplitudes applied in each condition did not differ, and were 5.7 mA (±1.9) in C1 and 6.0 mA (±2.2) in C2 (SD in parenthesis). In the following, the results will be described for saccades and smooth EMs separately.

Saccadic eye movements

Saccades were induced at 7 bipolar stimulation sites in three patients. All saccades evoked during the stimulation were conjugate and directed contralaterally. Of the 43 trials that induced saccadic EMs, the large majority of responses was horizontal (66%); 34% were oblique, with 26% going up and 8% directed downward (Fig. 3, *left column*).

From the primary position (C1), saccades were induced in 27 trials. Evoked saccade direction remained constant at each tested site. At five of seven saccade sites only horizontal saccades were obtained, and at two sites responses were oblique upward. Of all electrically induced saccades in C1, 71% were purely horizontal, and the remaining saccadic responses were oblique upward (Fig. 3, *middle column*). No evoked saccade in C1 was purely vertical or oblique downward.

In C2 saccades were induced in 16 trials. Oblique responses were more frequent than in C1, and were found in half of the trials. Moreover, oblique down responses — not found in C1 — were induced as often as oblique upward saccades (25%, see Fig. 3, *right column*). The analysis for each saccade site shows that at three of the seven sites only horizontal responses and at one only oblique responses were induced. At these four sites, the induced responses were the same as in C1. At the three

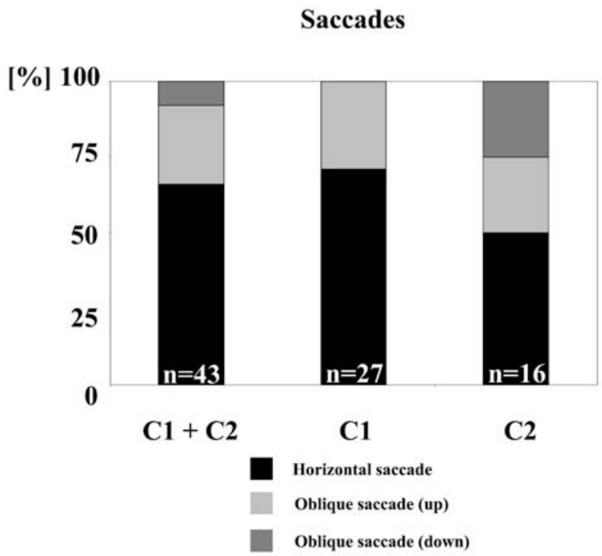

Fig. 3 Saccade directions induced by electrical cortical stimulation in conditions C1 and C2 for all saccade sites. The distribution of directional responses is shown for the total of 43 trials that induced saccades (*left column*), for the trials in C1 (*middle column*) and for those in C2 (*right column*). The percentage of horizontal responses is depicted in *black*, oblique upward responses in *light grey* and oblique downward saccades in *dark grey*. Note that in C1 only horizontal and oblique upward saccades are induced. In C2 oblique responses are more frequent (50%) and downward responses were as often as upward responses

remaining sites (Fig. 4), a change in evoked direction as an effect of orbital position was observed. This change was induced if the eyes were deviated along the vertical axis. A description of the induced responses at these three sites is given below. At one site (Fig. 4, *left*), oblique downward saccades were induced if the eye was elevated prior to stimulation, and an oblique upward movement was induced if the eyes were depressed. A purely horizontal saccade was noted if the eye started from an eccentric horizontal position. At another site (Fig. 4, *middle*), identical responses were obtained (although induced EM direction was not tested from the depressed position). At the remaining saccade site (Fig. 4, *right*), ECS induced oblique upward saccades if the eye started from the primary position or the eccentric horizontal position. If the eyes were elevated, horizontal saccades resulted. Note that the eye direction at these three sites only changed if the eye is deviated along the vertical axis, never if the eye is deviated horizontally (as at the remaining four saccade sites where vertical starting positions were not tested).

Smooth eye movements

Smooth EMs were induced in 35 trials at five sites in four patients. As with saccades, all induced smooth EMs were conjugate and directed contralaterally. Of the 35 trials that induced smooth EMs (in C1 and C2), 51% were horizontal and 49% oblique (31% up, and 17% down; see Fig. 5, *left column*).

