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Saccadic Preparation in the Frontal Eye Field Is Modulated by Distinct Trial History Effects as Revealed by Magnetoencephalography

Adrian K. C. Lee[1,2], Matti S. Hämäläinen[2,3], Kara A. Dyckman[1], Jason J. S. Barton[4] and Dara S. Manoach[1,2]

[1]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02215, USA, [2]Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA 02129, USA, [3]Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02215, USA and [4]Department of Neurology and Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada

Address correspondence to Dara S. Manoach, Department of Psychiatry, Massachusetts General Hospital, 149 13th Street, Room 1.111, Charlestown, MA 02129, USA. Email: dara@nmr.mgh.harvard.edu.

Optimizing outcomes involves rapidly and continuously adjusting behavior based on context. While most behavioral studies focus on immediate task conditions, responses to events are also influenced by recent history. We used magnetoencephalography and a saccadic paradigm to investigate the neural bases of 2 trial history effects that are well characterized in the behavioral eye movement literature: task-switching and the prior-antisaccade effect. We found that switched trials were associated with increased errors and transient increases in activity in the frontal eye field (FEF) and anterior cingulate cortex early in the preparatory period. These activity changes are consistent with active reconfiguration of the task set, a time-limited process that is triggered by the instructional cue. Following an antisaccade versus prosaccade, there was increased activity in the FEF and prefrontal cortex that persisted into the preparatory period of the subsequent trial, and saccadic latencies were prolonged. We attribute these effects to persistent inhibition of the ocular motor response system from the prior antisaccade. These findings refine our understanding of how trial history interacts with current task demands to adjust responses. Such dynamic modulations of neural activity and behavior by recent experience are at the heart of adaptive flexible behavior.

Keywords: antisaccade, frontal eye field, magnetoencephalography, saccade, task-switching

Introduction

To optimize outcomes, it is necessary to rapidly and continuously adjust behavior based on context. While most studies of behavior focus on immediate task conditions, to be adaptive, behavior must also be influenced by recent history (Fecteau and Munoz 2003). Using magnetoencephalography (MEG) and a saccadic paradigm, we investigated the neural basis of 2 trial history effects that have been well characterized in behavioral eye movement studies: task-switching and the prior-antisaccade effect. Antisaccades require inhibition of the prepotent response of looking toward a suddenly appearing visual stimulus (i.e., a prosaccade) and the substitution of a gaze in the opposite direction (Hallett 1978).

Task-switching often increases both error rate and response latency (Meiran et al. 2000; Barton et al. 2006). Such "switch costs" have been attributed to an active reconfiguration of the task set (Rogers and Monsell 1995). However, even when the interval between the cue that indicates which task to perform and the stimulus, which prompts the response, is long enough to permit completion of active task-set reconfiguration, "residual costs" remain. These residual costs are thought to reflect passive carryover effects from the prior trial (Rogers and Monsell 1995; Meiran et al. 2000). If the prior trial was an antisaccade, the net residual cost is to prolong the onset latency of the upcoming saccade—the "prior-antisaccade effect" (Cherkasova et al. 2002; Barton et al. 2006).

We have hypothesized that the prior-antisaccade effect reflects inhibitory activity from the previous antisaccade that reduces preparatory activity in the frontal eye field (FEF) and increases the time needed to surpass the threshold for triggering a saccade (Barton et al. 2006; Manoach et al. 2007). This hypothesis is based on observations from monkey neurophysiology studies and human neuroimaging and behavioral studies. First, compared with a cue to perform a prosaccade, an antisaccade cue suppresses the preparatory activity of saccade-related neurons in the FEF and superior colliculus, an effect that correlates with increased saccadic latency (Everling et al. 1999; Everling and Munoz 2000). Human neuroimaging studies also provide evidence that the FEF is inhibited for antisaccades compared with prosaccades (e.g., O'Driscoll et al. 1995; Sweeney et al. 1996; Connolly et al. 2002; Ford et al. 2005; for review, see McDowell et al. 2008) and that FEF activity correlates with saccadic latency (Connolly et al. 2005). Second, other aspects of saccades, such as directional congruency, influence both saccadic latency (Fecteau et al. 2004; Anderson et al. 2008) and preparatory activity in the FEF and superior colliculus in the subsequent trial (Dorris et al. 2000; Bichot and Schall 2002). A prior study of countermanding performance in both humans and monkeys found that saccadic latency increased after successive stop-signal trials, which require inhibition of a planned saccadic response (Emeric et al. 2007). Thus, we speculated that the powerful inhibition required for an antisaccade might also persist in the ocular motor system, reducing preparatory activity and prolonging saccadic latency in the subsequent trial. Our prior functional magnetic resonance imaging (fMRI) finding of reduced FEF activation for trials preceded by antisaccades compared with prosaccades supports this hypothesis (Manoach et al. 2007).

In the present study, we expected the persistent effects of a prior antisaccade to result in differential FEF activity during the baseline period, which precedes the onset of the instructional cue, and to persist into the preparatory period of the present trial. We also expected to see differential preparatory FEF activity for switched versus repeated trials that was prompted by the instructional cue and represented active task-set reconfiguration.

Materials and Methods

This study used the same participants and the same saccadic paradigm as in our companion fMRI study of trial history effects (Manoach et al. 2007).

Participants

Twenty healthy participants were recruited by poster and website advertisements. The data from one participant were excluded from analysis because more than half of the saccadic trials were unusable due to the presence of blinks. The remaining 19 participants (12 males; mean age, 33 ± 12 years) were strongly right-handed as determined by a laterality score ⩾70 on the modified Edinburgh Handedness Inventory (White and Ashton 1976; Schachter 1994). Prior to scanning, participants practiced the task and were encouraged to respond as quickly and accurately as possible. In addition to a base rate of pay, they received a bonus of 5 cents for each correct response, an incentive intended to enhance attention and motivation. All participants gave written informed consent, and the study was approved by the Human Research Committee at Massachusetts General Hospital.

