

# Upward gaze and head deviation with frontal eye field stimulation

Kitti Kaiboriboon<sup>1</sup>, Hans O Lüders<sup>1</sup>, Jonathan P Miller<sup>2</sup>, R John Leigh<sup>3</sup>

<sup>1</sup> Epilepsy Center, Department of Neurology, University Hospitals Case Medical Center

<sup>2</sup> Department of Neurological Surgery, University Hospitals Case Medical Center

<sup>3</sup> Daroff-Dell'Osso Ocular Motility Laboratory, Louis Stokes Department of Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, Ohio

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**ABSTRACT** – Using electrical stimulation to the deep, most caudal part of the right frontal eye field (FEF), we demonstrate a novel pattern of vertical (upward) eye movement that was previously only thought possible by stimulating both frontal eye fields simultaneously. If stimulation was started when the subject looked laterally, the initial eye movement was back to the midline, followed by upward deviation. Our finding challenges current view of topological organisation in the human FEF and may have general implications for concepts of topological organisation of the motor cortex, since sustained stimulation also induced upward head movements as a component of the vertical gaze shift. [*Published with video sequences*]

**Key words:** brain mapping, eye movement, frontal eye field

Recent cortical stimulation (Blanke *et al.*, 2000; Thurtell *et al.*, 2009) and functional neuroimaging studies (Rosano *et al.*, 2002; Amiez and Petrides, 2009) indicate that the human frontal eye field (FEF) is located in the middle frontal gyrus, just below the intersection of the precentral sulcus and the superior frontal sulcus. Although it has long been known that the FEF probably contributes to voluntary and visually guided eye movements (EMs) (Leigh and Zee, 2006), few studies have explored the functional organisation of FEF in humans. Electrical stimulation of the FEF in humans consistently produces conjugate, contralateral EMs in either horizontal or oblique directions (Godoy

*et al.*, 1990; Blanke and Seeck, 2003). More recently, the contribution of FEF to disjunctive horizontal EM has been described (Thurtell *et al.*, 2009). Furthermore, functional magnetic resonance imaging (fMRI) studies also suggest that different subregions of the human FEF are responsible for pursuit and saccadic EMs (Petit and Haxby, 1999; Rosano *et al.*, 2002). Here, we provide evidence that electrical stimulation of the FEF can induce conjugate vertical EMs. Interestingly, we observed that the direction of induced EMs was independent of the orbital position and followed a Cartesian pattern, with a centering, horizontal movement preceding the onset of an upward gaze deviation. These



**Correspondence:**

Kitti Kaiboriboon  
11100 Euclid Avenue,  
Lakeside 3200,  
Cleveland OH 44106, USA  
<Kitti.Kaiboriboon@UHhospitals.org>

findings support previous observations that human FEF has distinct subregions, including a deep and most caudal part involving vertical upward conjugate EMs and a more superficial area involved in disjunctive, vergence EMs (Rosano *et al.*, 2002; Thurtell *et al.*, 2009). The area responsible for conjugate horizontal EMs is larger and slightly more anterior to these regions (Godoy *et al.*, 1990). In addition, the FEF plays an important role in the programming of head movements during gaze shifts in humans (Petit and Beauchamp, 2003).

