Abnormally persistent fMRI activation during antisaccades in schizophrenia: A neural correlate of perseveration?

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Objective: Impaired antisaccade performance is a consistent cognitive finding in schizophrenia. Antisaccades require both response inhibition and volitional motor programming, functions that are essential to flexible responding. We investigated whether abnormal timing of hemodynamic responses (HDRs) to antisaccades might contribute to perseveration of ocular motor responses in schizophrenia. We focused on the frontal eye field (FEF), which has been implicated in the persistent effects of antisaccades on subsequent responses in healthy individuals.

Method: Eighteen chronic, medicated schizophrenia outpatients and 15 healthy controls performed antisaccades and prosaccades during functional MRI. Finite impulse response models provided unbiased estimates of event-related HDRs. We compared groups on the peak amplitude, time-to-peak, and full-width half-max of the HDRs.

Results: In patients, HDRs in bilateral FEF were delayed and prolonged but ultimately of similar amplitude to that of controls. These abnormalities were present for antisaccades, but not prosaccades, and were not seen in a control region. More prolonged HDRs predicted slower responses in trials that followed an antisaccade. This suggests that persistent FEF activity following an antisaccade contributes to inter-trial effects on latency.

Conclusions: Delayed and prolonged HDRs for antisaccades in schizophrenia suggest that the functions necessary for successful antisaccade performance take longer to implement and are more persistent. If abnormally persistent neural responses on cognitively demanding tasks are a more general feature of schizophrenia, they may contribute to response perseveration, a classic behavioral abnormality. These findings also underscore the importance of evaluating the temporal dynamics of neural activity to understand cognitive dysfunction in schizophrenia.

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1. Introduction

Impaired antisaccade performance is consistently observed in schizophrenia. Antisaccades require inhibition of the prepotent response of looking towards a suddenly appearing visual stimulus (i.e., a prosaccade) and the substitution of a gaze in the opposite direction. Thus, antisaccades require both response inhibition and volitional motor programming, which are essential to adaptive, flexible responding. Here, we investigated the neural basis of antisaccade deficits in schizophrenia in relation to perseveration.

In schizophrenia, the antisaccade error rate is reliably increased (Gooding and Basso, 2008) and correct antisaccades have longer latencies (Manoach et al., 2002; Radant et al., 2007; Reuter et al., 2007) and more persistent effects on responses in subsequent trials (Barton et al., 2005, 2006a; Reuter et al., 2007). Specifically, while both healthy and schizophrenia participants demonstrate a ‘prior antisaccade effect’ – saccades have longer latencies when preceded by a correct antisaccade than prosaccade (Fecteau et al., 2004; Barton et al., 2006b; Lee et al., 2011) – in schizophrenia this effect lasts for two trials and only patients are more likely to commit an error in the same direction as the preceding antisaccade (Barton et al., 2005). These findings suggest that antisaccades have more persistent effects on the ocular motor system in schizophrenia, resulting in perseveration of responses.

We have hypothesized that these prior antisaccade effects are mediated by the frontal eye field (FEF, Barton et al., 2006b; Manoach et al., 2007). In monkey studies, FEF neurons show reduced firing in...
preparation for antisaccades compared to prosaccades, and lower activity predicts longer antisaccade latencies and fewer errors (Everling and Munoz, 2000). This reflects a speed-accuracy tradeoff: the lower the activity the longer it takes to reach the threshold for triggering a correct antisaccade and the less likely it is that an erroneous prosaccades will escape. In fMRI studies, there is more FEF activation for antisaccades than prosaccades (e.g., Ford et al., 2005b; Manoach et al., 2007), which has been interpreted to reflect heightened inhibitory input (DeSouza et al., 2003). These findings suggest that FEF activity is important both for response inhibition and generating the volitional antisaccade. Evidence from magnetoencephalography (MEG, Lee et al., 2011) and fMRI (Manoach et al., 2007) studies of healthy individuals supports the hypothesis that preparatory activity in the FEF also mediates prior antisaccade effects on latency. With MEG, FEF activation is greater following antisaccades than prosaccades, and this is sustained throughout the preparatory period of the subsequent trial. With fMRI, FEF activation is reduced during trials preceded by an antisaccade vs. a prosaccade. (For a discussion of differences in the direction of signal changes across techniques see, Lee et al., 2011). These findings suggest that the effects of a prior antisaccade persist into the current trial suppressing FEF activity and prolonging latency.