Saccadic Paradigm

Task stimuli were generated using the Vision Shell programming platform and presented with a Digital Light Processing InFocus 350 projector (Texas Instruments, http://www.dlp.com) through an opening in the wall of the room onto a back-projection screen placed 1 m in front of the participant. Each participant performed 8 task runs (Fig. 1). Each run lasted 5 min 22 s and consisted of a pseudorandom sequence of prosaccade, antisaccade, and fixation trials. Saccadic trials lasted 4 s and were balanced for right and left movements. They began with the presentation of an instructional cue at screen center for 300 ms, followed by a fixation ring for 1700 ms (for details, see Fig. 1). At 2000 ms, the green fixation ring shifted to either the right or the left target location with equal probability. This was the stimulus to which participants responded. At 3000 ms, the fixation ring returned to the center. Fixation trials lasted 2, 4, or 6 s. The total experiment lasted approximately 1 h and generated a total of 278 prosaccade, 285 antisaccade, and 107 fixation trials.

Saccadic trials were divided into 4 types according to the identity of both the current and the prior trial: antisaccades preceded by an antisaccade (as/AS), antisaccades preceded by a prosaccade (ps/AS), prosaccades preceded by an antisaccade (as/PS), and prosaccades preceded by a prosaccade (ps/PS). We combined trial types to examine each trial history effect. To examine task-switching, we compared FEF activity in switched (ps/AS, as/PS) versus repeated trials (as/AS, ps/PS). To examine prior-antisaccade effects, we compared FEF activity in trials preceded by antisaccades (as/AS, as/PS) versus trials preceded by prosaccades (ps/AS, ps/PS).

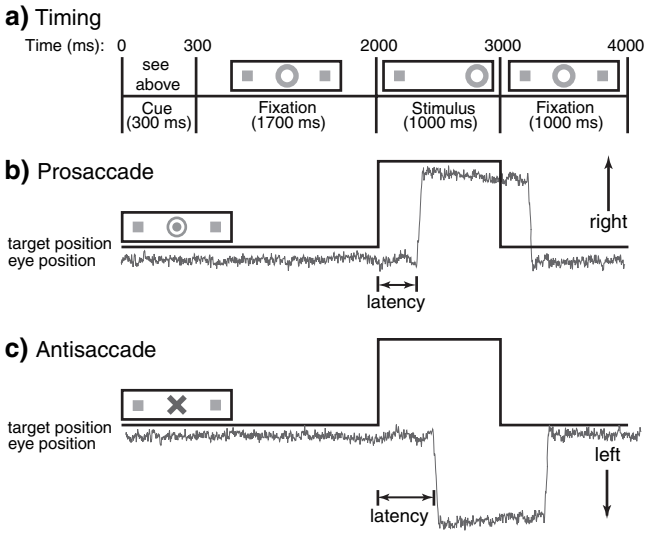

Figure 1. Saccadic paradigm with idealized eye position traces. Saccadic trials lasted 4000 ms and began with an instructional cue at the center of the screen. (*a*) At 300 ms, the instructional cue was replaced by a green fixation ring at the center of the screen, of 0.4° diameter and luminance of 20 cd/m^2. After 1700 ms, the ring shifted to one of the 2 target locations, right or left, with equal probability. This was the stimulus to which the participant responded. The green ring remained in the peripheral location for 1000 ms before the start of the next trial. Fixation intervals were simply a continuation of the fixation display that constituted the final second of the previous saccadic trial. For half of the participants, orange concentric rings were the cue for a prosaccade trial (*b*) and a blue X was the cue for an antisaccade trial (*c*). These cues were reversed for the rest of the participants. The cue was flanked horizontally by 2 small green squares 0.2° wide that marked the potential locations of targets, 10° left and right of center. These squares remained on the screen for the duration of each run.

MEG Data Acquisition

MEG data were acquired inside a magnetically shielded room (IMEDCO) using a dc-SQUID Neuromag VectorView system (Elekta-Neuromag) comprising 306 sensors arranged in triplets of 2 orthogonal planar gradiometers and a magnetometer, distributed at 102 locations around the entire scalp. The data were filtered to 0.1–200 Hz bandpass and sampled at 600 Hz. The horizontal and vertical components of eye movements were recorded concurrently with MEG, using 2 pairs of bipolar electrooculogram (EOG) electrodes.

To allow registration of MEG and MRI data and to record head position relative to the sensor array, the locations of 3 fiduciary points (nasion and auricular points) defining a head-based coordinate system, the sites of 4 head position indicator (HPI) coils, and a set of points from the head surface were digitized using a 3Space Fastrak digitizer (Polhemus) integrated with the Vectorview system. During the MEG recording, the position and orientation of the head with respect to the MEG sensor array were determined with the help of the HPI coils. In the beginning of each acquisition, currents were fed to these coils and their magnetic fields were used to calculate the relative location of the head and the MEG sensor array.

Structural MRI Acquisition

For source estimation and visualization, 2 T1-weighted high-resolution structural images were acquired for spatial normalization and cortical surface reconstruction using a 3.0 T Siemens Trio whole-body high-speed imaging device equipped for echoplanar imaging and a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time, 2530 ms; echo spacing, 7.25 ms; echo time, 3 ms; flip angle 7°; and voxel size, 1.3 × 1.3 × 1 mm). Each scan took 8 min 45 s. A 3D structural image was created for each participant by averaging the 2 MPRAGE scans after correcting for motion using FLIRT (Jenkinson and Smith 2001).