Smooth EM direction induced from the primary position (C1) was investigated in 17 trials. In this condition, evoked direction stayed constant at all tested sites (at four of five smooth EM sites only horizontal responses were obtained, and at one site only oblique upward smooth EMs were evoked). Of all electrically induced smooth EMs in C1, 76% were purely horizontal, and the remaining responses were oblique upward (Fig. 5, *middle column*). No evoked smooth EM in C1 was purely vertical or oblique downward.

Of the 18 trials that were carried out in C2, only few smooth EMs were purely horizontal (28%), with most responses being oblique (72%, Fig. 5, *right column*). Again, as for saccades, oblique smooth EM responses

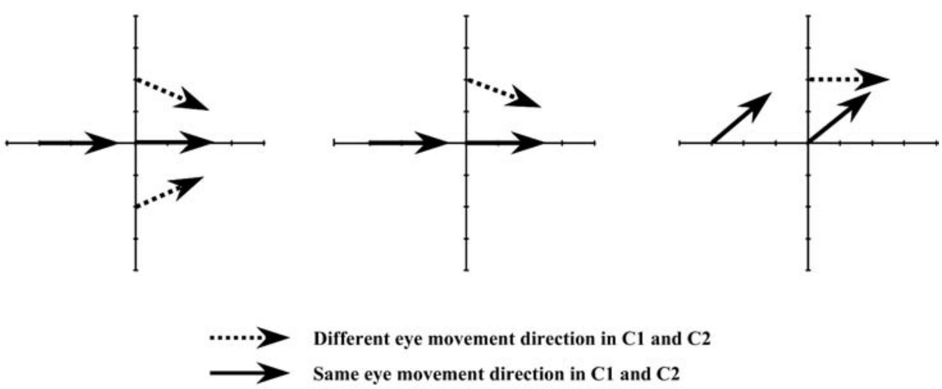

Fig. 4 Saccade directions induced by electrical cortical stimulation in conditions C1 and C2 for single saccade sites. Eye movement sites (EM-sites) are shown where the induced saccade direction varied depending on the initial orbital position. Each panel shows responses obtained at a single EM-site. The *left diagram* shows that the evoked saccades converge onto a point in the orbit: in C1, a horizontal saccade results. If the eyes are elevated an oblique downward saccade results (*dashed downward arrow*) and if the eyes are depressed an oblique upward eye movement results (*dashed upward arrow*). The *middle diagram* shows a different site with similar responses, but only the vertically elevated starting position was tested. The *right diagram* shows a saccade site where oblique upward saccades were encountered in C1 and in C2 if the eyes were deviated horizontally. If the eyes were elevated the direction was horizontal

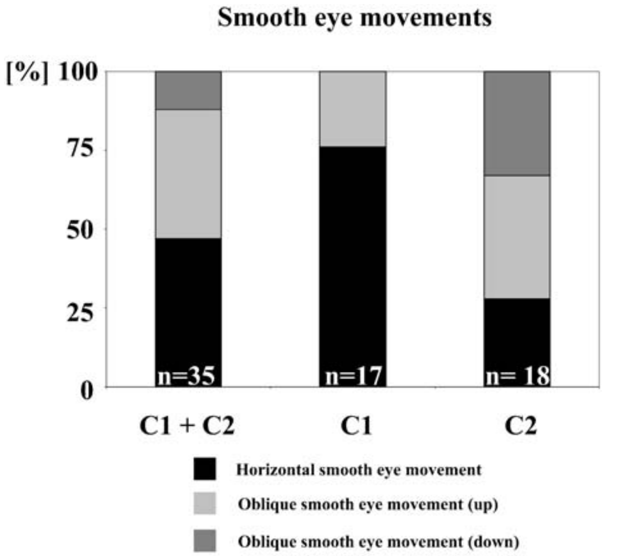

Fig. 5 Smooth eye movement (EM) directions induced by electrical cortical stimulation in conditions C1 and C2 for the smooth EM-sites. The distribution of directional responses is shown for the total of 35 trials that induced smooth eye movements (*left column*), the trials in C1 (*middle column*) and in C2 (*right column*). The percentage of horizontal responses is depicted in *black*, oblique upward responses in *light grey* and oblique downward responses in *dark grey*. Note that in C1 only horizontal and oblique upward saccades are induced. In C2 oblique responses are much more frequent (72%) and often downward

