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Removal of epileptically compromised tissue in the frontal cortex restores oculomotor selection in the antisaccade task

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The frontal cortex is heavily involved in oculomotor selection. Here, we investigated the neural correlates of eye movement selection during an antisaccade task in a young epileptic patient in whom the seizure focus included the frontal cortex and affected its function. Before resection surgery, the patient had difficulty in performing correct antisaccades towards the visual field contralateral to the seizure focus. Because the FEF is the only area in the human frontal cortex that is known to have a lateralized oculomotor function in the antisaccade task, this behavioural imbalance between the two visual fields suggests a disruption of FEF functioning by the nearby seizure focus. Electrocorticographic recordings at the seizure focus indeed showed that the seizure focus interfered with correct antisaccade performance. These results were in line with fMRI recordings revealing less task-related frontal activity for the hemisphere of the seizure focus, possibly reflecting diminished top-down engagement of the oculomotor system. Two months after removal of the compromised tissue, the seizures had disappeared, and antisaccade performance was the same for both visual hemifields. We conclude that a seizure focus in the frontal cortex can induce a dysfunction in the selection of eye movements, which is resolved after removal of interfering tissue.

We execute eye movements to select a part of our visual environment for detailed inspection. Eye movements can be evoked by top-down influences, such as our intention to foveate a book on a shelf, or bottom-up influences, such as the visual input due to a person suddenly entering the room. At each moment in time, there might therefore be multiple active eye movement programmes in the oculomotor system. Because we can only execute one eye movement at a time, the oculomotor competition between these eye movement programmes has to be resolved by selecting the correct eye movement programme most relevant to the situation at hand and inhibiting the other eye movement programmes.

The most frequently used paradigm to study this oculomotor competition is the antisaccade task in which participants are presented with an abrupt appearance of a

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visual stimulus in the periphery after which they have to execute a saccade away from this stimulus to its mirror opposite position (Chen & Machado, 2016; Hallet, 1978; Munoz & Everling, 2004). The eye movement programme that is automatically evoked by the stimulus has to be inhibited, whereas a top-down generated eye movement has to be executed to the mirror location of the stimulus. A failure of oculomotor inhibition will result in the execution of an erroneous eye movement towards the stimulus.

One of the neural areas in the frontal cortex that is known to play an important role in resolving the oculomotor competition between eye movement programmes is the frontal eye fields (FEF). The role of the FEF is evident from neuroimaging (Clementz, Brahmbhatt, McDowell, Brown, & Sweeney, 2007; Curtis & D'Esposito, 2003), transcranial magnetic stimulation (Bosch, Neggers, & Van der Stigchel, 2013; Jaun-Frutiger, Cazzoli, Müri, Bassetti, & Nyffeler, 2013) and neurophysiological studies in non-human primates (Bichot, Rao, & Schall, 2001; Bichot & Schall, 2002). Studies in patients with a lesion in the FEF have shown that antisaccade performance for the contralesional visual field is impaired, resulting in more errors and/or increased latencies of antisaccades to the contralesional visual field (Guitton, Buchtel, & Douglas, 1985; Hodgson *et al.*, 2007; Machado & Rafal, 2004; Van der Stigchel, Van Koningsbruggen, Nijboer, List, & Rafal, 2012). Interestingly, the observed deficits in the antisaccade task after a lesion to the human FEF are observed for the contralesional visual field. This is in contrast to the deficits observed after a lesion to the dorsolateral prefrontal cortex (Pierrot-Deseilligny *et al.*, 2003) or the supplementary eye fields (Husain, Parton, Hodgson, Mort, & Rees, 2003), where deficits are present for both the contra- and ipsilesional visual field.

Here, we investigated the neural correlates of eye movement selection in a 15-year-old girl, suffering from partial epilepsy, who had subdural electrodes temporarily implanted to localize the seizure focus prior to surgical resection. Because her first seizure sign was a forced deviation of the eyes towards the right that she could not suppress, and a presumed MRI abnormality was located in an anatomical location near the left FEF, subdural electrodes were placed over the left frontolateral part of the cortex including the FEF (see Figure 4 for the positions of the grid electrodes). The lateralized nature of the onset of the seizure signs was taken as indication for the disruption of FEF functioning, evoked due to the proximity of the seizure focus.

Three different approaches were used to address our question. First, electrocorticographic (ECoG) signals were obtained from the implanted electrodes during performance of an antisaccade task to track rapid brain signal changes by studying high-frequency broadband activity (HFB). HFB is thought to represent an electrophysiological measure of local cortical activation produced by neural firing (Miller *et al.*, 2010), which has good temporal resolution and spatial correspondence to the fMRI BOLD signal (Conner, Ellmore, Pieters, DiSano, & Tandon, 2011; He, Snyder, Zempel, Smyth, & Raichle, 2008; Ojemann, Ramsey, & Ojemann, 2013; Siero *et al.*, 2014). By recording neural signals from the different electrodes, we could record the spatiotemporal evolution of cortical processes related to antisaccade performance. Second, the results of the spectral power analysis were compared to the results of a functional magnetic resonance imaging (fMRI) session performed prior to electrode implantation surgery. Third, we studied the consequences of removing the seizure focus in the frontal cortex on oculomotor selection by comparing antisaccade behaviour before and after resection surgery.