Scoring of Eye Movement Data

EOG data were scored in MATLAB (Mathworks) using a partially automated program that determined the directional accuracy of each saccade with respect to the required response and the latency from stimulus onset. Saccades were identified as horizontal eye movements with velocities exceeding 46.9°/s. The onset of a saccade was defined as the point at which the velocity of the eye first exceeded 31.3°/s. Only trials with initial saccades in the correct direction and with latencies between 130 and 800 ms were included in the analyses. The cutoff of 130 ms excluded anticipatory saccades, which are not true responses to the appearance of the stimulus (Fischer and Breitmeyer 1987; Doricchi et al. 1997; Straube et al. 1999). Trials with eye blinks (defined as vertical peak-to-peak EOG amplitude exceeding 200 μV) prior to saccadic response were rejected from further analysis. We also excluded trials if a saccade occurred during the baseline period or the cue–stimulus interval (Fig. 1*a*; i.e., 0–2000 ms). To capture the historical effects of interest, we excluded both error trials and trials preceded by an error. On average, there were 188 ± 51 prosaccade (as/PS: 93 ± 26; ps/PS: 95 ± 27) and 180 ± 62 antisaccade trials (as/AS: 88 ± 31; ps/AS: 92 ± 31) included in the analysis for each participant. Latency and error rate data were analyzed with repeated measures analyses of variance of current trial type, prior trial type, and their interaction. Error rate data were logit-transformed before analysis.

Preprocessing of MEG Data

All channels were processed using the signal-space separation method (Taulu et al. 2005). This algorithm suppresses both environmental noise

and biological artifacts while maintaining the neuromagnetic signals based on Maxwell's equations and the geometry of the sensor array only, with the assumption that the sensors are located in a current free volume. For off-line averaging, each participant's continuous MEG data were low-pass filtered at 40 Hz. The waveforms for each of the 4 trial types were then averaged for each participant. Only trials meeting amplitude criteria (gradiometer peak-to-peak limit: 3000 fT/cm and magnetometer peak-to-peak limit: 10 pT) were included. A 200-ms interval prior to the appearance of the cue was used as baseline and subtracted from each epoch before the trial was added to the average.

Individual Source Estimates on the Cortical Surface

For source estimation, we used the analysis stream implemented in our MNE software (http://www.martinos.org/martinos/userInfo/data/sofMNE.php). The geometry of each participant's cortical surface was reconstructed from their 3D structural MRI data using FreeSurfer software (http://surfer.nmr.mgh.harvard.edu). This high-resolution triangulation of each hemisphere comprised ~100 000 vertices and was decimated to a subset of approximately 3000 dipole locations (vertices) per hemisphere. The forward solution was calculated using a single-compartment boundary-element model (Hämäläinen and Sarvas 1989) with the inner skull surface segmented from the MRI data. The head position information from the start of each run was used in the calculation of the forward solution for each run. The amplitudes of the dipoles at each cortical location were estimated every 4 ms using the anatomically constrained linear estimation approach (Hämäläinen and Ilmoniemi 1984; Dale and Sereno 1993; Dale et al. 2000). The orientations of the dipoles were loosely constrained to the cortical normal direction by setting source variances for the transverse current components to be 0.1 times the variance of the currents normal to the cortical surface (Lin et al. 2006). The inverse solutions were temporally smoothed by integrating over an interval extending 2 ms in each direction.

Intersubject Registration for Group-Level Source Estimates on the Cortical Surface

As a first step for averaging the source amplitudes across participants, we applied a spreading operation in each participant, which distributes the values from the vertices employed in the source estimation to neighboring vertices so that every vertex in the dense triangulation of the cortical mantle had a value associated with it. Specifically, at each of the 5 successive applications of the spreading operator, the new value at a vertex was the sum of its own value and the values of the immediate neighbors, divided by the number of nonzero values included. Each participant's inflated cortical surface was then registered to a template brain consisting of the averaged cortical surface of an independent sample of 40 adults from the Buckner laboratory at Washington University (St Louis, MO) by optimally aligning individual sulcal–gyral patterns (Fischl et al. 1999). This technique provides more accurate intersubject alignment of cortical regions than volume-based approaches (Fischl et al. 1999; Van Essen and Dierker 2007). Using this surface-based registration, the dense individual source localization data from the first step were then mapped to the averaged cortical surface and decimated a second time to yield an identical set of vertices for each participant. Finally, the results were averaged across participants.

Region of Interest Definition

Our a priori hypotheses concerned the FEF, located in and around the precentral sulcus and gyrus (Paus 1996; Koyama et al. 2004) with distinct regions in the superior and inferior portions (Luna et al. 1998; Simo et al. 2005). Since MEG is best able to detect tangential sources (i.e., those in sulci rather than gyri on the lateral surface), our anatomical constraints were the superior and inferior precentral sulci defined by an automated surface-based parcellation (Fischl et al. 2004). Within these sulci, we functionally constrained the FEF regions of interest (ROIs) to vertices showing activity (i.e., differences in dipole strengths) in the all trials versus fixation contrast in the averaged group data at a threshold of $P < 0.01$. This contrast captures all vertices showing saccadic activity regardless of the identity of either the current or the prior trial and is therefore unbiased with regard to hypotheses concerning trial history or the current trial type. For this analysis, activity was estimated every 20 ms between 100 and 2400 ms and vertices meeting criteria at any time point were included in the ROI. The resulting 2 FEF ROI labels, one in each hemisphere, are shown in Figure 2. Inflated cortical surfaces are employed in visualization to display activity in the sulci. We defined ROIs for 2 additional cortical regions, the inferior frontal sulcus (IFS) and the dorsal anterior cingulate cortex (dACC), based on our findings. These findings and the methods of ROI definition are described in results.

Evaluation of Trial History Effects

The trial history contrasts of interest were 1) switched versus repeated trials and 2) prior antisaccade versus prior prosaccade trials. Activity estimates for these contrasts were computed at each vertex on the cortical surface and within each ROI using paired *t*-tests. For the ROI-based analyses, activity was averaged across all vertices in the right and left ROIs. We examined these trial history contrasts during 3 intervals: 1) baseline interval (−200 to 0 ms, cue-locked). Activity for trials preceded by an antisaccade versus a prosaccade was averaged over the 200 ms that preceded the appearance of the cue (0 ms); 2) cue–stimulus interval (0–2000 ms, cue-locked). This is an analysis of trial history effects during the present trial using baseline-corrected data; and 3) saccade preparation interval (−300 to 0 ms, saccade-locked). This analysis of baseline-corrected data was time-locked to saccadic initiation (0 ms). For 2 and 3, the cue–stimulus and saccade preparation intervals, respectively, trial history contrasts were computed for the average activity in each 4-ms time window.