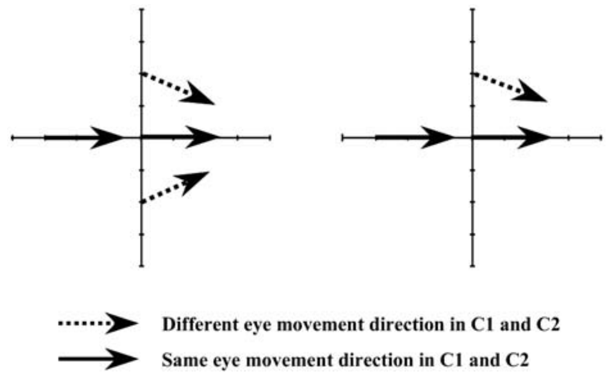

Fig. 6 Direction of smooth eye movements (EMs) induced from the primary position (C1) and eccentric positions (C2). The responses obtained at sites where the induced direction of the smooth EM depended on the initial orbital position prior to electrical cortical stimulation (ECS) are depicted. EM direction and position is indicated as in Fig. 4. If the eyes were elevated an oblique downward movement resulted (*dashed downward arrow*) and if starting from the vertical down position an oblique upward movement resulted (*dashed upward arrow*). If the eyes started in the primary position and if deviated horizontally, a purely horizontal smooth EM was obtained at both sites. This was found at three of four smooth EM-sites (*left diagram*). At the remaining site (*right diagram*), responses were identical, but EM direction was not tested with the eyes depressed prior to ECS

were either upward (39%) or downward (33%) depending on the initial orbital position. A change in induced EM direction was found at four of five smooth EM-sites. At the remaining site only oblique upward smooth EMs were evoked in either condition. At the four other smooth EM-sites, ECS in C1 led only to horizontal smooth EMs (Fig. 6). In C2, induced direction was found to depend on the initial orbital position: if the eyes were in the central up position, oblique downward smooth EMs occurred, and if the eyes were in the central down position an oblique upward EM occurred (Fig. 6). Pure horizontal deviation into the ipsilateral space did not alter the EM direction, and led to a horizontal smooth EM.

Head movements

Head movements (HMs) were induced in three patients in 22 trials (28% of all trials that induced EMs) at 42% of the EM-sites. HMs were never evoked alone but were always associated with EMs. This is concordant with the data reported by Godoy et al. (1990), who induced HMs at 58% of the EM-sites. However, the latter authors did not analyze eye–head association separately for saccade and smooth EM-sites. For this reason it is not known whether HMs can be induced only with saccades, only with smooth EMs, or with both. The present data show that 95% of all HMs were induced at saccade sites (at four of seven saccade sites). The threshold to induce an HM was identical to or higher than the saccade threshold. The direction of the HM was always contralateral and never preceded saccade onset. At three of four saccade sites, the HM even followed the onset of the last saccade within the saccade sequence. (At the remaining saccade site, the HM occurred after the first saccade.) No difference in the incidence of head movements in C1 and C2 was observed. Furthermore, in both conditions approximately half of the saccade responses were accompanied by a HM (40% of the trials in C1, and 50% in C2). At two of the three EM-sites, where saccade direction was found to depend on the orbital position, combined eye-head movements were present in C1 and C2. At the remaining site no HMs were observed in either conditions. At the five smooth EM-sites, only one trial (in C2) induced a combined eye-head movement. Thus, combined eye-head movements are extremely rare at smooth EM-sites and may only be induced from eccentric starting positions.

Discussion

The present results confirm that the direction of saccades and smooth EMs induced electrically from the human dorsolateral frontal cortex, including the FEF, may be horizontal, oblique up or oblique down. No induced response was purely vertical or ipsilateral. Horizontal responses were most frequent (61%), as was found by Rasmussen and Penfield (1948) (64%), by Godoy et al. (1990) (79%) and by Förster (1936). The present data show that oblique responses are more often induced from vertical eccentric orbital positions than from the primary position or from horizontal eccentric orbital positions. Concerning oblique responses, the present data also confirm the finding of Rasmussen and Penfield (1948) that oblique downward EMs can also be induced (not found by Förster or by Godoy and co-workers). However, we show that oblique downward responses can only be induced if the eyes start from a vertical eccentric position. Downward EMs were neither found from the primary position nor from horizontal eccentric positions. Since this was the case for saccades and smooth EMs, the present data suggest that the oblique downward responses observed by Rasmussen and Penfield (1948) during intraoperative ECS might be related to vertical variations of the initial orbital position instead of the frequent induction of smooth EMs.

