



# Electroencephalography/magnetoencephalography study of cortical activities preceding prosaccades and antisaccades

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The temporal and spatial characteristics of brain activity preceding prosaccades and antisaccades were investigated using source reconstructions of 64-channel electroencephalography and 148-channel magnetoencephalography data. Stimulus-locked data showed early cuneus activity was stronger during antisaccades, and later occipital gyrus activity was stronger preceding prosaccades, which suggests a top-down influence on early visual processing. Response-locked data showed that supplementary eye field, prefrontal cortex, and medial frontal eye field activity was greater

for antisaccades than for prosaccades prior to saccade generation. Lateral frontal eye field activity appeared to be inhibited prior to antisaccade response generation. The spatial and temporal resolution of combined electroencephalography/magnetoencephalography data allows the evaluation of specific cortical activities preceding saccades and for demonstration of how activities differ as a function of response contingencies. *NeuroReport* 00:000–000  
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## INTRODUCTION

The neural correlates of human saccadic performance are relatively well defined. Functional imaging studies (positron emission topography, functional magnetic resonance imaging; e.g. [1]) have demonstrated that simple prosaccades to the sudden appearance of a visual target are associated with increased activity in parietal, frontal and supplementary eye fields (e.g. [2–5]). With more complex response contingencies, such as antisaccade generation, additional brain areas are recruited to support the required behavior (e.g. [4]). Antisaccade tasks [6] require a movement to the mirror image location of a peripheral cue, and are useful for studying the flexibility and distributed nature of neural processes supporting saccades. Correct performance of antisaccade tasks seems to require support from prefrontal regions [3–5]. There is some debate, however, about the specific region(s) of the prefrontal cortex critical for the correct execution of antisaccades [7].

To demonstrate in humans that a brain region mediates execution of a response, the neuroimaging method should have a sampling rate faster than behavioral response latency; in this case, it should be able to distinguish presaccadic from postsaccadic activity. Data indicate that the lateral prefrontal cortex is part of the functional anatomy correlated with correct antisaccade performance (e.g. [3,5]). However, these studies used neuroimaging methods with relatively slow temporal resolution. Electroencephalography (EEG) and magnetoencephalography (MEG) techniques

provide for direct measurement of neuronal activity with millisecond temporal resolution. Use of EEG/MEG data combined with source localization analysis techniques, therefore, may help determine which brain regions have onset latencies consistent with mediating correct antisaccade performance.

EEG studies of saccadic performance have examined voltages at individual sensor locations (e.g. [8–10]), and have provided information about global brain activity preceding saccades. EEG/MEG measurement at an individual sensor, however, is insufficient to describe the location from which activity is arising in the brain (e.g. [11]). A 32-channel EEG study [12] is the only manuscript in the archival literature that used source modeling to address the time course and distributed nature of neural activity preceding prosaccades and antisaccades.

To evaluate the temporal and spatial characteristics of brain activity preceding prosaccades and antisaccades, data were recorded from 64 EEG and 148 MEG channels. A distributed source algorithm (L2 minimum norm) with sources confined to fixed cortical locations was used to estimate the spatial distribution of brain activity across time using combined EEG/MEG data. This approach allows the localization of multiple centers of brain activity simultaneously [13] and is well suited for analyses of tasks with multiple simultaneously activated sources.

## MATERIALS AND METHODS

**Study participants:** Ten normal right-handed participants (five women, five men; mean age 28.6 years, range=23–43) took part in the study after providing informed consent. EEG and MEG data were recorded on different days (counterbalanced). On a third day structural magnetic resonance images were acquired in order to create a cortical model for source reconstruction. This study was approved by the IRB at the University of Konstanz.