Case report

Summary of case

A 15-year-old right-handed girl suffered from medically intractable partial and secondary generalized seizures since the age of 9. She was admitted to the Dutch Collaborative Epilepsy Program to evaluate the possibility of epilepsy surgery. All procedures were performed for clinical diagnostic reasons. The patient and her parents gave informed consent for use of the data for research. This procedure was approved by the Ethics Committee of the University Medical Center, in agreement with the Declaration of Helsinki 2013. Seizures were characterized by a forced deviation of the eyes towards the right of which she was aware but which she was unable to suppress. This was sometimes followed by clonias in the right side of her face and right arm. Before medication, this could result in a secondary generalized tonic–clonic seizure. She experienced daily seizures that interfered with school performance. Her neurological evaluation was normal. Pre-implantation 3T MRI imaging revealed a suspicious blurring of the grey–white matter boundary in a tiny region of the posterior part of the middle frontal gyrus, near the FEF.

Formal neuropsychological testing of the patient revealed higher than average scores on the Wechsler Intelligence Scale for Children – Revised (Dutch version: WISC-III-NL): verbal IQ 111, performance IQ 112 and full-scale IQ 113. She showed average language functioning (Peabody Picture Vocabulary Test (PPVT-III-NL) 98), and her memory performance was higher than average, as measured using the Test of Memory and Learning (Memory for Stories 14) and the WISC-III-NL (Digit Span 12). Executive functioning was normal (Stroop interference score 46).

Eye movement recording (Pre-implantation surgery)

For behavioural measures, the task included both pro- and antisaccade trials and was performed by the patient in the week before electrode implantation surgery.

Apparatus. Eye movements were recorded using an EyeLink 1000 system. The patient performed the experiment in a sound-attenuated setting, viewing a display monitor from a distance of 57 cm.

Pro- and antisaccade paradigm. The patient viewed a display containing a plus sign (0.70°) on a black background in the centre of the display, which was used as fixation point. The colour of the plus sign indicated the type of trial: red indicated an antisaccade trials, and green indicated a prosaccade trial. After 1000 ms, the fixation stimulus disappeared, followed by a 250-ms blank screen, after which a circle (1.30° in diameter) appeared at a distance of 10° either to the right or left side (i.e., stimulus onset). The stimulus was presented for 1200 ms, after which the display was emptied (see Figure 1).

To ensure that possible differences between pro- and antisaccades could not be attributed to differences in the proportion of trials in which these two conditions were presented, half the trials were prosaccade trials, and the other half were antisaccade trials. The sequence of trials was fully randomized. The experiment consisted of 160 experimental trials.

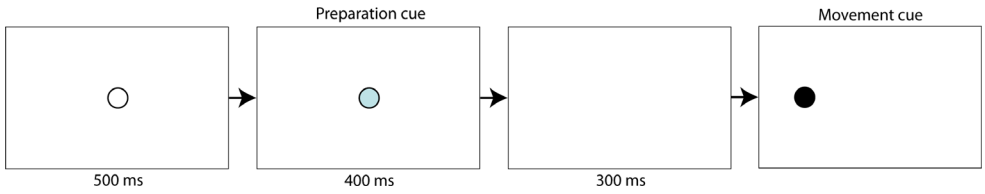

Figure 1. Graphical layout of the anti- and prosaccade experiment used during the fMRI and ECoG recordings. For the eye movement recordings before and after the surgery, a slightly modified paradigm was adopted (see Methods). The colour of the preparation cue instructed the patient to either perform a pro- or an antisaccade. [Colour figure can be viewed at wileyonlinelibrary.com]

Analyses. Trials with a saccadic latency lower than 80 ms (anticipatory saccades), higher than 800 ms (too slow saccades) or further than two and a half standard deviations away from the mean latency were excluded. Moreover, trials were excluded from analysis in which no saccade or a too small first saccade (<2°) was made. These criteria led to a loss of 6.3% of trials for the pre-surgery session.

Results. Correct antisaccades had a longer latency than prosaccades (prosaccades (mean: 153 ms; *SD* 51), antisaccades, mean: 204 ms; *SD* 40), $t\,(133) = 4.77$, $p < .0001$.

During the antisaccade trials, the patient made more erroneous saccades to the stimulus in the left visual field compared to a stimulus in the right visual field, 26.3% vs. 7.9% errors; $\chi^2\,(1) = 4.55$; $p < .04$. See Figure 2 for an illustration of these findings. This imbalance was not mirrored by saccade latencies, as the latencies for antisaccades were similar for leftward and rightward saccades, $t\,(61) = 0.56$; $p = .58$.

Functional MR imaging (Pre-resection surgery)

The goal of this fMRI-experiment was to determine the location of the FEF in both hemispheres. Due to equipment availability, no eye movements were recorded. Note also that we were not interested in specific activity associated with errors, but merely used the task to localize the FEF. The fMRI was performed 6 weeks before implantation with the subdural electrodes.

Apparatus. The experiment was performed in a clinical 3T Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands) with an 8-channel head coil. For functional scans, we used 3D PRESTO, which eliminates signals from large blood vessels (van Gelderen, Duyn, Ramsey, Liu, & Moonen, 2012; Neggers, Hermans, & Ramsey, 2008). During a single run of the experiment, 800 whole brain volumes were acquired (FOV 224 × 256 × 160 mm, TE/TR 33/22 ms, time per volume 0.609 s, FA 10 degrees, voxel size 4 mm isotropic). Using Presentation software (Neurobehavioral Systems), stimuli were projected on a 1-m-wide screen that was placed at a distance of 2 m from the patient. The patient could view the stimuli through a mirror mounted on the head coil.

