

## SHORT REPORT

## Functional organisation of saccades and antisaccades in the frontal lobe in humans: a study with echo planar functional magnetic resonance imaging

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### Abstract

**The cortical activation pattern of saccades and antisaccades (versus rest) in the frontal lobe was analysed using an echo planar imaging (EPI) technique in 10 healthy subjects. Statistical analysis of activity in the dorsolateral prefrontal cortex disclosed a significantly greater activation during antisaccades in this region than during saccades. On the other hand, activity in the frontal eye fields was not statistically different in both tasks. These results confirm the important role of the dorsolateral prefrontal cortex for the correct performance of antisaccades obtained by studies in humans with isolated lesions of the dorsolateral prefrontal cortex.**

*(J Neurol Neurosurg Psychiatry* 1998;65:374-377)

Keywords: eye movements; frontal eye field; dorsolateral prefrontal cortex; functional magnetic resonance imaging

Recent studies concerning the function of the prefrontal cortex disclosed its important role for many aspects of human behaviour.<sup>1,2</sup> For ocular motor control at least three important regions are located in the frontal lobe: the frontal eye fields, the supplementary eye fields, and the dorsolateral prefrontal cortex.

Patients with lesions of the prefrontal cortex fail to suppress unwanted responses and are impaired on cognitive tests such as the Wisconsin card sort test or the Stroop test. Antisaccades,<sup>3</sup> a paradigm in which the subject has to make a saccade away from the presented visual target, reliably test prefrontal function in ocular motor research: the task requires two steps of cortical processing: (1) inhibition of an unwanted reflexive saccade in the direction of the visual target, and (2) intentional saccade to the opposite side. It is still not clear how the frontal eye fields and the dorsolateral prefrontal cortex are involved in the control of the antisaccade paradigm. Some authors<sup>3,4</sup> argue that the frontal eye fields mainly control antisaccades, whereas others<sup>5,6</sup> have arguments for the dorsolateral prefrontal cortex being

responsible for the correct performance of the antisaccade task. If correct antisaccade performance needs a relevant contribution from the dorsolateral prefrontal cortex (for suppressing the unwanted reflexive saccade towards the visual target) we would expect an increased activity in the dorsolateral prefrontal cortex during the antisaccade versus rest condition, but not during the saccade (a saccade towards the visual target) versus rest condition. In this case, the activity in the frontal eye fields is expected to be the same during both conditions. The aim of this study was, therefore, to evaluate the role of these regions in the control of the antisaccade task using functional magnetic resonance imaging (fMRI). Preliminary results were presented in a poster.<sup>7</sup>

### Methods

Ten healthy subjects (three women, seven men with a mean age of 31 years and a range of 24 to 40 years, all right handed) who gave their informed consent were examined. The study was approved by the local ethics committee. Saccades and antisaccades were elicited by projecting the visual targets by a video projection system on to a screen in the magnet bore. Firstly, a central fixation point was given for a pseudorandomised duration between 1 to 2 seconds. Then, simultaneously with the extinguishing of the central fixation point a lateral visual target with a constant amplitude of 15 degrees but randomised direction was lit for 700 ms; finally, the central fixation point was shown again for the next visual stimulation. Instruction for the saccade task was to look as quickly and precisely as possible at the lateral visual target. For the antisaccade task, the instruction was to look directly opposite to the appearing visual target, and to avoid looking first on the visual target. If this was the case it was counted as an error. To reduce head movement artefacts, head restraints were used, which allowed immobilisation of the volunteer's head with lateral foam pads and a velcro band across the forehead. The task performance during fMRI was controlled by an adapted electro-oculography (EOG) system.<sup>8</sup>

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Received 22 August 1997  
and in revised form 18  
December 1997  
Accepted 5 February 1998

