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The role of the frontal eye fields in the oculomotor inhibition of reflexive saccades: Evidence from lesion patients

S. Van der Stigchel[a,*], M. van Koningsbruggen[b], T.C.W. Nijboer[a], A. List[b], R.D. Rafal[b]

[a] Experimental Psychology, Helmholtz Institute, Utrecht University, Utrecht, The Netherlands
[b] School of Psychology, Bangor University, Bangor, United Kingdom

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ABSTRACT

The current study investigated the role of the frontal eye fields (FEF) in the suppression of an unwanted eye movement ('oculomotor inhibition'). Oculomotor inhibition has generally been investigated using the antisaccade task, in which an eye movement to a task-relevant onset must be inhibited. Various lines of research have suggested that successful inhibition in the antisaccade task relies heavily on the FEF. Here, we tested whether the FEF are also involved in the oculomotor inhibition of reflexive saccades. To this end, we used the oculomotor capture task in which the to-be-inhibited element is task-irrelevant. Performance of four patients with lesions to the FEF was measured on both the antisaccade and oculomotor capture task. In both tasks, the majority of the patients made more erroneous eye movements to contralesional elements than to ipsilesional elements. One patient showed no deficits in the antisaccade task, which could be explained by the developmental origin of his lesion. While we confirm the role of the FEF in the inhibition of task-relevant elements, the current study also reveals that the FEF play a crucial role in the oculomotor inhibition of task-irrelevant elements.

1. Introduction

While exploring our environment, we make eye movements to inspect possible relevant locations. The decision on where to make the next eye movement is influenced by both top-down (or endogenous) factors, like task demands, and bottom-up (or exogenous) factors, like the abrupt onset of an element (Godijn & Theeuwes, 2002; Trappenberg, Dorris, Munoz, & Klein, 2001). There is, therefore, continuous competition between these two factors. For example, while driving, our eyes may be captured by a flashing billboard when our goal is to keep our eyes on the road. The suppression of an unwanted eye movement is called 'oculomotor inhibition' and refers to the rejection of a distractor to enable a saccade to the target location. Previous research has indicated that oculomotor inhibition often fails, resulting in erroneous eye movements that conflict with task requirements (Theeuwes, Kramer, Hahn, & Irwin, 1998).

Oculomotor inhibition has generally been investigated using the antisaccade task (for reviews, see Everling & Fischer, 1998; Munoz & Everling, 2004). In this task, participants are presented with an abrupt appearance of a visual stimulus in the periphery ('onset') after which they have to execute an eye movement away from the onset location to its mirror opposite position. The eye movement that is automatically evoked by the presence of the onset has to be inhibited, while a top-down generated eye movement has to be executed to the mirror location of the onset. A failure of oculomotor inhibition will result in the execution of an erroneous eye movement toward the onset. Results on the antisaccade task have shown that participants frequently make an erroneous saccade to the onset location.

Various lines of research have suggested that successful inhibition in the antisaccade task relies heavily on the Frontal Eye Fields (FEF). Neuro-imaging studies have shown that FEF activity is greater for anti- than for prosaccades (Clementz, Brahmbhatt, McDowell, Brown, & Sweeney, 2007; Curtis & D'Esposito, 2003), an effect that is especially noticeable just before saccade generation (McDowell et al., 2005). Chronic FEF lesions lead to an increased number of contralesional errors in the antisaccade task, pointing to a failure in oculomotor inhibition in the visual field contralateral to the lesion (Guitton, Buchtel, & Douglas, 1985; Hodgson et al., 2007; Machado & Rafal, 2004a). Furthermore, TMS application over the FEF results in an increased number of erroneous prosaccades to an onset contralateral to the site of stimulation (Terao et al., 1998).

The current study investigates whether the FEF are also involved in the oculomotor inhibition of reflexive saccades. Errors in the antisaccade are not fully reflexive because the onset is task-relevant: participants must direct their attention to the onset and use this object's location to direct their attention and eyes to the mirror location. Furthermore, there is an explicit instruction not to look at

* Corresponding author.
E-mail address: s.vanderstigchel@uu.nl (S. Van der Stigchel).