Antisaccade task. Due to differences in hardware imposed by strict and different requirements for fMRI and ECoG, we used a different version of the antisaccade task in

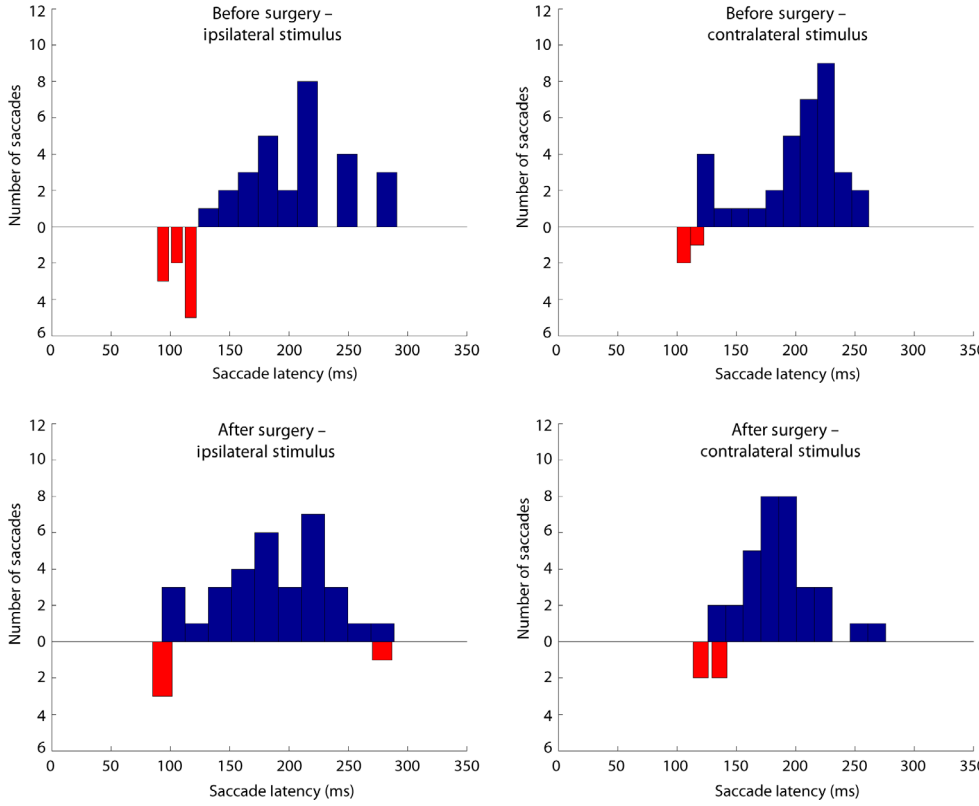

Figure 2. Histogram plot for the antisaccade conditions. Error saccades are plotted below the zero, whereas correct saccades are plotted above the zero. It can be seen that error saccades were most frequent before the surgery when the stimulus was presented in the ipsilateral visual field (requiring a contralateral saccade). [Colour figure can be viewed at wileyonlinelibrary.com]

the scanner compared to the behavioural version. The task consisted of alternating blocks of randomly mixed pro- and antisaccade trials, and blocks of fixation (rest). Each saccade trial started with a white circle (1 × 1° visual angle) at the centre of a black screen (see Figure 1). After 500 ms, the central white circle turned either red or blue. This coloured circle (preparation cue) was presented for 400 ms. When the circle was red, the patient had to make a prosaccade (towards the following peripheral stimulus); a blue circle indicated an antisaccade (diametrically opposed from the peripheral stimulus with same eccentricity); 300 ms after the coloured circle cue disappeared, a peripheral stimulus appeared (movement cue) for 800 ms positioned 3.8 or 14.8 degrees to the left or right from the centre. The peripheral stimulus was a white circle (1 × 1° visual angle). The patient was instructed to make a saccade towards or away from this stimulus as fast as possible, depending on the colour of the preparation cue. Each block consisted of 10 trials and took 20 s. After each block of saccade trials, a fixation block followed (also lasting 20 s), during which the patient had to fixate on a fixation cross at the centre of the black screen (1 × 1° of visual angle, line thickness 0.1°). The functional scanning session consisted of 12 saccade and 12 fixation blocks, amounting to 8 min.

Analyses. Functional scans were motion corrected by realigning to the first scan and coregistered with the anatomical scan using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). No spatial smoothing was applied, as data were analysed on a single-subject level. Statistical analysis involved fitting the data to a general linear model (GLM, SPM8), which included a regressor for the active blocks (prosaccades/antisaccades intermixed). The contrast map (pro- and antisaccades intermixed versus rest) was projected onto a 3D rendering of the anatomical scan, to visualize brain areas that show task-related activation. For visualization of the t-maps, we used a standard threshold of $t > 4.66$ ($p < .05$, FWE-corrected).