**Saccadic tasks:** Blocks of prosaccade ( $N=400$ ) and antisaccade ( $N=400$ ) trials were presented. All trials started with a central yellow fixation cross. The cross was turned off simultaneously with illumination of a peripheral stimulus (yellow diamond) at either  $\pm 8^\circ$  (80% of trials) or  $\pm 4^\circ$  (20% of trials) visual angle. Only responses to  $8^\circ$  targets were analyzed. On prosaccade trials, the fixation cross was presented for 2000 ms, followed by peripheral stimulus presentation for 500 ms and a blank screen for 500 ms. Participants were told to quickly move their eyes from the fixation point to the peripheral stimulus. Antisaccade trials differed only in that peripheral stimulus presentation lasted 1000 ms (antisaccade responses take longer) and participants were told to quickly move their eyes from the fixation point to the mirror image of the stimulus. Only trials with saccades generated after 90 ms (lower limit of a visually-guided saccade) and before the onset of the blank screen were analyzed.

**Electroencephalography procedure:** Participants were seated 1 m from a color monitor. EEG was recorded continuously from 64 channels referenced to Cz (Neuroscan Medical Systems Inc., Sterling, Virginia, USA) using an Easy Cap positioning system (Falk Minow Inc., Herrsching-Breitbrunn, Germany). Data were sampled at 1000 Hz with an analog bandpass filter of 0.1–200 Hz. Eye movements were recorded using horizontal and vertical electrooculogram. Following data collection, fiducial point and electrode locations were digitized (Polhemus Inc., Colchester, Vermont, USA).

**Magnetoencephalography procedure:** Participants were positioned supine and viewed stimuli projected onto the ceiling of a magnetically shielded room (via a mirror-projection system). MEG was recorded continuously using a 148-channel whole head system (Magnes 2500WH, 4D-Neuroimaging, San Diego, California, USA). Data were sampled at 1017.25 Hz with a bandpass filter of 0.1–200 Hz. Eye movements were recorded using horizontal and vertical electrooculogram. Fiducial point locations and head shape were digitized (Polhemus Inc.) for coregistration of head position relative to MEG sensor locations. Head motion monitoring showed that no participant moved more than 3 mm in any plane.

**Structural magnetic resonance imaging procedure:** Whole brain magnetic resonance images (TR=19, TE=5.6, flip angle=30°, FOV=256, 1 mm isotropic resolution) were acquired across a 256 mm slab using a Philips Gyroscan 1.5T magnet. Individual images were transformed into normalized space and an averaged magnetic resonance image of the group was created (Brain Voyager 2000, Brain Innovation, Maastricht, The Netherlands).

**Data screening:** Raw data were inspected offline for bad channels (fewer than four bad EEG and MEG channels for any participant; bad channels were not used in source reconstruction estimates). Data were screened to eliminate trials with blinks and/or other artifacts in the presaccade period (250 ms before target presentation to saccade onset). EEG data were transformed to an average reference, and MEG data were resampled to 1000 Hz (for synchronization with the EEG data sampling rate) using Matlab (The Mathworks Inc., Natick, Massachusetts, USA). EEG and MEG data were digitally bandpass filtered from 1–40 Hz (6 dB/octave rolloff; forward direction only to avoid introduction of saccade-related activity into preparatory period for generating the saccadic response). Data were scored for saccade latency and percentage of correct antisaccade responses. Stimulus and response-locked averages were generated.

**Combined analyses:** The accuracy of source modeling is enhanced by the simultaneous use of EEG and MEG data [14,15]. Participants' performances (reaction times, correct antisaccades) during EEG and MEG recordings were similar, so these data were used conjointly to estimate sources of neural activity associated with saccade preparation. A conductivity matching factor adjusted EEG data for the impediment to current flow caused by intervening tissues, and, therefore, placed the two measurements on the same strength of neural activity scale [14]. This factor was estimated as 2.25 based on EEG/MEG dipole strengths of the somatosensory evoked response for other participants tested in our laboratory. This estimate is similar to published values (e.g. [14]), and is probably within 50% of the actual value for current participants, suggesting that the combined source reconstructions will be good estimates of their true values [15].

The averaged magnetic resonance image was used for source reconstruction analyses across participants because this procedure simplifies across-participant comparisons with minimal loss of localization accuracy [16,17]. A three-compartment (skin, skull, and liquor) boundary element method realistic head model with standard homogeneous conductivities (0.33, 0.0042, 0.33  $1/\Omega\text{m}$ ) for the three compartments was constructed for the averaged magnetic resonance image (Curry V5.0, Neurosoft Inc., Sterling, Virginia, USA). The cortical gray matter was segmented, and sources were constrained to reside within the cortex, which had 6474 fixed source locations separated by an average of 3.1 mm.