To correct for multiple comparisons over time, we considered a difference to be statistically significant only if 5 consecutive time points met a threshold of $P < 0.05$ (Chait et al. 2007). This method would give rise to an alpha value of $P = (0.05)^5 = \sim 10^{-6}$, if each of the 4-ms time periods was independent and identically distributed. However, since low-pass filtering of the MEG data results in correlations between time points, we used a simulation to quantify the likelihood that 5 consecutive time points would meet a threshold of $P < 0.05$ by chance. We generated 2 zero-mean Gaussian time series and low-pass filtered with the same filter that was applied to the MEG data. We then performed *t*-test comparisons at each time point and recorded the number of instances that 4, 5, 6, 7, or 8 consecutive time points met a threshold of $P < 0.05$. We repeated this procedure 10 000 times for Gaussian distributions with standard deviations (SDs) of 0.1, 1, and 10. The simulations for all 3 SDs indicated that using 5 consecutive time points at a threshold of $P < 0.05$ sets the overall alpha to $P < 0.05$.

Evaluation of Timing Differences

To evaluate whether the timing of the onset of significant activity in FEF and other ROIs differed significantly, we employed bootstrapping procedures (Efron and Tibshirani 1993) tailored to the data produced by the contrast of interest: 1) switched versus repeated trials and 2) prior antisaccade versus prior prosaccade trials. In both cases, the overall alpha level was set to $P < 0.05$. The general procedure consisted of the following 2 initial steps: 1) computing a difference waveform for the contrast of interest for each participant and 2) generating 5000 averaged bootstrap samples using random draws with replacement from these participant waveforms ($n = 19$). For the task-switching contrast, which gave rise to brief discrete epochs of differential activation, we then 3) computed *t*-tests at each time point; 4) identified the statistically significant epoch (i.e., 5 consecutive time points meeting a threshold of $P < 0.05$); and 5) computed 95% confidence intervals (CIs) for the onset time of the identified significant period. For the prior-antisaccade contrast, which gave rise to sustained differences in activation, we wanted to determine whether the timing of the onset of this activation differed by region. This involved 3) parameterizing the bootstrapped iterations of the difference waveform using a sigmoidal function; 4) determining the time of divergence based on the time at which the sigmoidal function reached 50% of the bounded values; and 5) computing 95% CIs for the time of divergence.

Results

Behavioral Data

Only correct nonanticipatory saccades were included in the latency analyses (Fig. 3 and Table 1). To examine the effects of trial history on latency, we only analyzed correct trials preceded by correct trials. One participant, who showed a prior-antisaccade latency effect that was more than 2 SDs from the group mean, was excluded from these analyses. The main effects of current and prior saccade type were both significant. Antisaccades had longer latencies than prosaccades ($F_{1,17}$ = 71.4, P < 0.001). In addition, compared with a prior prosaccade, an antisaccade in the prior trial was associated with slower latencies ($F_{1,17}$ = 6.59, P = 0.02). There was no interaction between current and prior saccade types ($F_{1,17}$ = 2.08, P = 0.17) reflecting that a prior antisaccade slowed latencies regardless of whether the current trial was a prosaccade or an antisaccade.

The pattern of findings for accuracy was different. There was a main effect of current saccade type reflecting a higher error rate for antisaccades than prosaccades ($F_{1,18}$ = 20.62, P < 0.001; 13.00 ± 14.1% vs. 4.0 ± 3.4%), but there was no main effect of a prior antisaccade on error rate ($F_{1,18}$ = 2.80, P = 0.11). Rather, a prior antisaccade affected antisaccade and prosaccade error rates differently (current trial type × prior trial type: $F_{1,18}$ = 17.01, P = 0.001). This interaction reflected that there were more errors for switched than repeated trials of both types as revealed by pairwise t-tests (prosaccades: t_{18} = 3.19, P = 0.005; antisaccades: t_{18} = 3.88, P = 0.001).

These findings are consistent with our previous reports and demonstrate divergent effects of trial history on latency and accuracy (Cherkasova et al. 2002; Barton et al. 2006; Manoach et al. 2007). With cue–stimulus intervals that are long enough to allow completion of active task-set reconfiguration, as in the present paradigm, task-switching dominates error costs, but the prior-antisaccade effect dominates latency costs.

MEG Data

Baseline Interval (−200 to 0 ms, Cue-Locked)

This analysis of averaged activity in the 200 ms that precedes the appearance of the cue reveals persistent effects of the prior trial before the current trial type is known. During this baseline interval, there was greater FEF activity for trials preceded by an antisaccade than a prosaccade in the left inferior FEF (maximum vertex P = 0.002) (Fig. 4). There was also greater baseline activity in the central sulci, intraparietal sulci, and IFS, primarily in the left hemisphere. The signal in the IFS is of particular interest since it reflects activity in dorsolateral and/or ventrolateral prefrontal cortex, which are thought to be involved in the generation of antisaccades (Dyckman et al. 2007; McDowell et al. 2008). Since MEG is best able to detect tangential sources, this activity would be most apparent in lateral prefrontal sulci such as the IFS. To evaluate whether the IFS also showed a prior-antisaccade effect in the preparatory period of the present trial, we defined an ROI for IFS as vertices in either left or right IFS that showed a prior-antisaccade effect during the baseline interval (P < 0.05).