Prior neuroimaging studies report both decreased amplitude of FEF activation during antisaccades in schizophrenia (Nakashima et al., 1994; Camchong et al., 2008) and no difference (McDowell et al., 2002; Raemaekers et al., 2002; Tu et al., 2006). Here, we studied both the amplitude and temporal dynamics of the FEF hemodynamic response (HDR) to understand these discrepancies and to illuminate the neural bases of slower and more perseverative correct saccades in schizophrenia. We expected that FEF activation to antisaccades would be abnormally prolonged in schizophrenia and that this would correlate with the magnitude of prior antisaccade effects. We also expected that longer latencies for correct antisaccades, which suggest slower volitional motor programming, would be accompanied by a later time-to-peak of the HDR in the FEF.

2. Methods

2.1. Participants

Twenty schizophrenia outpatients were recruited from an urban mental health center. They had been maintained on stable doses of atypical antipsychotic medications for at least six weeks, with the exception of one participant taking fluphenazine. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al., 1997). Clinical status was characterized with the Positive and Negative Syndrome Scale (Kay et al., 1987) and the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). Sixteen healthy control participants, screened to exclude a personal history of mental illness (SCID-Non-patient edition, First et al., 2002) and a family history of schizophrenia spectrum disorder, were recruited from the community. All participants were screened to exclude substance abuse or dependence within the past six months, a history of significant head injury, and neurological illness. The data from two patients and one control could not be used due to eye tracker malfunction. The remaining 18 patients and 15 controls did not differ in age, gender, handedness (White and Ashton, 1976), parental socioeconomic status (Hollingshead, 1965), or an estimate of pre-morbid verbal IQ (Table 1, Blair and Spreen, 1989). The study was approved by the Partners Human Research Committee and participants gave written informed consent.

2.2. Saccadic paradigm

Participants practiced in a mock scanner. They were instructed to respond as quickly and accurately as possible by making a saccade to the stimulus on prosaccade trials and in the opposite direction on antisaccade trials. In addition to a base rate of pay, they received 5 cents for each correct response.

The task consisted of a pseudorandom sequence of prosaccade and antisaccade trials that were balanced for right and left movements and 2, 4, and 6 s intervals of fixation (Fig. 1). The schedule of events was determined using a technique that optimizes the statistical efficiency of event-related designs (Dale, 1999). Participants performed six task runs (5 m 22 s each) that generated a total of 211 prosaccade trials, 211 antisaccade trials, and 80 fixation intervals. The ISCAN fMRI Remote Eye Tracking Laboratory (ISCAN, Burlington, MA) recorded eye position during scanning using a 60 Hz video camera.

2.3. Analysis of eye movements

Eye movements were scored in MATLAB (Mathworks, Natick, MA) using a partially automated program. As in our prior studies (e.g., Manoach et al., 2007), saccades were identified as horizontal eye movements with velocities exceeding 47°/s. The onset of a saccade was defined as the point at which the velocity of the eye first exceeded 31°/s. Accuracy was based on whether the initial saccade was in the correct direction. Error rate and the latency of correct saccades with latencies over 130 ms (to exclude anticipatory saccades, Fischer and Breitmeyer, 1987) were analyzed using randomized block ANOVAs with factors for Group, Task, and subjects nested within group. To examine prior antisaccade effects on the subsequent trial (t+1) we included a factor for the Prior Task. To test whether this effect was more persistent in schizophrenia, lasting for two trials (t+2) rather than one, we included a factor for the Penultimate Task. We also calculated prior antisaccade effects for each participant, defined as the difference in latency between trials preceded by an antisaccade vs. a prosaccade without regard to the identity of the current trial (antisaccade/XX latency–prosaccade/XX) or in the case of the t+2 effect, without regard to the identities of the current or intervening trials (antisaccade/XX/XX latency–prosaccade/XX/XX).

2.4. Image acquisition

Images were acquired with a 3.0 T Siemens Trio whole body high-speed imaging device equipped for echo planar imaging (Erlangen, Germany). Two high resolution structural images were acquired in the sagittal plane using a high resolution 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR), 2530 ms; echo spacing, 7.25 ms; echo time (TE), 3 ms; flip angle 7°) with an in-plane resolution of 1 mm and 1.3 mm slice thickness. Functional images were collected using a gradient echo T2* weighted sequence (TR/TE/Flip = 2000 ms/30 ms/90°). Twenty contiguous horizontal slices parallel to the intercommissural plane (voxel size: 3.13×3.13×5 mm)

Table 1

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</tbody>
</table>

* A lower score denotes higher status.

were acquired interleaved. The functional sequences included prospective acquisition correction (PACE) for head motion (Thesen et al., 2000).