Prior to source analyses, sensors were coregistered to the segmented skin surface using each participant's digitized head shape (from the electrode locations for EEG and the actual digitized head shape for MEG). Distributed source activities were calculated given the combined EEG-MEG data at each time point using L2 minimum norm (Curry V5.0). Noise estimates were obtained from the 250 ms prestimulus period.

Results were smoothed using routines written in Matlab by averaging over each source location and its nearest neighbors (six on average). Source results were averaged over 10-ms segments from 0 to 170 ms *after* each stimulus (yet preceding saccade generation) and 10-ms segments from 160 to 10 ms *before* each response. High signal-to-noise ratio regions of interest were defined by visual inspection of

grand-averaged source reconstruction results (Figs. 1 and 2). Bilateral regions of interest were located in the middle occipital gyrus, cuneus/precuneus at the occipital–parietal border, middle frontal gyrus in the vicinity of the human frontal eye field region (FEF-lat), and superior frontal gyrus in the vicinity of a frontal eye field region associated with volitional saccade generation (FEF-med; [18]). A mesial supplementary eye field location and a right lateral prefrontal cortex area also constituted regions of interest. Average activity over time for an ellipsoid centered on each region was calculated (Figs. 1 and 2). Repeated measures analyses of variance were conducted using within-participants factors of task (prosaccade, antisaccade), time (three periods: stimulus-locked ranges were 50–90, 90–130, and 130–170 ms after stimulus onset; response-locked ranges were 160–110, 110–60, and 60–10 ms before response-onset), and hemisphere (right, left).