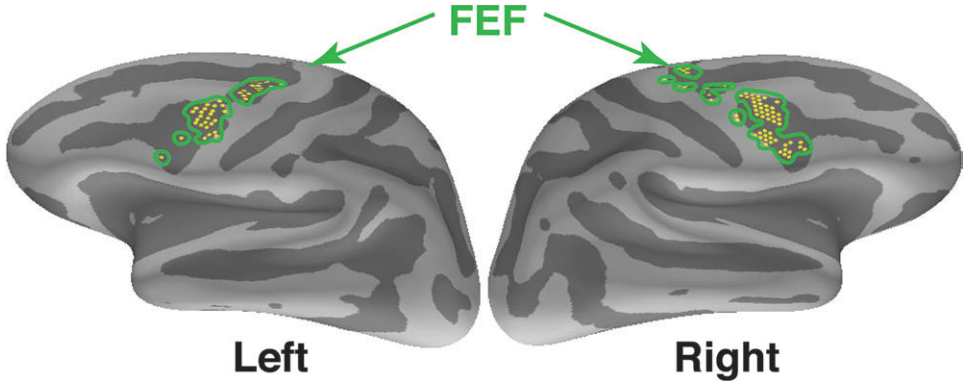

Figure 2. FEF ROI, defined using anatomical and functional criteria (see "ROI definition" in Materials and Methods) displayed on the inflated lateral cortical surfaces. Yellow dots represent included vertices and the green outlines show the spatial coverage after smoothing.

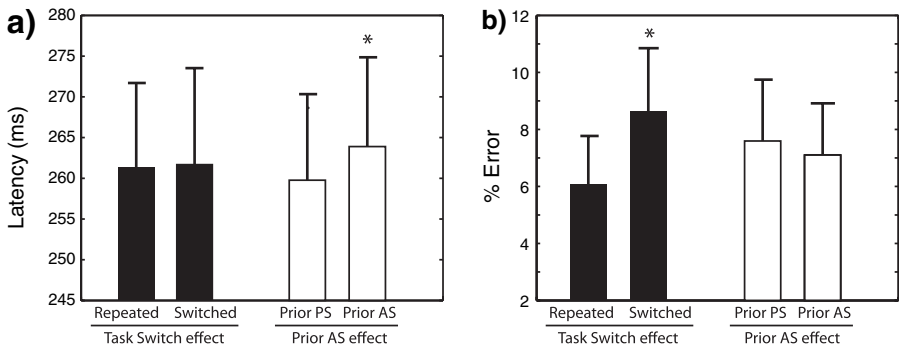

Figure 3. Trial history effects on behavior. Bar graphs with SE bars for task-switching and the prior-antisaccade effect: (*a*) latency in milliseconds and (*b*) percent errors. An asterisk denotes statistical significance based on a repeated measures analyses of variance at P < 0.05. AS, antisaccade; PS, prosaccade, SE, standard error.

Cue–Stimulus Interval (0–2000 ms, Cue-Locked)

Activity in this period was examined after adjusting for differences in baseline activity. This activity reflects general task preparation but not the planning of the actual saccadic response since the required direction of the eye movement is not known until the stimulus appears. We first evaluated the task-switch effect. The FEF showed a brief transient period of significantly greater activity for switched versus repeated trials that began shortly after the appearance of the instructional cue and rapidly dissipated (432–456 ms; Fig. 5). This difference was most pronounced in the left inferior FEF. We also observed a similar transient increase for switched versus repeated trials in the dACC (296–316 ms; Fig. 5). This finding is noteworthy because it is consistent with a previous study showing that neurons in the dACC show greater task-selective activity when monkeys switch between prosaccades and antisaccades (Johnston et al. 2007). To compute the time course of activity in the dACC, we defined a dACC ROI by dividing the anterior cingulate cortex, as defined by an automated surface-based parcellation system (Fischl et al. 2004), into dorsal and rostral segments by drawing a line perpendicular to the intercommissural plane at the anterior boundary of the genu of the corpus callosum (Devinsky et al. 1995). A bootstrapping analysis confirmed that the onset of significant activity related to task-switching occurred earlier in the dACC than the FEF (dACC: 357 ± 3 ms, FEF: 447 ± 4 ms), corresponding to a difference of 90 ± 5 ms (mean and 95% CI). The IFS, in contrast, did not show a significant task-switch effect.

We next evaluated the prior-antisaccade effect. In the FEF, there was greater activity for prior antisaccades than prior prosaccades that reached significance at 460 ms and was sustained for the rest of the cue–stimulus interval (Fig. 6). This difference was most pronounced in the same left inferior FEF region that showed greater activity for a prior antisaccade during the baseline period. The IFS also showed greater activity for a prior antisaccade that first reached significance at 344 ms and was sustained for the rest of the prestimulus period. A bootstrapping analysis confirmed that the prior-antisaccade effect started earlier in the IFS than in the FEF (IFS: 447 ± 11 ms, FEF: 688 ± 11 ms), corresponding to a difference of 241 ± 15 ms (mean and 95% CI). In contrast to the FEF and the IFS, there was no prior-antisaccade effect in the dACC.

Saccade Preparation Interval (–300 to 0 ms, Saccade-Locked)

Finally, we examined preparatory activity time-locked to saccadic initiation (0 ms). Activity in this interval likely reflects preparation to execute a saccade in a specific direction. No significant task-switch or prior-antisaccade effects were observed in the FEF, IFS, or dACC.

Table 1

Means, SEs, and paired *t*-tests for latency and error data by trial type

Latency

Current task	AS		PS	
Prior task	as	ps	as	ps
Mean ± SE (ms)	294.4 ± 13.2	287.8 ± 13.5	237.5 ± 9.8	235.2 ± 8.9
Paired *t*-test	$t_{17} = 2.28$, $P = 0.036$		$t_{17} = 1.63$, $P = 0.121$	

% Error

Current task	AS		PS	
Prior task	as	ps	as	ps
Mean ± SE (%)	12.7 ± 4	16.3 ± 6	3.8 ± 0.7	1.8 ± 0.3
Paired *t*-test[a]	$t_{18} = 3.88$, $P = 0.001$		$t_{18} = 3.19$, $P = 0.005$	

[a]Based on logit-transformed error rates. AS, antisaccade; PS, prosaccade; SE, standard error.