## Case report

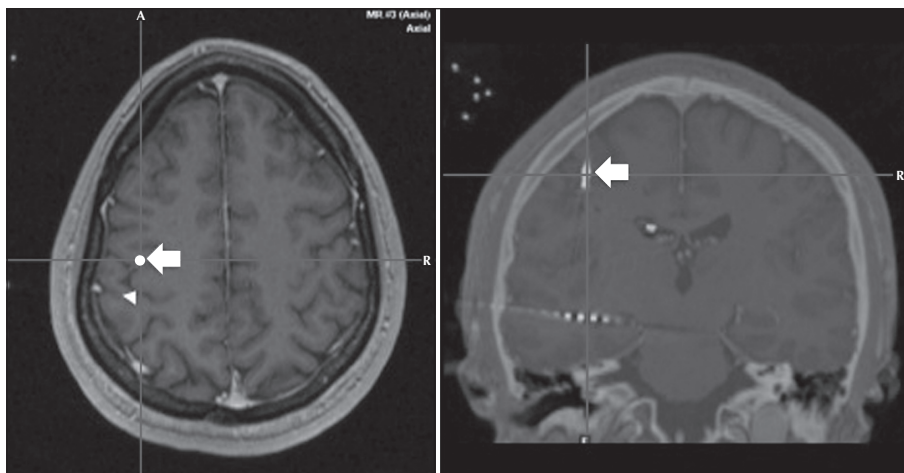
We report the case of a 22-year-old, right-handed man with non-lesional medically intractable temporal lobe epilepsy who underwent stereotactic depth electrode implantation as part of diagnostic investigations. Twelve contact depth electrodes (Integra LifeSciences, Plainsboro, New Jersey, USA), with a diameter of 1.3 mm, a contact length of 2.5 mm, and a centre-to-centre distance of 5.0 mm, were stereotactically placed to the right medial and lateral basal frontal, temporal pole, amygdala, hippocampal head and body, temporo-parietal junction, cingulate, and anterior and posterior insular using Leksell Stereotactic System Model G Frame (Elekta). The trajectory and placement of the electrodes were planned using preoperative MRI loaded onto an iPlan workstation (BrainLAB, Feldkirchen, Germany). Each depth electrode was placed under fluoroscopic guidance to the target and secured in place with an anchor bolt. A volumetric computer tomography (CT) scan of the head was obtained after the surgery and then coregistered with presurgical volumetric MRI by iPlan 2.6 Cranial software (BrainLAB, Feldkirchen, Germany) to reconstruct three dimensional images of the electrode positions. There were no electrodes placed in the primary motor cortex, the supplementary motor area, or the supplementary eye field. Electrical stimulation consisted of 5-10-second trains of 50-Hz bipolar square wave pulses with a duration of 0.2 to 0.5 milliseconds generated by a constant current generator (Ojemann stimulator, Radionics Inc., Burlington, MA, USA). We used monopolar stimulation with a remote reference electrode over the non-eloquent cortex. The stimulation was started at 1 mA with 0.5-1-mA increments until the patient exhibited symptoms or signs, afterdischarges were elicited, or a maximum of 20 mA was reached. The electrical activity was monitored in the stimulated and surrounding electrodes throughout the procedure. At the beginning of the trials, the patient was instructed to look straight ahead and fixate on a picture. Head position was steady and in the central position. Eye movements were readily induced at stimulation intensities over

7 mA. To investigate the influence of the initial orbital position and the direction of EMs, three eccentric eye positions were tested. First, the patient was asked to look straight downwards without any horizontal deviation of the eyes. Then the patient was asked to look horizontally towards the right and the left, respectively, without any vertical deviation of the eyes. An identical fixation target was presented during all trials. A series of stimulations were performed on two occasions, 24 hours apart, to confirm the reproducibility of the findings over time.

Stimulation of the deep caudal end of the middle frontal gyrus (*figure 1*) induced conjugate eye deviation in a vertical upward direction (see *video sequence*). No oblique EMs were elicited. Stimulations at the same site with three different eccentric eye positions demonstrated similar results; EMs typically commenced 3 seconds following the onset of stimulation. When the patient looked downwards, stimulation induced pure upward vertical conjugate EMs. When the patient's eyes were in horizontal eccentric positions, the first part of the response consisted of horizontal conjugate EMs towards the midline, which were followed by pure upward vertical movements (see *video sequence*). In addition, the patient demonstrated upward head movements that followed full-range upward gaze direction in every trial. The head movements never preceded the initiation of EMs. The patient was fully awake during the stimulations. He reported that he was unable to control his eye and head movements. As the stimulation current was increased, the eye and head deviations became more pronounced. There were no afterdischarges in the adjacent electrodes immediately following stimulations. Long trains of stimulation provoked facial and head twitching after eye and head deviations had occurred. No eye or head movements were elicited when stimulating the neighbouring sites.