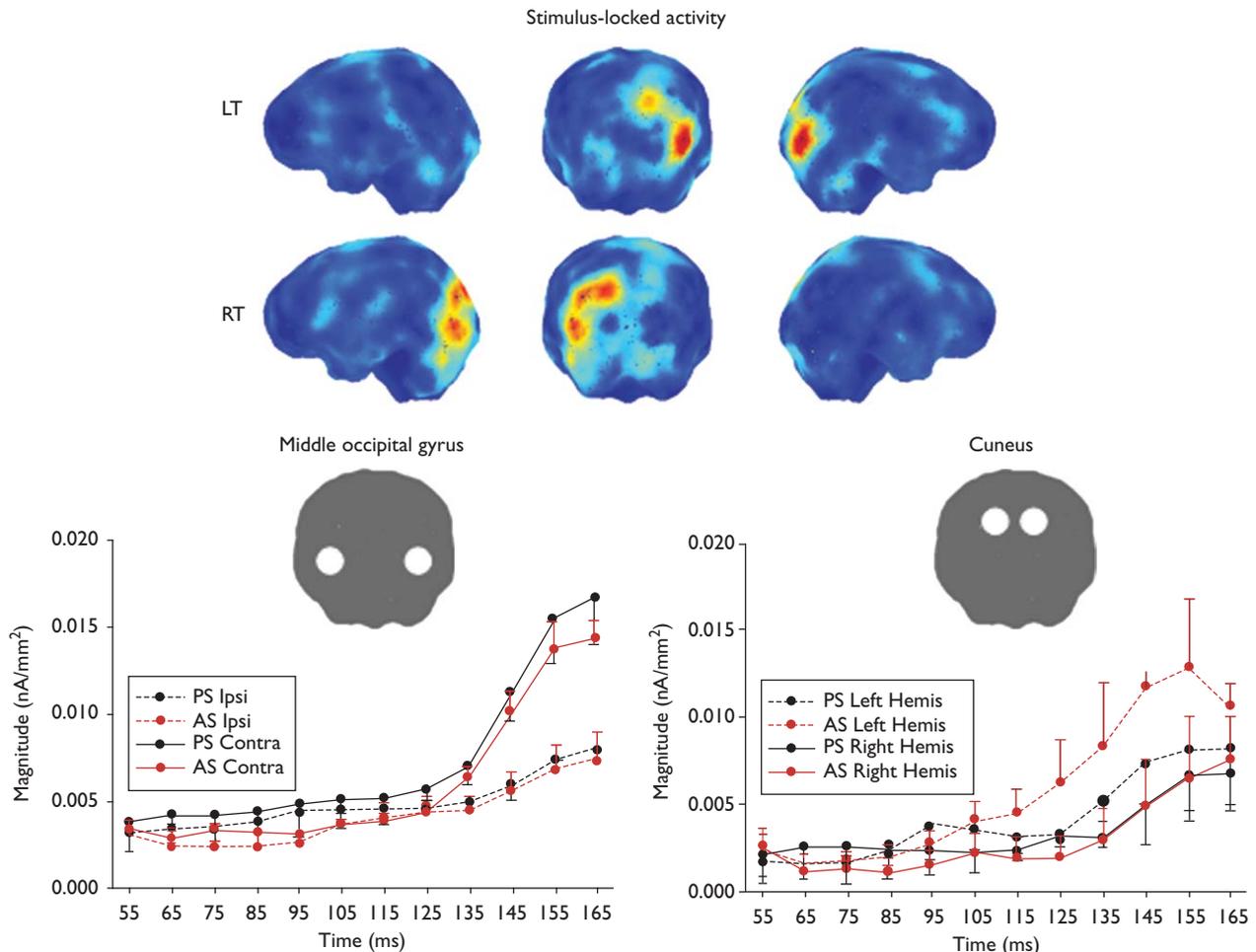
## RESULTS

**Eye movement data:** No significant differences were found between EEG and MEG measures of saccadic latencies (EEG saccades: prosaccade  $M=207$  ms,  $SD=16$ ; antisaccade

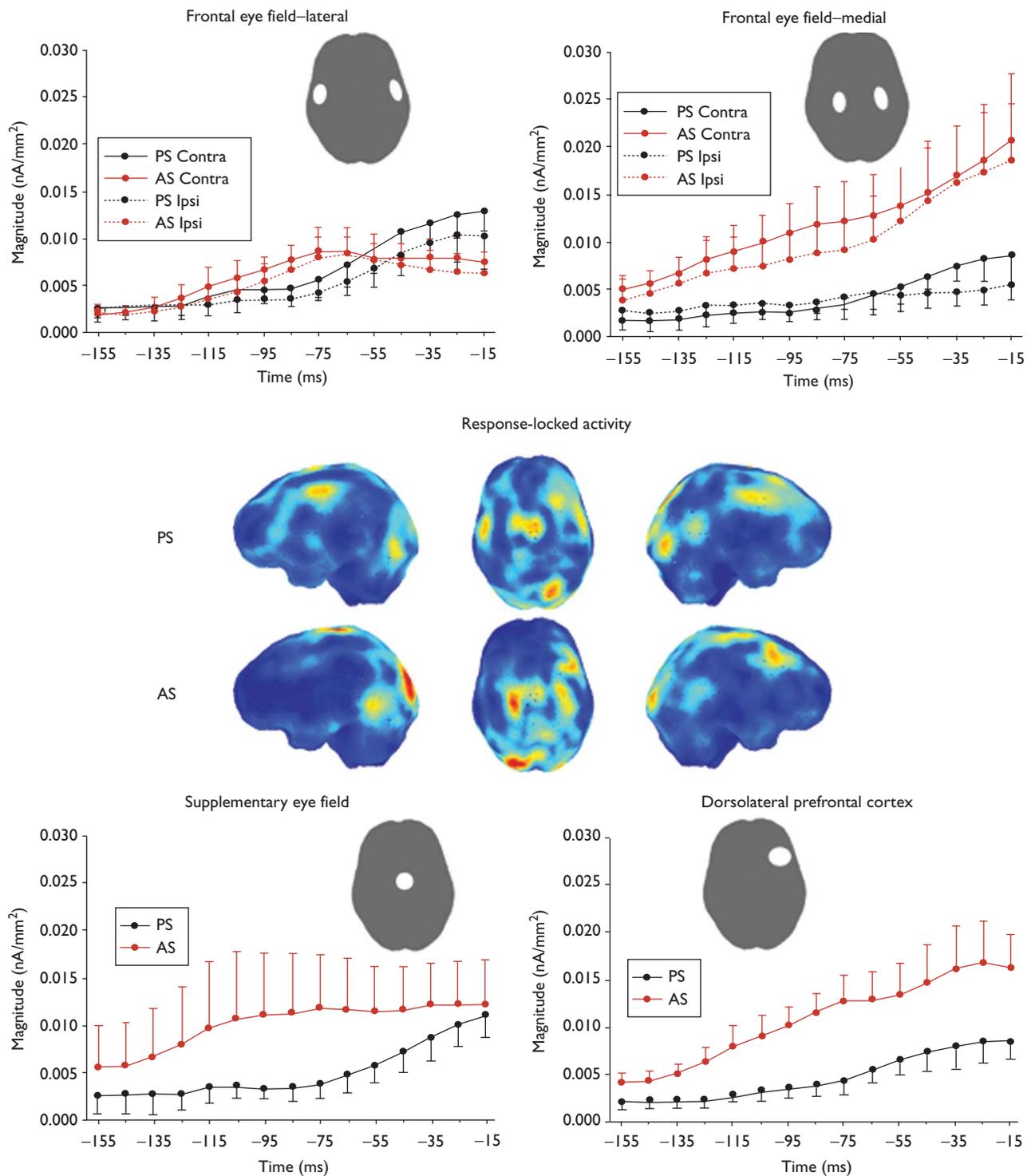
$M=279$  ms,  $SD=30$ ; MEG saccades: prosaccade  $M=206$  ms,  $SD=13$ ; antisaccade  $M=270$  ms,  $SD=26$ ) or percentage of correct antisaccade responses (EEG:  $M=87$ ,  $SD=11$ ; MEG:  $M=88$ ,  $SD=18$ ).