Results. During the prosaccade/antisaccade blocks of the fMRI task, activity was observed in frontal and parietal areas bilaterally (see Figure 3). Clear differences in frontal activity were observed between the two hemispheres; whereas the FEF was strongly activated in both hemispheres, there was overall less frontal activity in the left (and affected) hemisphere.

An overview of the coordinates of the various activated clusters is given in Table 1.

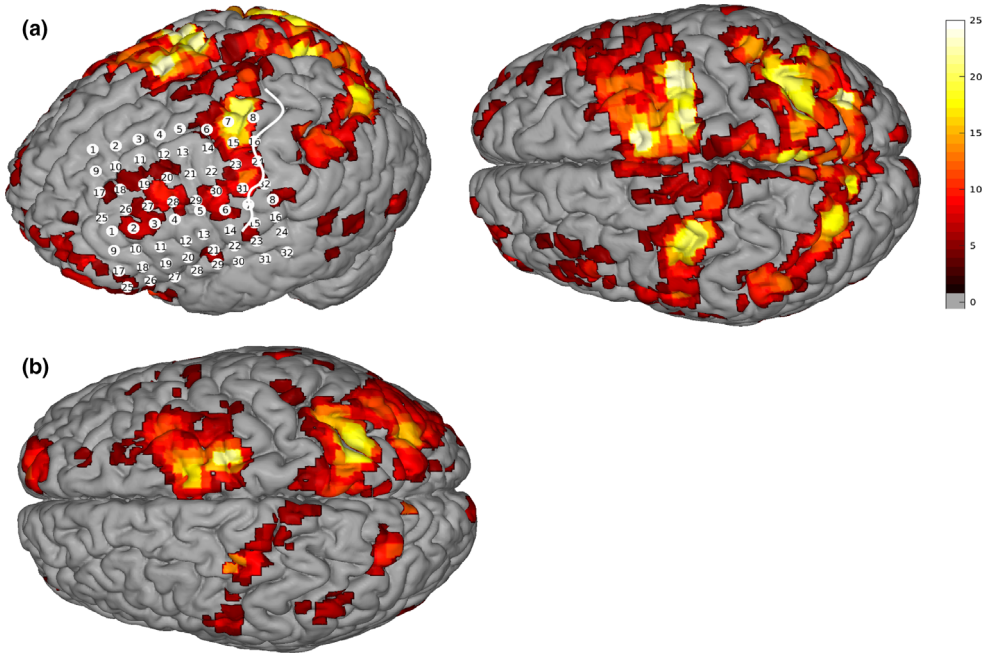

Figure 3. (a) fMRI activation during the antisaccade task for both hemispheres projected on a T1-weighted image of the patient's brain. In both hemispheres, the FEF is clearly activated during the prosaccade/antisaccade blocks (around electrode 7 in the left hemisphere). For the left (affected) hemisphere, the seizure focus (around electrodes 5, 13 and 21) is not activated. The central sulcus is illustrated by the inserted line at the right side of the grid electrodes. (b) Illustration of the difference in activity between the two hemispheres. Activity within a hemisphere indicates that activity was greater for that specific hemisphere compared to the other hemisphere. It can clearly be seen that activity patterns are much more widespread in the right hemisphere compared to the left hemisphere. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1. An overview of the MNI coordinates of the various activated fMRI clusters (subject brain normalized to MNI space, $t > 4.66$, $p < .05$, FWE-corrected). Clusters are minimally 10 voxels. The values presented in bold reflect the maximum values within a cluster. For each cluster, maximally three local maxima are given

X	y	z	*t*-value	(closest) Broadman Area	Hemisphere
36,00	**−8,00**	**68,00**	**25,27**	**6**	**R**
−40,00	−8,00	52,00	21,19	6	L
12,00	−76,00	48,00	21,14	7	R
−40,00	**−68,00**	**12,00**	**14,16**	**19**	**L**
−36,00	**28,00**	**32,00**	**12,06**	**9**	**L**
−48,00	24,00	40,00	10,84	8	L
−40,00	24,00	24,00	8,63	9	L
−48,00	**−44,00**	**28,00**	**10,82**	**39**	**L**
−48,00	−52,00	16,00	9,55	39	L
36,00	**44,00**	**−20,00**	**10,28**	**47**	**R**
−36,00	**52,00**	**−16,00**	**10,18**	**10**	**L**
−16,00	**−44,00**	**−48,00**	**9,92**	**Cerebellum**	**L**
−16,00	−56,00	−52,00	7,38	7	L
60,00	**−44,00**	**−16,00**	**8,93**	**37**	**R**
60,00	−60,00	−12,00	6,98	37	R
24,00	**−88,00**	**−32,00**	**8,88**	**Cerebellum**	**R**
28,00	−84,00	−40,00	8,04	Cerebellum	R
−60,00	**−56,00**	**8,00**	**8,08**	**39**	**L**
36,00	**24,00**	**−8,00**	**7,88**	**47**	**R**
48,00	16,00	−4,00	7,47	13	R
60,00	8,00	0,00	5,77	6	R
−40,00	**56,00**	**4,00**	**7,86**	**10**	**L**
−32,00	60,00	8,00	7,02	10	L
−52,00	**0,00**	**4,00**	**7,15**	**6**	**L**
−56,00	8,00	4,00	6,02	44	L

Corticectomy information

Intracranial monitoring with grid electrodes was used for precise demarcation of the ictal onset zone and functionally important areas (see Figure 4). The invasive recording indicated a circumscript seizure onset location in the predicted posterior part of the middle frontal gyrus, just above Broca's area. This led to a corticectomy that included the posterior 2 cm of the gyrus and the cortex bordering the sulcus between the middle and superior frontal gyri (see Figure 5). Two days after surgery, we replicated the pre-surgery imbalance in antisaccade performance in a session of 160 antisaccades, albeit at trend level (recordings were made using a high-speed digital camera (Casio Exilim EX-S200); 25.0% vs. 11.7% errors; χ^2 (1) = 3.56; p = .059). One and a half year after the operation, she remains seizure-free and is off medication.