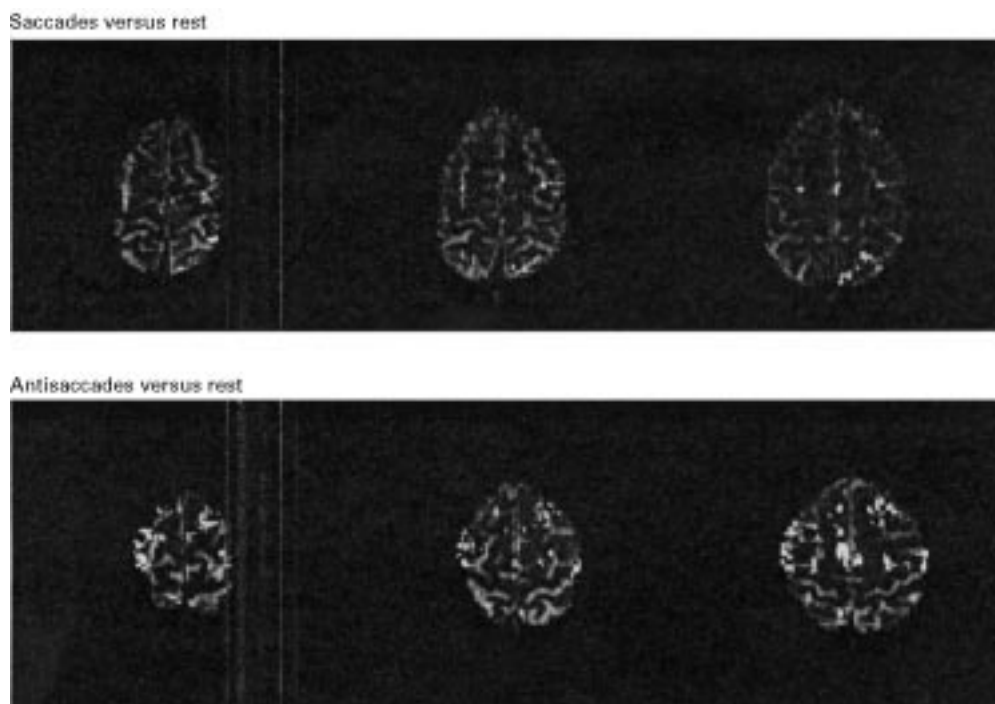


Figure 1 Functional activation of frontal eye fields, supplementary eye fields, and dorsolateral prefrontal cortex during saccade versus rest and during antisaccade versus rest task. Three representative original EPI slices with overlaid clustered activated pixels are shown.

This system allows on line registration of EOG during fMRI without reducing the image quality. The number of misdirected saccades or antisaccades was counted and calculated as the percentage of errors of all performed saccades during the task.

#### IMAGE ACQUISITION AND ANALYSIS

Firstly, in each subject T2 weighted spin echo images of the brain were acquired for exact individual anatomical localisation of the regions of interest (ROIs). Functional MRI was performed using a single shot 2D multislice gradient echo planar imaging (EPI) technique (axial slices in AC-PC orientation, 20 slices covering the whole brain, with a pixel size of

2.6×1.9 mm and a slice thickness of 5 mm, field of view 210×240 mm, matrix 90×128, TE=62 ms, flip angle 90 degrees, one series acquired in 3.56 seconds) on a 1.5 Tesla MR system (Magnetom VISION, Siemens). Images were acquired during four cycles of alternating rest (eyes closed) or activation periods (saccades or antisaccades), with a duration of 32 seconds each, resulting in 160 images during each period. During each activation period, a mean of 25 centrifugal and centripetal eye movements (saccades or antisaccades) were performed by the subject.

z Score maps with the activation—rest time function shifted by one period (3.56 s) and z score values >4.0—were generated and laid over the anatomical echo planar images. This avoids image mismatch due to different distortion effects. Head movement artefacts were detected by screening the images in cinema mode and by analysing the time course signal to detect abrupt changes of activity between two consecutive images. Quantitative group analysis of activity was performed for three ROIs defined in each subject using the T2 weighted anatomical images: (1) The ROI of the frontal eye fields, which lies at the posterior end of the middle frontal gyrus and in the pre-central sulcus or in the depth of the caudalmost part of the superior frontal sulcus<sup>9</sup>; (2) the ROI of the dorsolateral prefrontal cortex, which lies anteriorly on the middle frontal gyrus<sup>10,11</sup> including cortical grey matter and fundi of the adjacent sulci. The posterior limit of the ROI excluded the posterior end of the middle frontal gyrus; (3) the ROI of the supplementary eye fields (SEF),<sup>12,13</sup> which lies on the medial side of the superior frontal gyrus.