**Stimulus-locked posterior brain regions data (see Fig. 1):** In the middle occipital gyrus, responses to stimuli for prosaccades and antisaccades showed the same pattern of change over time, with contralateral increasing above ipsilateral hemisphere activity during the 130–170 ms post-stimulus interval,  $F(2,18)=4.7$ ,  $p=0.022$ . Nevertheless, a significant main effect of task,  $F(1,9)=5.4$ ,  $p=0.045$ , with greater middle occipital gyrus activity during prosaccade than during antisaccade trials, was observed.

Activity in the cuneus increased above baseline during the 90–130 ms interval,  $F(2,18)=24.0$ ,  $p<0.001$ . A task by time by hemisphere interaction,  $F(2,18)=5.6$ ,  $p=0.013$ , indicated that cuneus activity during antisaccade trials was higher than all other values only in the left hemisphere during the 130–170 ms time segment.



**Fig. 1.** Distributed source activities for stimulus-locked data averaged across prosaccades and antisaccades. The maximum activity across time (from 0–170 ms following stimulus) at each of the 6474 source locations is plotted on left, posterior, and right views of the averaged segmented cortex. Cooler colors indicate less activity and warmer colors indicate more activity. LT and RT indicate activity in response to left and right hemifield targets, respectively. Individual time by activity plots (with standard deviation bars) are shown for regions of interest. The spatial extents of the regions of interest are shown as ellipsoids on accompanying posterior views of the cortex.



**Fig. 2.** Distributed source activities for response-locked data averaged across left and right stimulus presentations (see Fig. 1 caption for details). The maximum activity across time (from 160–10 ms before response) is plotted on left, superior, and right views of the averaged segmented cortex. PS and AS indicate activity preceding prosaccades and antisaccades, respectively.

*Response-locked anterior brain regions data (see Fig. 2):* For FEF-lat, a significant main effect of task,  $F(1,9)=14.7$ ,  $p=0.004$ , with activity in preparation for prosaccades being higher overall, was observed. A significant task by time interaction,  $F(2,18)=23.4$ ,  $p=0.002$ , however, revealed that FEF-lat activity was (1) higher during the

110–60-ms prerespone period preceding antisaccades but (2) higher during the 60–10-ms prerespone period preceding prosaccades.