Discussion

Our findings complement recent work demonstrating that behavioral and neural responses to events are modulated by recent history. Here, we exploited the high temporal resolution of MEG to characterize 2 trial history effects on FEF activity: the task-switching and the prior-antisaccade effect. Compared with repeating a task, having to switch tasks was associated with a higher error rate, consistent with our prior behavioral work using this task (Cherkasova et al. 2002; Barton et al. 2006). Correct switched versus repeated trials were associated with significantly greater preparatory FEF activation that started 432 ms following the onset of the instructional cue and rapidly dissipated. This activation was most pronounced in the inferior FEF, a region that consistently shows increased fMRI activity during task-switching (Derrfuss et al. 2005). This discrete period of increased activity for task-switching is consistent with behavioral findings suggesting that active task-set reconfiguration is triggered by the instructional cue and completed within 600 ms (Rogers and Monsell 1995). Although our "a priori" ROI was the FEF, we also observed a task-switch effect in the dACC. This is consistent with single-unit recordings in monkeys showing increased task-selective activity of dACC neurons when switching between prosaccades and antisaccades (Johnston et al. 2007). The dACC projects to the FEF and the superior colliculus (Leichnetz et al. 1981; Wang et al. 2004) and may contribute to top–down control of these structures during task-switching (Johnston et al. 2007).

Concerning the prior-antisaccade effect, trials preceded by an antisaccade had greater activity not only in the "a priori" ROI, the FEF, but also in the IFS during the baseline period, immediately prior to the instructional cue, than trials preceded by a prosaccade. This demonstrates persistent effects of

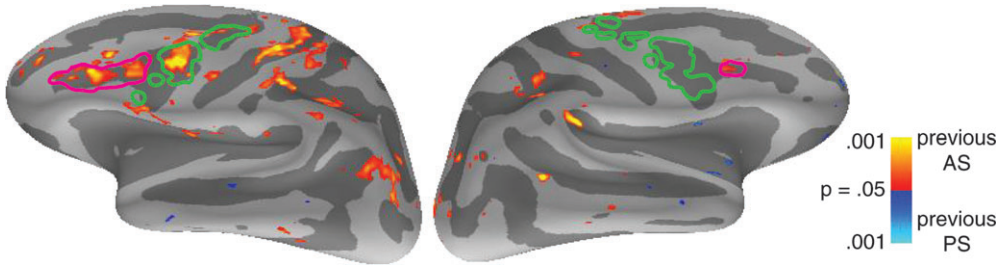

Figure 4. Prior-antisaccade effects during the baseline interval. Vertices showing increased activation for trials preceded by an antisaccade versus a prosaccade are displayed on the inflated lateral cortical surfaces in warm colors at a threshold of $P < 0.05$. The FEF ROI is outlined in green and IFS is outlined in magenta.