## Discussion

We have demonstrated that stimulation at a deep part of the most caudal region of the FEF (*figure 1*) can produce pure upward conjugate gaze deviation. With one exception, pure upward or downward vertical EMs have not been reported in response to electrical stimulation of FEF (Blanke and Seeck, 2003). Rasmussen and Penfield used a small electrical probe for their intraoperative cortical mapping and induced pure upward vertical EMs during stimulation in the Rolandic lip of the precentral gyrus (Rasmussen and Penfield, 1948). Together, these data suggest that human FEF has a functional organisation with a sub-region controlling upward gaze deviation located deep in the precentral sulcus, which is inaccessible



**Figure 1.** Axial (left) and coronal (right) views demonstrate the site where electrical stimulation evoked a pure upward vertical eye movement. This electrode was located in the deep and most caudal part of the frontal eye fields. Arrows indicate electrode position obtained from coregistration of presurgical volumetric MRI with postimplantation volumetric CT scanning of the head. This electrode was part of the oblique trajectory targeting the posterior insula. Arrowhead points towards the precentral sulcus. For each stimulation, constant current between 1.0 mA and 9.0 mA with biphasic rectangular pulses of 0.2 milliseconds duration at 50 Hz was applied for 5-10 seconds. Eye movements were readily induced at stimulation intensities over 7 mA.

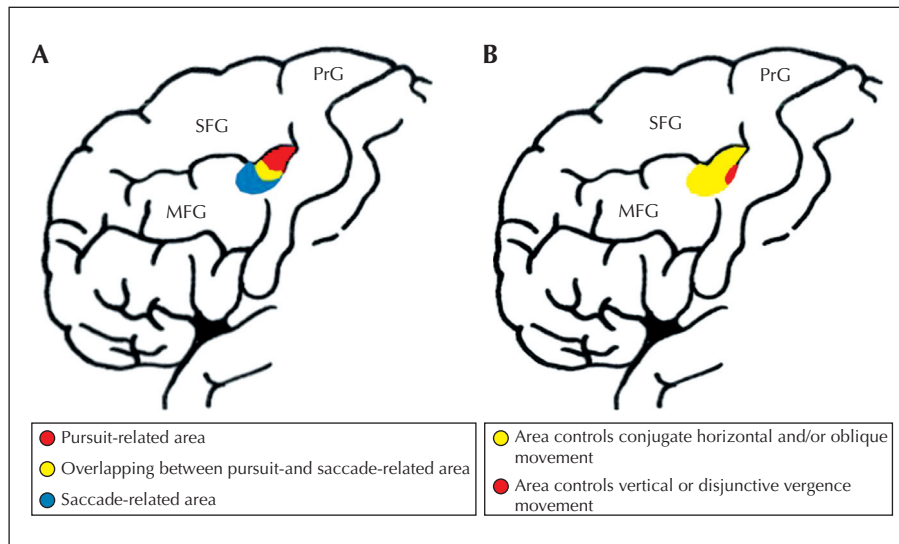
to stimulation by subdural electrode arrays used in prior studies. Our results contrast with prior studies of FEF stimulation, which report predominant horizontal components, and postulate cancelling out of vertical (up versus down) influences (Blanke and Seeck, 2003). The neuronal population we stimulated appears to be anatomically and functionally distinct from other subregions controlling horizontal or oblique EMs.

A prior report suggested that initial eye position may influence the direction of electrically elicited EMs in humans (Blanke and Seeck, 2003), although in monkeys the direction of induced smooth EMs elicited depends on the region of the FEF that is stimulated (Gottlieb *et al.*, 1993). Our subject's eyes first moved to the midline from any eccentric position and then deviated upwards. Re-centering the eyes to a position, in which the retinotropic and egocentric reference frame are aligned, might serve as an efficient means to explore the visual environment. Sustained upward gaze deviation is unusual during natural activities, since most proximate aspects of the visual environment lie in the lower field of gaze. The latency to onset of the response that we observed is typical for mapping of human cortex using electrical stimulation, possibly reflecting temporal summation of synaptic potentials. One interpretation of induced changes of gaze during the period of stimulation is that a network of neurons, which normally controls the direction of gaze by integrating component signals, develops an imbalance. Sustained upgaze in alert patients is encountered in oculogyric crisis (Leigh *et al.*, 1987), which has

been attributed to imbalance in the gaze-holding mechanism.