Since humans normally rely on a combined eye-head movement to look from one point of interest to another (Gresty 1974; Barnes 1979; Zangemeister and Stark 1982), we conjectured that different orbital starting points might alter the association of eye and head movements, and thereby the direction of the induced EM. This has recently been suggested to be the case in the monkey for stimulation-induced gaze shifts in an oculomotor structure closely connected to the FEF — the superior colliculus (Freedman et al. 1996). These investigators showed that ECS at certain sites does not produce fixed vector saccades, but rather "gaze shifts of similar directions and amplitudes which can be accomplished with many combinations of eye and head components, depending on the initial positions of the eyes in the orbits" (Freedman et al. 1996). However, the present analysis only found changes in EM direction, and did not reveal any influence of the initial orbital position on the occurrence, onset and direction of accompanying HMs. Yet, since gaze shifts induced by ECS from the FEF have not yet been investigated systematically in the head-free monkey, it is not known if more subtle changes in eye–head coordination that were not detected in the present study might be found in monkey.

Even though the clinical situation did not allow for more numerous repetitions in each condition, our findings show that it is fundamental to control the position of the eyes and the head prior to stimulation. Moreover, they demonstrate that saccades and smooth EMs need to be analyzed separately before we can speculate about the coding of EM metrics in the human FEF and surrounding cortex based on the direction of electrically induced EMs. It can be argued that the present results cannot be applied to normal brain function since ECS has been carried out in epileptic patients. However, the epileptic focus in all patients was found outside the FEF (Table 1): in four patients it was outside the frontal lobe, and in patient DK the focus was at more 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 sensorimotor functions. In the following, the present results for the direction of stimulation-induced saccades and smooth EMs are discussed with respect to their anatomical origin and the coding of EMs in the primate FEF and surrounding cortex.

Eye movements induced from the primary position

Concerning electrically induced saccades, the preponderance of purely horizontal responses can be explained by the representation of saccade metrics in the primate FEF (Robinson and Fuchs 1969; Bruce et al. 1985). While the amplitude of a saccade is topographically coded in the FEF, its direction has no global topography but a local organization with different directions coded at different tangential depths. Since ECS in the present study activates a large pool of neurons (which code overall contralateral directions), upward and downward components may cancel each other out, resulting in mainly horizontal saccades (Bruce 1990). Robinson and Fuchs (1969) examined the effect of longer stimulus durations on the induced EM direction during microstimulation in the monkey FEF (comparable to stimulus durations used in our study), and indeed found a tendency toward more horizontal saccades with longer stimulus trains. The predominance of horizontal saccades in our study might thus be explained by long stimulus trains and the activation of a large pool of saccade neurons. A preponderance of oblique upward saccades as found in our and other human studies, however, has not been observed in the monkey FEF. Three explanations are suggested. Firstly, the vertical upward bias might be related to a more superficial representation of saccade neurons in the FEF, which code for upward directions since ECS is applied on the cortical surface and might interfere mainly with superficial neurons. Secondly, neurons with a directional upward preference might be more numerous than neurons coding for downward saccades. Thirdly, thresholds of neurons coding for upward saccades might have lower saccade thresholds than neurons coding for the downward direction.