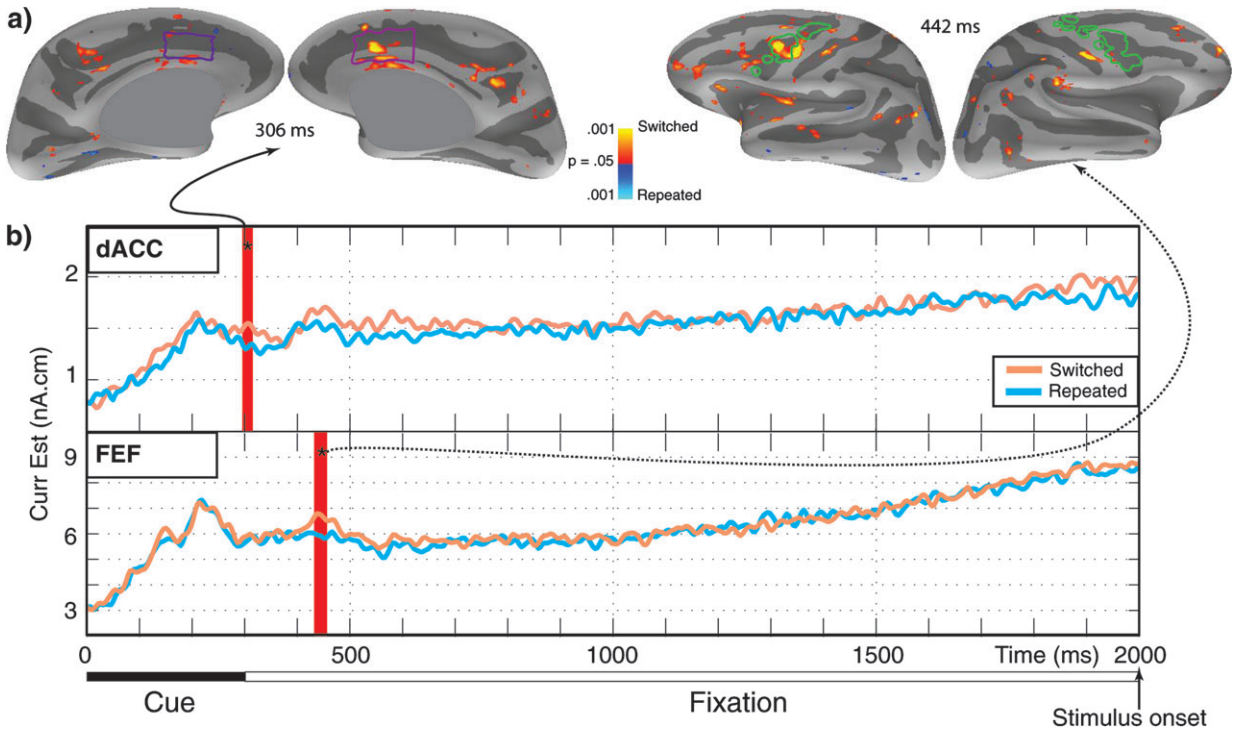

Figure 5. Task-switching effects during the cue–stimulus interval. (*a*) Statistical group difference maps for switched versus repeated trials are displayed on the inflated medial and lateral cortical surfaces at time points showing significant effects at a threshold of $P < 0.05$. Vertices showing greater activity for switched versus repeated trials are displayed in warm colors. dACC and FEF ROIs are outlined in purple and green, respectively. (*b*) Average activity in dACC and FEF ROIs for switched versus repeated trials at each time point. Differences between trial types that reached an overall alpha of $P < 0.05$ (i.e., differences at $P < 0.05$ for 5 consecutive 4-ms epochs, see Materials and Methods) are displayed as vertical stripes. The asterisks denote the time points shown on the cortical surfaces maps (*a*). Only one brief period in the dACC (296–316 ms) and one in the FEF (432–456 ms) met criteria for statistical significance, showing greater activity on switched versus repeated trials.

performing an antisaccade that may carry over into the subsequent trial. Even after correcting for differences in baseline activity, there was a sustained increase in preparatory FEF and IFS activity for trials preceded by an antisaccade during the interval that followed the instructional cue and preceded stimulus appearance. Trials preceded by antisaccades also had longer response latencies, consistent with previous studies (Cherkasova et al. 2002; Fecteau et al. 2004; Barton et al. 2006). These findings of task-switching and prior-antisaccade effects demonstrate that trial history interacts with current task demands to modify neural and behavioral responses.

Based on converging evidence, we interpret the prior-antisaccade effect in the FEF to reflect that the powerful inhibition required for an antisaccade persists in the ocular motor system, reducing preparatory activity in the subsequent trial, and prolonging the latency of the upcoming saccade (Barton et al. 2006; Manoach et al. 2007). First, both human neuroimaging and monkey neurophysiology findings suggest that preparatory activity in the FEF is inhibited during an antisaccade. fMRI studies consistently show greater FEF activation for antisaccades than prosaccades (for review, see McDowell et al. 2008), including on the task used here (Manoach et al. 2007), and when the comparison of activation is restricted to the preparatory period (Connolly et al. 2002; Ford et al. 2005). This increased activation has been interpreted to reflect inhibition of the FEF in preparation to perform an antisaccade. Monkey neurophysiology findings, however, show "reduced" preparatory activity in the FEF for antisaccades versus prosaccades (Everling and Munoz 2000). These seemingly discrepant findings likely arise from the different sources of signals in these 2 techniques, and both findings are thought to reflect inhibition of the FEF (Ford et al. 2009). While single-unit recordings are biased toward the spiking of pyramidal cells (Fromm and Bond 1964), fMRI is more likely to reflect local field potentials, which are generated by the summation of excitatory and inhibitory synaptic signals at dendrites. Thus, a heightened level of inhibitory input to the FEF and/or increased activity of local inhibitory interneurons may generate an enhanced blood oxygen level–dependent (BOLD) signal and also lead to the decreased spiking of FEF pyramidal cells that is seen in single-unit recordings (Ford et al. 2009).

Second, although the direction of activity changes was different, both our prior fMRI (Manoach et al. 2007) and present MEG findings concerning trial history are consistent with the interpretation that the inhibition from a prior antisaccade persists into the subsequent trial. In the FEF, a prior antisaccade was associated with reduced BOLD activity but "increased" MEG signal. This difference in the direction of signal change serves to constrain hypotheses about underlying mechanisms. We previously hypothesized that the powerful inhibition generated by an antisaccade persists in the ocular motor system and reduces local field potentials and spiking, which reduces BOLD signal during the present trial (Manoach et al. 2007). Since MEG is dominated by synchronous input (Hämäläinen and Hari 2002), if the persistent effect of a prior antisaccade is a low-amplitude synchronous inhibitory input, it could give rise to a strong MEG signal, even if the effect on overall neural activity level, as reflected in the BOLD signal, is decreased. Such persistent low-level synchronous inhibitory input to FEF is a potential mechanism for "keeping one's foot