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the onset, but to saccade to the opposite direction. To test whether the FEF are also involved in the inhibition of purely reflexive eye movements, one needs a task in which the to-be-inhibited object is not task-relevant. For this, we used the oculomotor capture task developed by Theeuwes et al. (1998) and Theeuwes, Kramer, Hahn, Irwin, and Zelinsky (1999). In this paradigm, the task requires the participant to make an eye movement to a target defined by its unique color. In half of the trials, an additional 'distractor' circle is presented with an abrupt onset. In a large portion of trials, participants are unable to inhibit an eye movement to the location of the distractor before executing a saccade to the target (i.e., 'capture trials') (Theeuwes et al., 1998; Theeuwes et al., 1999). In contrast to the antisaccade task, erroneous saccades in the oculomotor capture paradigm are purely reflexive, because the distractor does not need to be attended in order to successfully perform the task. Moreover, there is no explicit task instruction to ignore the distractor. The distractor is therefore task-irrelevant (see also Godijn & Kramer, 2006).

The difference between the antisaccade and the oculomotor capture tasks is not trivial, as previous research has revealed that different groups perform differently in these tasks. For instance, whereas antisaccade performance improves with increasing age (i.e., older children make fewer antisaccade errors than younger children), younger and older children are not differently captured by the onset in the oculomotor capture task (Kramer, Gonzalez de Sather, & Cassavaugh, 2005). Similarly, older adults do not make more errors in the standard oculomotor capture task, whereas they make more errors than younger adults in the antisaccade task (Kramer, Hahn, Irwin, & Theeuwes, 2000; Nieuwenhuis, Ridderinkhof, de Jong, Kok, & van der Molen, 2000). Furthermore, children with ADHD perform worse than controls on the antisaccade task (Klein, Raschke, & Brandenbusch, 2003; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Munoz, Armstrong, Hampton, & Moore, 2003), whereas they do not make more errors than controls in the oculomotor capture task (Van der Stigchel et al., 2007). Therefore, the mechanisms and neural substrates underlying oculomotor inhibition in both tasks may differ.

In the current study, we tested four patients, with unilateral lesions involving the FEF, on both the oculomotor capture task and the antisaccade task. Thus, we were able to compare performance on both tasks to investigate whether both types of oculomotor inhibition can be disentangled in patients with lesions to the FEF. From studies in non-human primates, it is known that the FEF code for saccades in contralateral oculomotor space, and thus control contralateral saccades (Bruce, Goldberg, Bushnell, & Stanton, 1985; Sommer & Tehovnik, 1997). Because any behavioral deficits are predicted to be lateralized, the critical analysis for each task is a within-subject comparison of performance in the contra- vs ipsilesional visual fields. This way, the patients act as their own controls. Previous studies have already revealed that there is no imbalance in the oculomotor capture task between both visual fields in healthy controls (Van der Stigchel, Arend, van Koningsbruggen, & Rafal, 2010; Van der Stigchel & Nijboer, 2010). If the FEF are involved in the inhibition in the oculomotor capture task, more saccades to the onset distractor are expected when the distractor is presented in the contralesional visual field compared to the ipsilesional visual field. Similarly, more erroneous prosaccades are expected in the antisaccade task when the onset is presented in the contralesional compared to the ipsilesional visual field.

2. Methods

2.1. Patients

Case 1 is a 72-year old woman who suffered a right middle cerebral artery territory stroke 4 years prior to testing. She initially had left hemiparesis and hemispatial neglect. Symptoms of her neglect recovered, as did her left leg strength. She is living independently and is left with residual spastic weakness and loss of dexterity in the left hand. There is no sensory deficit and clinical examination did not reveal any obvious impairment in eye movements. Her lesion involves part of the dorsolateral prefrontal cortex, the precentral gyrus motor and premotor cortices, undercutting the posterior frontal eye field in the depth of the intersecting precentral and superior frontal sulci.

Case 2 is a 52-year old man with congenital spastic, left hemiplegia and a seizure disorder due to right hemisphere open-lip schizencephally, affecting the frontal operculum, motor and premotor cortices and dorsolateral prefrontal cortex.