Electrocorticography (ECoG) (Pre-resection)

Apparatus. ECoG data were acquired with a 128-channel recording system (MicroMed, Treviso, Italy, 22 bits, band-pass filter 0.15–134.4 Hz) with 512-Hz sampling rate. In addition, EOG electrodes were positioned above the eyes to record eye movements. Note that the patient was lying in bed which made eye tracking using a remote eye tracker

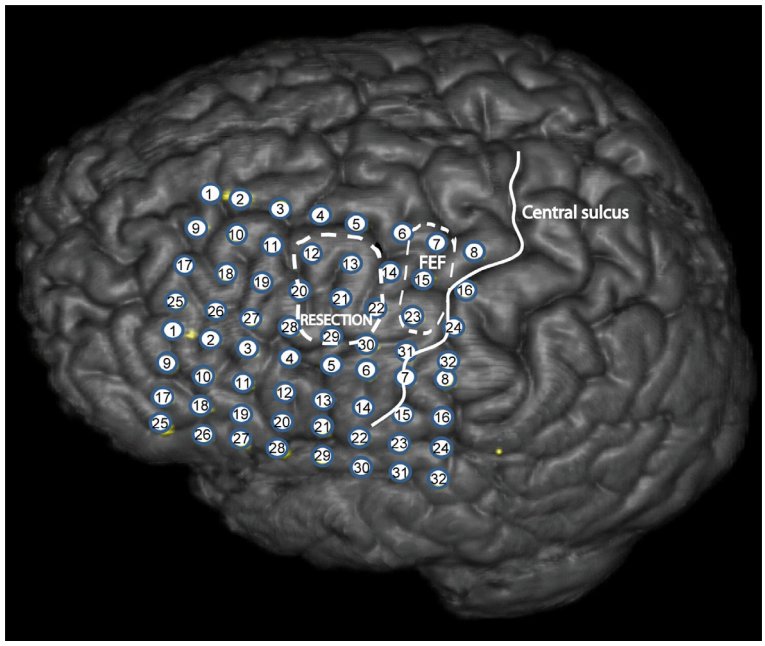

Figure 4. Rendering of a pre-implantation anatomical T1-weighted MRI scan of the patient's brain with the positions of the grid electrodes superimposed. [Colour figure can be viewed at wileyonlinelibrary.com]

extremely challenging. Furthermore, external equipment was not allowed near the patient for risk of interference with the ECoG recording equipment. We therefore decided to use EOG to measure eye movements. EOG activity was recorded in synchronization with the ECoG channels.

Antisaccade paradigm. The same version of the pro- and antisaccade task as used in the fMRI protocol was used for the ECoG recordings. The task was implemented and synchronized to the ECoG data recordings using Presentation® software (Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

Analyses. Offline, the data were notch-filtered from 49 to 51 Hz and 97 to 103 Hz to exclude the effects of 50-Hz line noise and rereferenced to the common average of all electrodes of the grid. Although we recorded from all electrodes in the grid, our analyses focused on nine electrodes: the seizure focus (i.e., 5, 13 and 21, see Figure 1), the electrodes covering the neural areas with the highest activity as revealed from the fMRI analyses (i.e., the FEF: 7, 15, and 23) and the electrodes in between (i.e., 6, 14, and 22). The electrodes in between were included because of their spatial proximity to the neural areas showing the highest activity as revealed from the fMRI analyses and the seizure focus. We tested for significance of the task-related changes in the high-frequency broadband activity (HFB) for each of these nine electrodes during two task periods. The first period ('preparation period') reflected the 300 ms before the onset of the stimulus for both antisaccades and prosaccades. As the patient knew at the start of each trial which type of saccade she had to perform, this

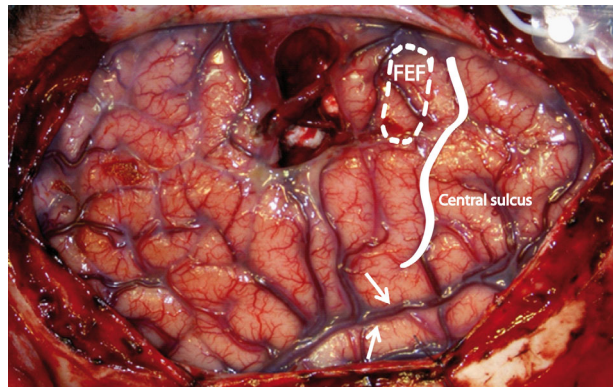

Figure 5. Intraoperative photograph of the left hemisphere after resection of the posterior 2 cm of the gyrus and the cortex bordering the sulcus between the middle and superior frontal gyri (arrows mark the Sylvian fissure). The dorsal side is up, and left is rostral/anterior. [Colour figure can be viewed at wileyonlinelibrary.com]

period reflected the preparation for an upcoming anti- or prosaccade. Any difference in the HFB response observed during this period would indicate an involvement of the neural area in the preparation for the upcoming task (before the onset of the stimulus). The second period ('movement period') reflected the 500 ms after the onset of the stimulus.