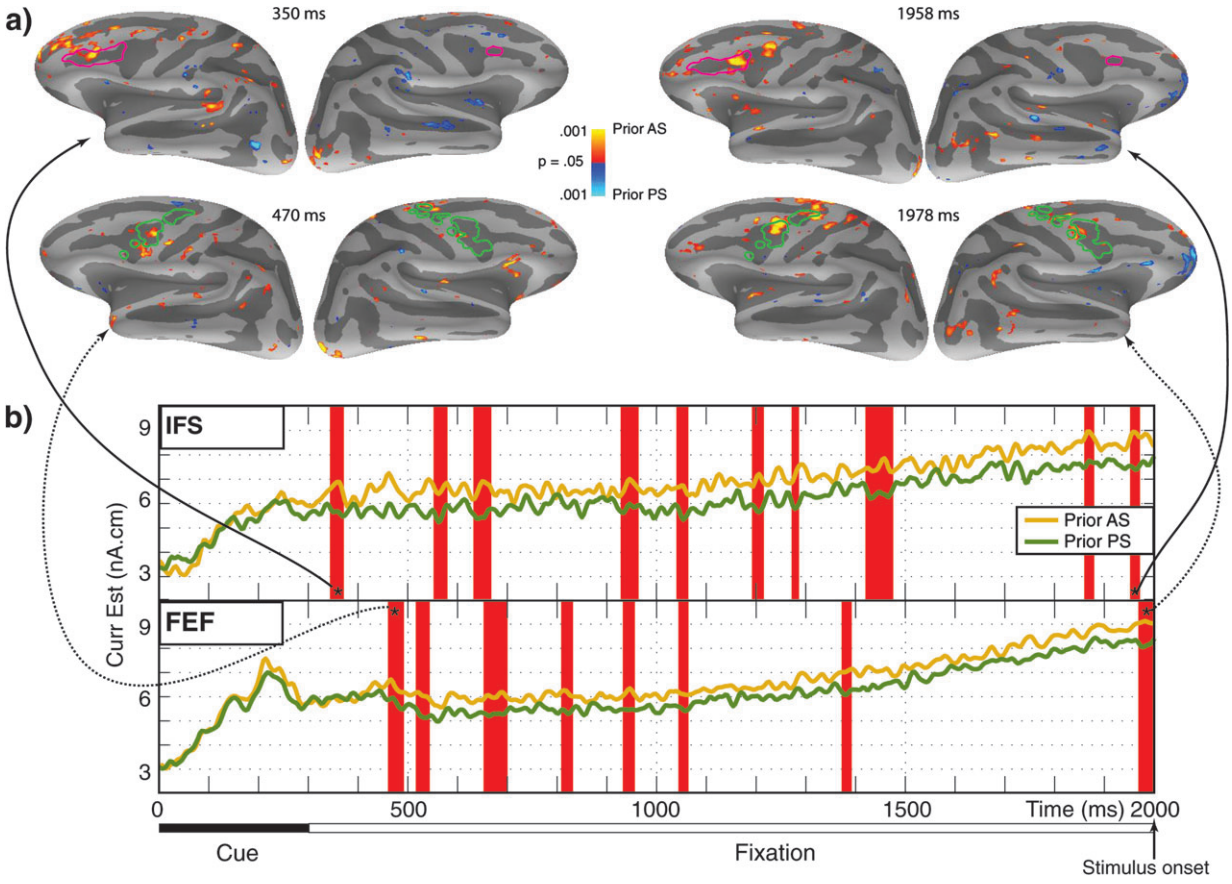

Figure 6. Prior-antisaccade effects during the cue–stimulus interval. (*a*) Statistical group difference maps for trials preceded by an antisaccade versus a prosaccade are displayed on the inflated lateral cortical surfaces at time points showing significant effects. FEF and IFS are outlined in green and magenta, respectively. (*b*) Average activity in FEF and IFS ROIs for trials preceded by an antisaccade versus a prosaccade at each time point. Differences between trial types that reached an overall alpha of $P < 0.05$ (i.e., differences at $P < 0.05$ for 5 consecutive 4-ms epochs, see Materials and Methods) are displayed as vertical stripes. The asterisks denote the time points shown on the cortical surfaces maps (*a*). All significant differences indicated greater activity for a prior antisaccade than a prior prosaccade.

on the brake" in the ocular motor system in the wake of a challenging task in order to slow responses and increase accuracy. This speed–accuracy trade-off has been observed in monkey neurophysiology studies, which report that lower preparatory neural activity in the FEF and the superior colliculus for antisaccades correlates with longer latencies and lower error rates (Everling et al. 1999; Everling and Munoz 2000). While this explanation reconciles our fMRI and MEG findings concerning trial history effects, other possibilities exist. At present, interpretation is limited by fundamental ambiguities concerning the source of fMRI and MEG signals, both of which are fields of intense investigation (Murakami et al. 2003; Murakami and Okada 2006; Logothetis 2007).

In addition to the FEF, we observed greater preparatory activity in the left IFS following an antisaccade. Both the dorsolateral prefrontal cortex (McDowell et al. 2008), which projects to the FEF (Selemon and Goldman-Rakic 1988), and, to a lesser extent, the ventrolateral prefrontal cortex (Dyckman et al. 2007) have been hypothesized to provide inhibitory input to the FEF during antisaccades. Greater IFS activity in trials following antisaccades than prosaccades suggests that trial history effects are not confined to ocular motor regions but are also seen in prefrontal cortex. The finding that trial history effects in the FEF, IFS, and dACC (for task-switching) were present in the cue–stimulus interval, but not in the analyses that were time-locked to saccadic onset, suggests that these effects reflect general preparation, rather than preparation to perform a saccade in a specific direction.

Both the dACC and the dorsolateral prefrontal cortex are hypothesized to provide top–down control of structures generating motor responses (Miller and Cohen 2001), including ocular motor responses (Johnston et al. 2007). Both regions project to the FEF (Selemon and Goldman-Rakic 1988; Wang et al. 2004), which is the key cortical region involved in generating saccades (Pierrot-Deseilligny et al. 1995). Our findings of differential preparatory activity in the dACC for task-switching and in the prefrontal cortex for a prior antisaccade are consistent with a role for these regions in modulating FEF activity based on trial history, particularly since the trial history effects occurred earlier in the dACC and the IFS than in the FEF. A caveat here is that the measurement of these timing differences can be influenced by technical factors such as the ROI definition and the distance of the sources from the sensors, so the findings of timing differences should be considered preliminary.

In summary, the present findings provide further evidence that behavioral and neural responses to events are modulated by recent history. We demonstrated 2 distinct trial history effects during a saccadic paradigm. First, task-switching was associated with early transient increases in preparatory activation of the dACC and the FEF, suggesting that these regions participate in active reconfiguration of the task set.

Second, in trials preceded by an antisaccade as opposed to a prosaccade, the lateral prefrontal cortex and the FEF showed increased baseline activation that persisted into the preparatory period of the subsequent trial, and saccadic latencies were prolonged. We attribute these effects to persistent inhibition of the ocular motor system from the prior antisaccade (i.e., keeping one's foot on the brake following a challenging task). Signal changes in both the dACC and the lateral prefrontal cortex likely reflect top–down control of the FEF in response to increased cognitive demand, the former occurring when a switch is required and the latter representing the persistence of activity from the difficult antisaccade task. These dynamic modulations of behavior and neural activity by immediate experience constitute a rapid form of learning that is at the heart of adaptive flexible behavior (Dorris et al. 2000). These findings add to a growing literature highlighting the importance of context in human behavior.

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