With respect to the direction of smooth EMs, stimulation of the macaque FEF results mainly in ipsilateral smooth EMs, and only in 30% of cases are they contralateral (MacAvoy et al. 1991; Gottlieb et al. 1993). Moreover, damage to the human FEF and surrounding cortex leads mainly to deficits for ipsilateral smooth EMs, although contralateral smooth EMs are also impaired (Rivaud et al. 1994; Gaymard and Pierrot-Deseilligny 1999). Based on these animal electrophysiological data and human lesion data, it might be speculated that ECS of the human FEF should mainly lead to ipsilateral smooth EMs. Yet this was not the case as only contralateral smooth EMs were observed by Godoy et al. (1990) and in the present study. However, the direction of smooth EMs is topographically organized in the monkey FEF, with ipsilateral EMs at the fundus of the arcuate sulcus and contralateral EMs at the adjacent, more superficial, posterior bank. In man, cortex buried in the sulci around the FEF (i.e. precentral and superior frontal sulcus) cannot be directly stimulated via subdural electrodes, which might thus explain the absence of ipsilateral responses in our patients. Rasmussen and Penfield (1948), who applied electrical currents by intraoperative stimulation (using small platinum wires with two carbon ball tips, which were 2–3 mm apart), could directly stimulate deeper parts of the FEF and rarely evoked ipsilateral EMs. The presence of only contralateral responses in the present study, which were induced at the posterior part of the EM-region, suggests that the observed responses might have resulted from ECS of the human homologue of the posterior bank of the arcuate sulcus (Gottlieb et al. 1993). As for saccades, the direction of electrically induced smooth EMs shows a preponderance for horizontal and oblique upward directions, which was not found in the macaque using microstimulation and single unit recordings (MacAvoy et al. 1991; Gottlieb et al. 1993, 1994). Again, the predominance of horizontal smooth EMs might be explained by the activation of a large pool of neurons with upward and downward components canceling each other out. The bias in favor of oblique upward responses might also be related to a more superficial, or more numerous representation of the oblique upward direction, or lower neuronal thresholds for upward smooth EMs in the human FEF.

Eye movements induced from eccentric positions

The present results show that the orbital position prior to stimulation onset influences the trajectory of saccadic EMs. Whereas induced EM direction was independent of different horizontal orbital positions, the elicited direction always changed if the eyes were elevated or depressed prior to stimulation. This led to the induction of frequent downward saccades, which were not observed from the primary position. Directional changes were approximately as large as 60° (between both eccentric vertical starting positions). As stated above, we cannot exclude the possibility that more subtle changes in eye–head coordination, which depend on the initial orbital position, might account for these changes in EM direction (see Freedman et al. 1996). Yet the present data are reminiscent of the directional changes in the monkey reported by Robinson and Fuchs (1969), who noted changes of the direction of saccades of up to 15° downward if the eyes were elevated, and 15° upward if the eyes were depressed prior to stimulation. The present changes were even somewhat larger and might therefore be compared to findings of Schlag and collegues (Schlag and Schlag-Rey 1987; 1990; Dassonville et al. 1992), who showed that the trajectory of saccades induced by microstimulation of the supplementary eye field and the frontal eye field can be changed systematically if stimulation is applied during or immediately after spontaneous saccades. These changes led the authors to suggest that saccades in these structures are coded in a goal-directed fashion. Others have proposed that the directional saccade changes induced by microstimulation during and especially after a saccade are rather explained by an interference with a central structure that integrates velocity signals prior to its effects on oculomotor neurons (resettable integrator) (Jürgens et al. 1981; Robinson 1975; but see Kustov and Robinson 1995; Nichols and Sparks 1995). However, for the demonstration of goal-directed saccades or the interference with the resettable integrator, not only the direction of saccades but also their amplitude needs to be analyzed. Based on the present results, it can thus not be decided which of these two mechanisms accounted for the observed directional changes. We do not think that the changes in induced EM direction in the present study are related to mechanical factors influencing the flight of the eyes at eccentric orbital positions. (Starting positions in C2 were situated close to the ocular motility range). Whereas the observed change at one site might have been related to the latter mechanisms (see Fig. 4, *right*), the directional changes at the other sites cannot be explained by the that mechanism.

The present study also shows that the direction of electrically induced smooth EMs depends on the initial orbital position. This has also been found in the monkey FEF and Gottlieb et al. (1993) reported that smooth EMs induced from the posterior bank of the arcuate sulcus — but not for sites buried on the arcuate fundus — were goal-directed. These authors thus suggested the presence of two functional areas within the smooth EM-region of the FEF: contralateral goal-directed smooth EMs were represented at the posterior bank of the arcuate sulcus, and ipsilateral vector-coded smooth EMs at the arcuate fundus. Both the influence of the orbital position on the EM-direction as well as the preponderance of contralateral horizontal smooth EMs, suggest that the smooth EMs in the present study resulted from electrical interference with the human homologue of the posterior bank of the arcuate sulcus (Gottlieb et al. 1993). However, to confirm the presence of goal-oriented coding in the human FEF future studies are needed that use more numerous eccentric orbital starting positions, that apply ECS during or immediately after spontaneous EMs, and that record eye movements quantitatively.