The HFB response was calculated from the common average rereferenced ECoG signal in a three-step process. First, a time-frequency representation of the signal was computed using wavelet decomposition (Gabor Wavelet) (Bruns, 2004) for all frequencies between 65 and 95 Hz. Wavelets were tapered per frequency to fit just four cycles in the full width at half maximum of the Gaussian window compromising frequency resolution to gain temporal resolution in accordance with our focus on the non-frequency-specific HFB signal. Second, the real (corresponding to the amplitude) component of the decomposition was squared to get the power of each of the 31 frequencies. Third, the sum over frequencies was computed for each sample point to give the HFB response over time.

For the entire period starting before the preparation cue until 1s after the movement cue, we converted HFB power values to z-scores using the standard deviation of the HFB in the 250-ms baseline period before the preparation cues (when a white circle was on the screen) for each trial (Figure 6). Significance of task effect on HFB power during the two time periods was tested between correct antisaccades and correct prosaccades and between incorrect antisaccades (i.e., saccades towards the movement cue on antisaccade trials) and correct prosaccades. This was done by computing the mean HFB response for each task trail during both periods and applying a paired t-test on the mean HFB powers to test differences between conditions, irrespective of the location of the movement onset. As two contrasts during two periods were tested for nine electrodes, the computed *p*-values were Bonferroni-corrected for 36 comparisons.

Results. Overall, the patient made no incorrect prosaccades and made a correct antisaccade in 80% of the trials. Mean saccade latency for prosaccades was 236 ms (*SD* 68), as measured with EOG. Correct antisaccades were on average initiated 307 ms after the presentation of the peripheral cue (*SD* 57), whereas incorrect antisaccades had a mean latency of 198 ms (*SD* 44).

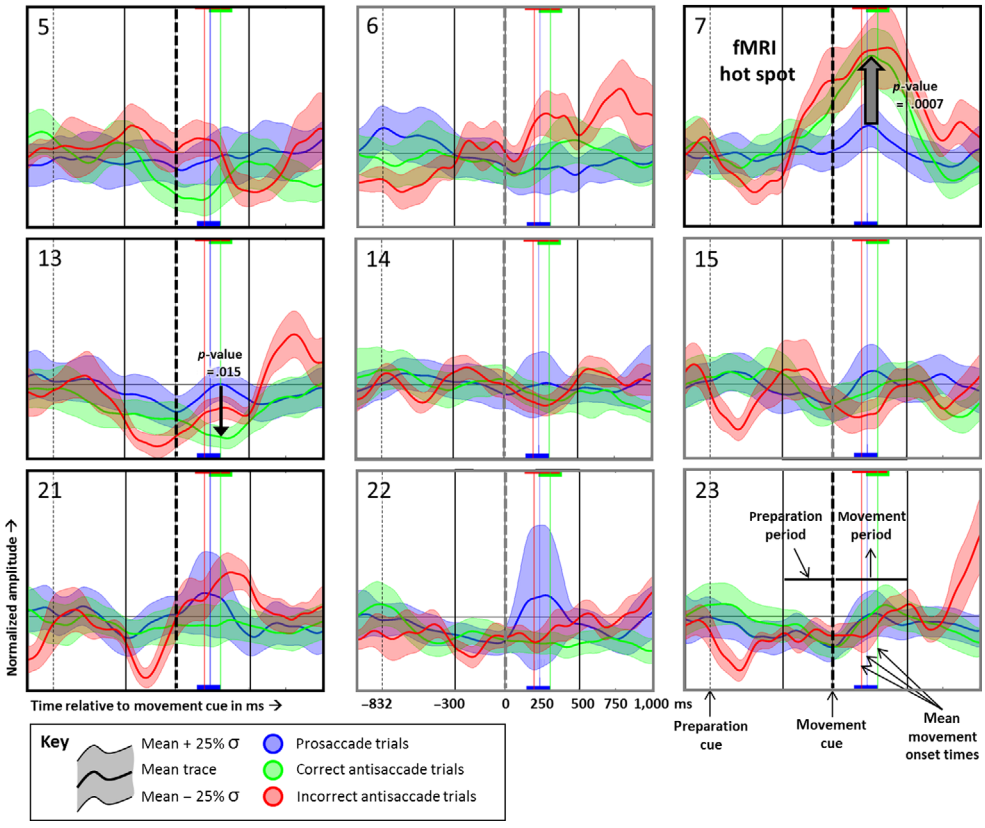

Figure 6. ECoG Results: Mean and standard errors of the HFB power recorded at the seizure focus and the sites of the strongest (anti)saccade activity obtained from fMRI. Normalized HFP power amplitudes at each of the nine electrodes are presented for the three different trial types: correct prosaccades (blue), and correct and incorrect antisaccades (green and red, respectively). Mean saccade latencies are indicated by the vertical lines, similar to the timing of the instruction cue and the peripheral stimulus. Significant differences in HFB activity during the movement period was observed at electrodes 7 and 13. [Colour figure can be viewed at wileyonlinelibrary.com]

No significant differences between the different trial types were observed during the preparation period. During the movement period, significant differences were observed between correct antisaccades and correct prosaccades for electrode 7, with higher HFB values for correct antisaccades compared to correct prosaccades (R^2 = .177, *p*-value = .007). The opposite pattern was observed for electrode 13, which reflects suppression during correctly performed antisaccade trials (R^2 = .125, *p*-value = .015).