Prior cortical stimulation studies in humans describe a relationship between head and eye deviation (Foerster, 1936; Penfield and Jasper, 1954; Blanke and Seeck, 2003), suggesting that FEF or adjacent motor cortex controls head movements. One study reported that, in most cases, FEF was situated at the level of the hand motor area or at the border between hand and face motor areas (Matsumoto *et al.*, 2002), which is slightly higher than those reported by Foerster (Foerster, 1936) and Penfield and Jasper (Penfield and Jasper, 1954). Based on the electrode position (*figure 1*), our site of stimulation is in fact slightly superior and far from the face motor cortex. Only with prolonged electrical stimulation did our patient develop facial and head movements, without hand or arm movement, suggesting spread of electrical activity from the FEF directly to the face motor area. These findings suggest that the FEF is functionally connected to the head representation of the motor cortex.

In our study, however, there are a few limitations worth noting. First, the stimulation intensities used to elicit vertical EMs in our case were higher than those usually used for depth electrode stimulations by other groups (Ostrowsky *et al.*, 2000; Mulak *et al.*, 2008; Chassagnon *et al.*, 2008). The reason for this is not clear. It has been suggested that the use of monopolar stimulation could result in stimulation of a larger area of the cortex (Nathan *et al.*, 1993). However, recently our group demonstrated that the result of insular stimulations obtained from monopolar technique, with higher



**Figure 2.** Location of the human frontal eye field (FEF) from electrical stimulation studies. The FEF is located in the middle frontal gyrus (MFG) immediately below the intersection of the precentral sulcus and the superior frontal sulcus, and contains several distinct subregions.

(A) The saccade-related area is located in the anterior part of the FEF and overlaps with the pursuit-related area.

(B) The FEF that controls horizontal and/or oblique eye movements is large, whereas the area involved in vertical or disjunctive vergence movements is much smaller and appears to be located in the most posterior part of the FEF.

SFG: superior frontal gyrus; PrG: precentral gyrus.

stimulation intensities, was comparable to those using the bipolar technique (Stephani *et al.*, 2011). On the other hand, without electrodes in the regions that could potentially be responsible for vertical EMs, such as primary motor cortex, supplementary motor cortex, or supplementary eye field, the involvement of these regions in elicited EMs observed in our case cannot be excluded. Typically, symptoms and/or signs elicited by electrical stimulations are caused by activation of brain regions that produce afterdischarges. The absence of afterdischarges in our case makes it unlikely that the primary motor area, the supplementary motor area, or the supplementary eye field were involved in the generation of the vertical EMs. Therefore, we conclude that the elicited vertical EMs observed in our case were likely the result of electrical stimulation to a deep part of the most caudal region of the FEF.

In summary, we postulate that human FEF comprises several distinct subregions (*figure 2*). The area involved in vertical EMs is likely to be smaller than those involved in horizontal EMs and probably located at the caudal end of the FEF. An area that generates upward gaze deviation lies deep in the precentral sulcus; the role of this cortical region in the normal control of gaze remains to be elucidated. □

#### Disclosures.

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#### Legend for video sequence

##### Eye Movement Video

This video demonstrates vertical upward eye movements induced by electrical stimulation of the frontal eye field.

##### Key words for video research on [www.epilepticdisorders.com](http://www.epilepticdisorders.com)

*Syndrome:* focal non-idiopathic temporal (TLE)

*Etiology:* unknown

*Phenomenology:* eye deviation

*Localization:* frontal premotor mesiolateral; frontal eye field

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