Anatomical considerations

There is a debate regarding the exact location of the human FEF. Studies using functional magnetic resonance imaging (fMRI) (Darby et al. 1996; Petit et al. 1997; Luna et al. 1998; but see reviews Paus 1996; Schall 1998; Petit et al. 1999; Tehovnik et al. 2000) and human lesions studies (Rivaud et al. 1994; Gaymard et al. 1999; Ploner et al. 1999) have situated the FEF along the precentral sulcus extending onto the precentral gyrus. A different site anterior to the precentral sulcus on the posterior part of the middle frontal gyrus has been proposed from studies using ECS (Förster 1931, 1936; Rasmussen and Penfield 1948; Godoy et al. 1990; Blanke et al. 2000) and from a study using transcranial magnetic stimulation combined with 3D-MRI (Ro et al. 1999). Lobel et al. (2001) localized the stimulation-defined FEF slightly more posterior and deeper (within the precentral sulcus) than previous stimulation studies, and thus closer to the site as proposed by fMRI. Yet in 75% of the subjects investigated by Lobel et al. the stereotactic coordinates of the stimulation-defined FEF was still found anterior to the range of the FEF as defined by 17 fMRI studies (see Petit et al. 1999; Blanke et al. 2000). At present, it can thus not be decided whether this anatomical disagreement between studies using fMRI and ECS or transcranial magnetic stimulation might be due to methodological differences inherent in the two brain mapping techniques or to differences in examined oculomotor behavior as discussed previously (Luna et al. 1998; Blanke et al. 2000; Tehovnik et al. 2000; Disbrow et al. 2000). Given the cortical extent of the EM-sites, it is thus not very likely that all induced EMs in the present study resulted from electrical interference with the human FEF, especially since current spread to adjacent functional areas and underlying white matter cannot be excluded by existing techniques of intracranial stimulation (Förster 1936; Rasmussen and Penfield 1948; Godoy et al. 1990; Blanke et al. 2000; Lobel et al. 2001). Whereas, the associated contralateral hand motor responses reported by Lobel et al. (2001) suggest posterior or subcortical current spread to the hand motor cortex in most of their subjects, it might be suggested that the more anterior EM responses as observed by Förster (1936), Rasmussen and Penfield (1948), Godoy et al. (1990), and in the present study reflect an interference with more rostral brain regions anterior to the FEF (or with subcortical pathways). Based on electrophysiological criteria and analysis of the induced oculomotor response, Blanke et al. (2000) have proposed a more restricted location of the FEF (compared to previous studies using ECS), namely at the middle frontal gyrus immediately anterior to the precentral sulcus. This stereotactic location — including the fundus of the precentral sulcus and the posterior end of the superior frontal sulcus — is concordant with the FEF location proposed by Lobel and colleagues. At more anterior sites on the middle frontal gyrus, the currents needed to induce an oculomotor response were found to be higher by Blanke et al. (2000), suggesting that these EM-sites might represent the human homologue of the macaque cortex extending from the anterior bank of the arcuate sulcus to the posterior banks of the principal sulcus. Whereas Bruce et al. (1985) did not include this latter area into the FEF as defined by microstimulation, it was included by Robinson and Fuchs (1969), who used higher currents between 0.1 and 0.5 mA to induce EMs. Most importantly for the present study, the latter authors did not observe differences in saccade metrics between both areas, although they remarked that higher currents were needed to induce saccades at more anterior sites and at sites close to the principal sulcus. Boch and Goldberg (1989) have confirmed the implication of this more anterior region in saccade-related processing, and that higher currents are needed to induce EMs. Given the similarities between these two functional oculomotor areas in the monkey and the similar responses found in the present study at all EM-sites, the obtained responses were discussed together.

Conclusion

The present data suggest that the human dorsolateral cortex including the FEF has a more numerous and/or a more superficial representation of neurons, which code for EMs directed in the contralateral and upward direction. The finding that the direction of saccades was dependent on the initial orbital position suggests either goal-directed coding or interference with the resettable saccade integrator. Head movements were only observed in combination with saccades, and did not depend on the initial orbital position suggesting that the observed directional saccade changes were not due to changes in eye-head gaze movements.

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