For the sake of completeness, we also examined the electrodes not shown in Figure 6. No other electrode showed any significant difference during the preparation or the movement period.

Eye movement recording (post-resection surgery)

To investigate the behavioural consequences of the surgery, the pro- and antisaccade task as in the behavioural recordings two months after resection surgery. Exclusion criteria led to a loss of 6.9% of trials for the post-surgery session.

Results. Also after tissue resection, correct antisaccades had a longer latency than prosaccades , prosaccades (mean: 149 ms; *SD* 51), antisaccades (mean: 186 ms; *SD* 40), t (139) = 4.77, $p < .0001$. Antisaccades were initiated faster after surgery than before surgery, t (126) = 2.58; $p < .02$, but this effect was absent for prosaccades, t (146) = 0.42; $p = .67$. This effect of antisaccades was not lateralized, as latencies for antisaccades were similar for leftward and rightward saccades, both before (reported above) and after surgery, t (63) = 0.06; $p = .95$.

Two months after surgery, the pre-surgery imbalance in antisaccade performance was completely gone, and antisaccade performance was the same for both visual fields, 11.1% vs. 10.8% errors; χ^2 (1) = 0.002; $p = .97$. See Figure 2 for comparing the pre- and post-surgery results.

To investigate whether basic oculomotor metrics changed because of the surgery, we analysed saccade duration and saccade amplitude for saccades to the left and to the right before and after surgery. Results showed that saccade amplitude was not influenced by the surgery, before: t (133) = 0.97, $p = .33$; after: t (139) = 0.38, $p = .71$, similar to saccade duration, before: t (133) = 1.41, $p = .16$; after: t (139) = 0.53, $p = .60$.

GENERAL DISCUSSION

In the present study, we investigated the role of the frontal cortex in oculomotor selection in a young epileptic patient in whom the seizure focus was near the left FEF. We measured eye movements during performance of the antisaccade task, which requires the inhibition of an automatically evoked saccade to a stimulus onset and the execution of a voluntary saccade in the opposite direction. This allowed us to examine to what extent a seizure focus can disrupt cognitive functions, like those required in the antisaccade task. Furthermore, the implantation of subdural electrodes enabled us to directly measure neural activity related to oculomotor selection. To summarize the results, the patient had difficulty in performing correct antisaccades towards the visual field contralateral to the seizure focus before surgery, consistent with the notion that the seizure focus interfered with correct antisaccade performance due to its proximity to the FEF. Furthermore, fMRI recordings revealed less task-related frontal activity for the hemisphere of the seizure focus. These results will now be discussed in more detail.

With respect to antisaccade performance, we observed that the patient was clearly impaired in the antisaccade task before surgery. This impairment was revealed by a deficit in initiating voluntary saccades to the visual field contralateral to the seizure focus: the patient made more erroneous saccades when the stimulus was presented in the ipsilateral visual field compared to when it was presented in the contralateral visual field. This result can mean two things: either the patient had a problem to inhibit the saccade programme towards the ipsilateral field and/or a problem initiating a voluntary saccade towards the contralateral visual field. Given that the FEF is the only oculomotor area in the frontal cortex with a lateralized function (Munoz, 2002; Munoz & Everling, 2004), we therefore reason that our results can only be explained by a problem in the contralateral visual field (i.e., difficulty performing correct antisaccades towards the contralateral visual field) evoked by the close proximity of the seizure focus. In terms of oculomotor selection, this indicates that on trials with erroneous saccades, the competition between the automatically evoked saccade towards the

stimulus and the required voluntary saccade towards the opposite location was won by the saccade towards the stimulus.

Responses in FEF are known to be somewhat mixed. FEF neurons are clearly responsive to task demands, which is shown for example by different responses to targets and distractors (Bichot & Schall, 2002), and different responses in the pro- and antisaccade tasks (Everling & Munoz, 2000). However, purely visual responses also have been reported (Bruce, Goldberg, Bushnell, & Stanton, 1985), and early firing is not always different for targets and distractors (Bichot & Schall, 2002). In line with the finding that the FEF in both hemispheres can be divided into various subregions with presumed different functions (Lobel *et al.*, 2001; Vernet, Quentin, Chanes, Mitsumasu, & Valero-Cabré, 2014), the FEF is therefore involved in both resolving oculomotor selection and the execution of the eye movement. It is important to note that we observed no differences in saccade latencies: there were no lateralized differences in the latencies of antisaccades, nor were the latencies of prosaccades influenced by the surgery. Our results can therefore not be explained by a general deficit in generating saccades to the right visual field and are best explained in terms of deficits in oculomotor selection processes in the FEF, most likely due to the proximity of the seizure focus.