Case 3 is an 82-year old man who suffered a small left hemisphere stroke 4 years prior to testing. The only resulting neurological impairment was tactile agnosia in the right hand. The lesion is in the distribution of the middle cerebral artery including the hand area of the precentral gyrus and premotor cortex. It undercuts the precentral sulcus at the intersection with the superior frontal sulcus and extends laterally into the opercular post-central gyrus.

Case 4 is a 52-year old woman who suffered a left hemisphere stroke 8 years prior to testing. The lesion involves Broca's area and extends into the FEF. She initially presented with aphasia and problems with writing and calculation, but these have recovered and she has no motor or visual deficits and no visual neglect or extinction.

Fig. 1 shows the individual scans and a composite group lesion reconstruction on a normalized template brain. The FEF was identified on axial images as the intersection of the superior frontal gyrus and the precentral sulcus, the posterior part of the middle frontal gyrus adjacent to these sulcal landmarks, or the white matter undercutting these landmarks.

None of the patients had additional neurological or psychiatric illness. All participants gave informed consent according to the standards of the Declaration of Helsinki for a protocol that was approved by the institutional review boards of the hospital and the university.

2.2. Apparatus

Eye movements were recorded by an Eyelink1000 system (SR Research Ltd., Canada), an infra-red video-based eye tracker that has a 1000 Hz temporal resolution and a spatial resolution of .01°. The participant's head was stabilized with a chin rest, and an infrared remote tracking system compensated for any residual head motion. The left eye was monitored. An eye movement was considered a saccade when either eye velocity exceeded 35°/s or eye acceleration exceeded 9500°/s^2. Participants performed both experiments in a sound-attenuated setting, viewing a display monitor from a distance of 57 cm.

2.3. Stimuli and procedure

Each experiment started with a nine-point grid calibration procedure. In addition, simultaneously fixating the center fixation point and pressing the space bar recalibrated the system by zeroing the offset of the measuring device at the start of each trial. In both experiments, the sequence of trials was randomized.

Antisaccade task. See Fig. 2 for an example of the display sequence. Participants were presented with a central fixation point (circle: 2°) and two white placeholders (square: 1°) on a grey background. The placeholders were presented 8° to the left and right of the fixation point and were present throughout the trial. After 400–600 ms, the onset (square: 2°) was presented for 1000 ms. The onset was presented either on the left or right side of fixation. Trials were arranged pseudo-randomly to prevent presentation of more than four successive onsets at the same location. The experiment consisted of 72 experimental trials and 10 practice trials.

Participants were instructed to fixate the center fixation point until the onset appeared. When the onset appeared, participants were to move their eyes to the mirror location of the onset in the opposite visual field. It was stressed that they should try to make a single accurate saccade.

Oculomotor capture task. Participants viewed a display containing a centrally presented fixation cross (1.38°) on a black background. Six green circles (2.30° in diameter) were positioned at one, three, five, seven, nine, and eleven o'clock on an imaginary circle around a central fixation point (radius: 11.50°). After 800 ms, all circles, except one, changed its color to red. The remaining green circle was the target circle. Note that in this task, the target is a singleton, but there is no luminance change at the target location. Thus, search for the target is entirely endogenous, with no reflexive component that might activate a collicularly mediated visual grasp reflex which drives the eyes to foveate a suddenly appearing peripheral stimulus (Machado & Rafal, 2004b).

The target circle was either located at one, five, seven or eleven o'clock (i.e., not on the horizontal meridian). In half of the trials, a red circle was presented simultaneously with an abrupt onset on the same imaginary circle as the other circles. The distractor was always positioned in the opposite field to the target at a fixed position, diametrically opposite to the location of the target. The target display was presented for 2000 ms. The experiment consisted of 344 experimental trials and 24 practice trials. Case 3 was only able to perform 160 experimental trials.

Participants were instructed to fixate the center fixation point until the target was presented, when they were to move their eyes to the target. It was stressed that they should try to make a single accurate saccade.