For FEF-med, a significant main effect of task,  $F(1,9)=16.2=0.003$ , with activity in preparation for antisaccades being higher overall, was observed. The anti/

prosaccade difference steadily increased in magnitude over time,  $F(2,18)=6.9$ ,  $p=0.006$ , and was larger for contralateral than for ipsilateral FEF-med activity,  $F(1,9)=5.4$ ,  $p=0.045$ .

For the supplementary eye field, antisaccade activity was greater than prosaccade activity during the entire presaccade period,  $F(1,9)=12.1$ ,  $p=0.007$ . Likewise, for the prefrontal cortex, antisaccade activity was greater than prosaccade activity over the entire preparatory period,  $F(1,9)=16.3$ ,  $p=0.003$ . This difference was largest, however, during the 110–60 ms period preceding saccade onset,  $F(2,18)=12.5$ ,  $p<0.001$ .

## DISCUSSION

The main results of this study enhance our understanding of neural processing preceding correct prosaccades and antisaccades. The conclusions can be organized around the stimulus and response-locked analyses. Interestingly, the stimulus-locked results provided a better evaluation of activity in posterior brain regions, and the response-locked results yielded better information about activity in frontal brain regions.

Four main findings may be highlighted from the stimulus-locked analyses. First, the middle occipital region demonstrated an expected pattern of increased activity in the hemisphere contralateral to the field of stimulation. Second, activity in this region was greater during prosaccades than during antisaccades throughout the initial 170 ms of stimulus evaluation. Lower activity in this region during antisaccades may reflect a top-down influence on stimulus evaluation as it is considered incorrect to look at the stimulus during this task. Top-down influences on early visual processing are often assumed in similar tasks (e.g. [19]), but this is among the first reports that demonstrates clear evidence of a specific and early top-down influence on neural activity during antisaccade processing. Third, during initial stimulus processing the cuneus region showed above-baseline activity by 90 ms, a more rapid onset than was observed in middle occipital regions. This result is consistent with previous work in human [20] and nonhuman primates [21] suggesting that cuneus activity may influence activity in earlier visual association regions like the middle occipital gyrus. Fourth, after 130 ms, cuneus activity during antisaccade trials rose above that observed during prosaccade trials, which may be consistent with the thesis that parietal cortex activity during correct antisaccade trials computes the requisite coordinate transformation prior to response generation (e.g. [21]).

The response-locked results suggest two primary conclusions. First, they support indications from the stimulus-locked data that antisaccade performance may be mediated by top-down processing, because even the early activity (up to 160 ms before response generation) is greater prior to antisaccade responses than to prosaccade responses (see e.g. [22] for a similar baseline shift finding in the visual attention literature). This baseline difference was present in the medial frontal and supplementary eye fields, and in the prefrontal cortex. Although this analysis was not presented, the same pattern of higher activity during antisaccades than during prosaccades was also demonstrated for the cuneus region (similar to that observed during the stimulus-locked data). Tonic activity may be the cortical manifestation of maintenance of an instructional set (e.g. [4]).

Second, lateral FEFs demonstrate a distinct pattern of activity. After an initial rise, lateral FEF activity leveled off approximately 70 ms before the antisaccade response. Conversely, the pattern for prosaccades showed a rapid rise continuing up until response generation. Given the putative role of FEF in saccade triggering [23], the patterns may indicate that the initial saccade toward the cue is programmed but subsequently aborted during antisaccade trials. The inhibitory message received by the FEF may come from the supplementary eye field [24], prefrontal cortex, or even medial FEF, all of which showed strong activity during antisaccade trials. The present, simple paradigms, however, do not allow for differentiation of these latter brain regions' functional roles during antisaccade performance. Using tasks that help separate neural responses to an abruptly appearing stimulus from those associated with preparation for a response (e.g. [25]) will help to more clearly evaluate their unique contributions to correct antisaccade performance.

## CONCLUSION

Stimulus-locked cuneus activity and lower activity in the middle occipital region during antisaccades may be evidence of top-down processing. Response-locked activity in the medial FEF, supplementary eye field, and prefrontal cortex, greater for antisaccades than for prosaccades, observed prior to response generation suggests that these areas may be involved in the inhibition of a glance toward the peripheral cue.

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