It is important to stress that these results are different from what is generally observed after a lesion to the FEF itself, which is associated with more errors to the contralesional visual field (Guitton *et al.*, 1985; Hodgson *et al.*, 2007; Machado & Rafal, 2004; Van der Stigchel *et al.*, 2012). Note that the selection processes of the FEF play two roles during performance of an antisaccade trial: when the stimulus is presented in the contralateral visual field, the FEF is involved in inhibiting the saccade towards it, together with the dorsolateral prefrontal cortex and the supplementary eye fields (SEF, Munoz & Everling, 2004). When the stimulus is presented in the ipsilateral visual field, the FEF is involved in executing a voluntary saccade towards the contralateral visual field. As it is known that the FEF in both hemispheres can be divided into various subregions with presumed different functions (Lobel *et al.*, 2001; Vernet *et al.*, 2014), it could be that the seizure focus specifically influenced the subregion involved in the control processes required to execute a voluntary saccade towards the contralateral visual field. Alternatively, a dysfunctional FEF could result in diminished performance of the cortical oculomotor network as a whole, for instance due to difficulties in the communication between the FEF and other oculomotor areas, such as the SEF (Huerta & Kaas, 1990; Parthasarathy, Schall, & Graybiel, 1992; Schall, Morel, & Kaas, 1993) or the parietal eye fields (Gottlieb & Goldberg, 1999; Munoz & Everling, 2004).

Interestingly, the imbalance in antisaccade performance between the two visual fields was resolved after removal of the seizure focus, and performance for the two visual fields was at a level comparable to the ipsilateral performance before surgery. Contrary to the idea that removal of the part of the frontal cortex can result in an impairment in the antisaccade performance, as observed in patients with a brain lesion (Machado & Rafal, 2004; Van der Stigchel *et al.*, 2012), in this case removal of the seizure focus actually resulted in an improvement in antisaccade performance, providing further evidence for the idea that the seizure focus compromised oculomotor function.

The idea that the seizure focus resulted in a dysfunction in oculomotor behaviour was supported by pre-resection fMRI and the ECoG recordings during implantation. Clear differences were observed in activity between the two hemispheres in fMRI: as expected,

the FEF was strongly activated in both hemispheres (Bosch *et al.*, 2013; Curtis & D' 2003), but there was overall less task-related frontal activity for the impaired hemisphere compared to the intact hemisphere. Although speculative, the decreased frontal activity could be related to the reduced top-down control on the oculomotor system by the hemisphere of the seizure focus observed in the present study.

The fMRI results were elaborated in more detail by results of the ECoG recordings. In the interval in which the oculomotor competition had to be resolved, the highest HFB values for correct antisaccades relative to correct prosaccades were observed at the electrode which was most active during fMRI and which was positioned right over the FEF. In contrast, we observed lower HFB values for correct antisaccades compared to correct prosaccades at an electrode on the seizure focus. Given the impaired antisaccade performance before surgery, this strongly suggests that the seizure focus near the FEF interfered with correct antisaccade performance. After removal of the seizure focus, this interference was resolved, resulting in performance comparable to performance produced by the FEF in the right hemisphere.

The presence of the seizure focus may have resulted in a lack of top-down control exerted by the impaired hemisphere. The lateralized nature of the effects observed in the present study is taken as indication for the disruption of FEF functioning by the nearby seizure focus. As mentioned in the introduction, the human FEF is the only region that is associated with a contralateral deficit after a brain lesion during performance of the antisaccade task (Guitton *et al.*, 1985; Hodgson *et al.*, 2007; Machado & Rafal, 2004; Van der Stigchel *et al.*, 2012). One might argue that this statement is in contrast to a study by Ploner, Gaymard, Rivaud-Péchoux, and Pierrot-Deseilligny (2005), in which visual inspection of the data plots of individual patients with a lesion to Brodmann area 46 in the dorsolateral prefrontal cortex reveals a potential lateralized deficit in three of the six impaired patients. It should be noted, however, that performance between the contra- and ipsilesional visual field was not significantly different at a group level. Furthermore, neurophysiological recordings in monkeys have provided evidence for a lateralized oculomotor activity in the supplementary eye fields (Coe, Tomihara, Matsuzawa, & Hikosaka, 2002), although in this task the participant could decide on and plan a saccade in advance, in contrast to the antisaccade task. We would therefore like to argue that the present findings are best comparable to findings of lesion studies and magnetic stimulation in human observers during the antisaccade task, which are clearly in line with the current reasoning of a unique lateralized oculomotor function of the human FEF. Indeed, reports on antisaccade performance of a patient with a lesion to the supplementary eye fields reveal no lateralized deficits during the antisaccade task (Husain *et al.*, 2003).

Interestingly, cryogenic deactivation of the frontal cortex leads to detrimental effects on antisaccade performance in monkeys (Johnston, Koval, Lomber, & Everling, 2014; Johnston, Lomber, & Everling, 2016; Peel, Johnston, Lomber, & Corneil, 2014). Although such temporary and acute deactivation is profoundly different from the current case description in which there was a long-term disruption by the seizure focus, these results are in line with the idea that a seizure focus in the frontal cortex can interfere with antisaccade performance.

We conclude that an epileptic seizure focus in the left frontal cortex, near the FEF, interfered with saccade selection under conditions of competition. After removal of the seizure focus, this neural area no longer interfered with the oculomotor selection processes and saccade performance normalized.

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