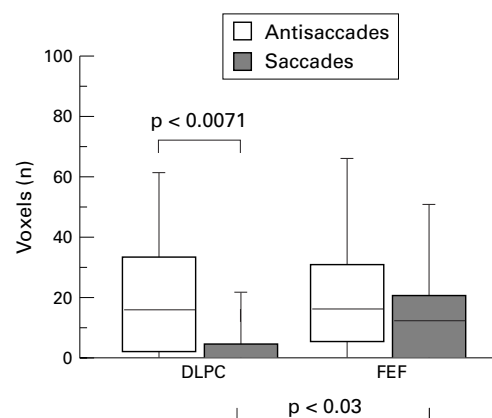


Figure 2 Tukey box graph of activated clustered pixels in 10 subjects during saccade versus rest and antisaccade versus rest task, showing median, 10th, 25th, 75th, and 90th percentiles. There is a significant difference (1) for saccades between the frontal eye fields (FEF) and the dorsolateral prefrontal cortex (DLPC) ( $p < 0.03$ ), and (2) between antisaccades and saccades for the dorsolateral prefrontal cortex ( $p < 0.0071$ ).

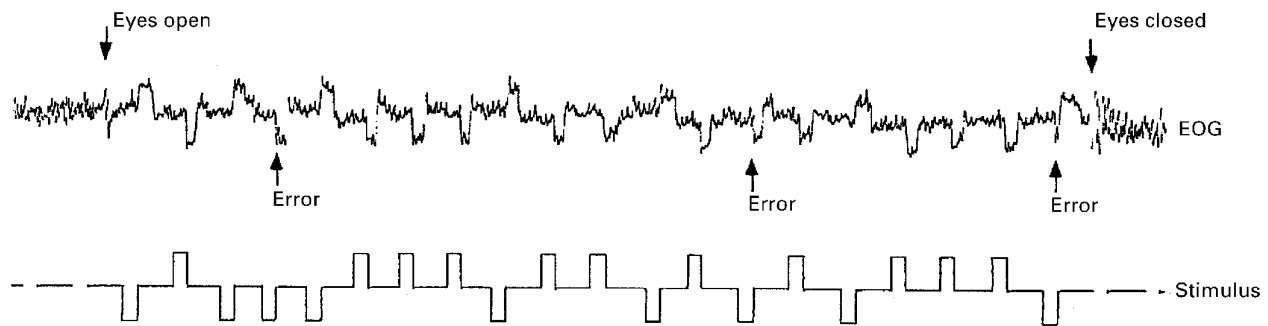


Figure 3 Online EOG during fMRI showing a period of the antisaccade task. Three errors—a saccade towards the visual target, during one block of antisaccades—occurred (marked by arrows).

To reduce the influence of isolated, randomly activated pixels, only clusters of more than four neighbouring activated pixels with  $z$  score values  $>4$  were used for further analysis. Statistical analysis of clustered activated pixels during different conditions was performed by Mann-Whitney  $U$  test.

### Results

Figure 1 shows an example of an individual activation during saccades or antisaccades (versus rest) for three original echo planar slices with overlaid clustered activated pixels. In this subject, activity in the frontal eye fields was found in the precentral sulcus, activation of the dorsolateral prefrontal cortex was found anteriorly in the superior frontal sulcus and gyrus (fig 1, bottom right), and activity in the supplementary eye field was located on the medial side of the superior frontal gyrus. Although both the ROI for the frontal eye fields and the dorsolateral prefrontal cortex are close together, in all subjects, activation was never overlapping between both ROIs.

There was no significant side difference of activated voxels during saccades versus rest in the frontal eye fields (right: median 13 voxels, range 0–100 voxels and left median 5.5 voxels, range: 0–74 voxels) or in the dorsolateral prefrontal cortex (median 0 voxels, range 0–25 voxels on the right side; median 0 voxels, range: 0–42 voxels on the left side). The side difference in activity for antisaccades versus rest in the region of the frontal eye fields (right median 20 voxels, range 0–63 voxels; left median 7.5 voxels, range 0–74 voxels) or the dorsolateral prefrontal cortex (median: 10 voxels, range 0–68 voxels on the right side; median 18.5 voxels, range: 0–100 voxels on the left side) was not significant. Finally, there was no significant side difference of activation in the supplementary eye field (for saccades: right median 5 voxels, range 0–29 voxels; left median 2 voxels, range 0–7 voxels. For antisaccades: right median 19 voxels, range 0–56 voxels; left median 9 voxels, range 0–29 voxels).

The dorsolateral prefrontal cortex was significantly less activated during saccades than the frontal eye fields ( $p < 0.03$ , Mann-Whitney  $U$  test, fig 2). During antisaccades; however, there was no significant difference in activated voxels between the two regions. Statistical comparison of activated voxels in the dorsola-

teral prefrontal cortex during the saccade task versus the antisaccade task (fig 2) resulted in a significant difference ( $p < 0.0071$ , Mann-Whitney  $U$  test; median: 0 voxels for saccades versus median: 16 voxels for antisaccades). The activity in the supplementary eye fields was significantly increased during the antisaccade (median during antisaccades 28 voxels, range 0–85 voxels; median during saccades 6.5 voxels, range 0–29 voxels;  $p < 0.03$ ).

Analysis of EOG in six of the subjects during the saccade task disclosed no direction error. In the antisaccade task (fig 3) a mean percentage of errors of 11% (range 4–18%) was found.

### Discussion

As the main result of this study, the dorsolateral prefrontal cortex proved to be significantly more activated during the antisaccades than during the saccades. This finding confirms recent results obtained in patients with isolated lesions either in the frontal eye fields or dorsolateral prefrontal cortex.<sup>6–14</sup> It has been shown that patients with lesions restricted to the frontal eye fields had a normal percentage of errors in direction during the antisaccade task, but an increase of latencies of the antisaccades, suggesting that the frontal eye field is responsible for the triggering of antisaccades, but not for suppressing unwanted reflexive saccades. On the other hand, patients with lesions restricted to the dorsolateral prefrontal cortex showed an increased percentage of errors in the antisaccade task.<sup>14</sup> In another study,<sup>15</sup> patients with lesions restricted to the dorsolateral prefrontal cortex had difficulty in the suppression of a reflexive saccade task. Several PET or SPECT studies used the antisaccade task in healthy subjects<sup>4, 13, 16, 17</sup> or in patients.<sup>18</sup> Our results are in concordance with PET studies<sup>13, 16</sup> which showed increased activity in the dorsolateral prefrontal cortex during antisaccades, and with another study<sup>17</sup> showing no significant difference in activity in the frontal eye fields between the two tasks. Our results contrast with one recently published PET study<sup>4</sup> which found no significant differences in activity of the dorsolateral prefrontal cortex comparing saccades versus antisaccades. These authors found a significantly higher activity in the frontal eye fields during the antisaccade task. However, this is probably explained by the paradigm they used: the lateral visual target was flashed

only for 100 ms, and both the saccades and antisaccades were performed in the dark. Their subjects made <5% errors in direction during the antisaccade task, which is surprisingly low. It seems likely that the inhibitory demand in their paradigm was lower because the visual target was only flashed, and not persisting, as in our paradigm. This would also explain the higher percentage of errors in the antisaccade task (11%) in our subjects. Furthermore, it has been shown in monkeys<sup>19</sup> that the frontal eye fields seem to be more important for saccades generated to flashed targets than to saccades with persistent visual targets. Single cell recordings in the supplementary eye fields in monkeys have shown increased neuronal activity during reflexive saccades,<sup>20, 21</sup> and Fox *et al.*<sup>22</sup> found activation of the supplementary motor area (SMA) during saccades. However, other PET studies<sup>13, 23</sup> did not show activity in the SMA during reflexive saccades. Such differences were explained by differences in task paradigms or the frequency rate of performed saccades.<sup>13</sup> In our subjects, activation of the region of the supplementary eye field was regularly found during saccades versus rest, and a significant increase of the activity in the SMA was found during antisaccades, in our study as well as in the above mentioned PET studies. Such activation of the supplementary eye field subregion of the SMA during antisaccades probably reflects the role of the supplementary eye field in planning and initiation of internally guided behaviour.<sup>24</sup>

In conclusion, the results of the present study show the importance of the frontal regions in control of antisaccades. Specifically, a close interaction between the frontal eye fields and the dorsolateral prefrontal cortex seems to exist. Taking results from functional studies and studies of patients with lesions together, we speculate that the dorsolateral prefrontal cortex is involved to suppress the unwanted reflexive saccades towards the target, and that the frontal eye fields triggers the correct saccade to the contralateral side.

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