2.5. Analysis of fMRI data

Analyses used FreeSurfer (Fischl et al., 1999) and FreeSurfer Functional Analysis Stream (FS-FAST, Burbeck and Dale, 2000) software. In addition to PACE, functional scans were retrospectively corrected for motion using AFNI (Cox and Jesmanowicz, 1999), intensity normalized, and smoothed using a 3D 8 mm full-width half-max Gaussian kernel. Functional images were aligned to the averaged 3D structural image for each participant, which was used to construct inflated (2D) models of individual cortical surfaces. Finite impulse response (FIR) estimates of the HDRs were calculated for each of the four trial types (correct prosaccades, error prosaccades, correct antisaccades, and error antisaccades) for each participant. This involved using a linear model to provide unbiased estimates of the average signal intensity at each time point without making a priori assumptions about the shape of the HDR. HDR estimates were computed at 12 time points with an interval of 2 s (corresponding to the TR) ranging from 4 s prior to the start of a trial to 18 s after the start. Temporal correlations in the noise were accounted for by prewhitening using a global estimate of the residual error autocorrelation function truncated at 30 s.

To register data across participants, anatomical and functional scans were spatially normalized using a surface-based spherical coordinate system. Registered group data were smoothed with a 2D 4.6 mm FWHM Gaussian kernel. fMRI results were displayed on a template brain. Localization of activation was based on an automated parcellation algorithm (Fischl et al., 2004). To facilitate comparison with other studies, approximate Talairach coordinates were derived (see Supplementary data).

2.5.1. Group comparisons of activation

To restrict group comparisons to regions activated by the task we created a mask of all positively activated vertices (p < 0.001) on the cortical surface in the contrast of all correct saccades vs. fixation at 4 s, which is the time of peak activation in bilateral FEF in the averaged data of all participants. First, as is standard, we examined group differences in the amplitude of the HDR at 4 s in the contrast of correct antisaccades vs. prosaccades. Second, to determine whether the groups differed in the timing of the HDR, and whether differences were greater for antisaccades, we conducted a three-way ANOVA of Group, Task, and Time (0, 2, 4, 6, 8, 10 s) at each vertex. For regions showing a significant Group by Task by Time interaction, we calculated the mean percent signal change at each time point for antisaccades and prosaccades and used the ideal sinc interpolation kernel to construct the HDR functions for each task in each participant. From these HDR functions, we derived three parameters — time-to-peak, peak amplitude (this differs from the standard amplitude analysis since the time of the peak was allowed to vary), and full-width half-max — using the mspeaks function in MATLAB’s Bioinformatics Toolbox (The Mathworks, Inc., Natick, MA). HDR parameters were compared between groups using t-tests.

2.5.2. Relations of HDR parameters with performance

Regression of performance on HDR parameters included an interaction term of the HDR parameter by group to test whether the slope of the relation differed by group.

2.5.3. Correction for multiple comparisons

We used a clustering method based on 10,000 Monte Carlo simulations of synthesized white Gaussian noise using the smoothing, resampling, and averaging parameters of the functional analyses in the region of interest mask to determine the likelihood that a cluster
of a certain size would be found by chance for a given threshold (p ≤ .05) and to provide cluster-wise probability values (CWP).

2.5.4. Control analyses

Methods for comparing motion between groups and assessing the effects of antipsychotic medications and age on activation are described in the Supplementary data.

3. Results

3.1. Performance

Participants made more antisaccade than prosaccade errors (F(1,31) = 23.58, p = 0.0001) and patients made more errors than controls (F(1,31) = 8.19, p = 0.007). The group by task interaction (F(1,31) = 4.45, p = 0.04) reflected that patients made significantly more antisaccade [21 ± 17 vs. 9 ± 6%; t(31) = 3.55, p = 0.001] but not prosaccade [6 ± 7 vs. 3 ± 2%; t(31) = 0.84, p = 0.41] errors than controls.

Latency data from one patient and two controls could not be scored reliably, and were excluded from analyses. Antisaccades had longer latencies than prosaccades (F(1,28) = 108.10, p < 0.0001) and patients showed a trend toward longer latencies than controls (F(1,28) = 3.18, p = 0.09); antisaccades: 332 ± 70 vs. 293 ± 41 ms, t(28) = 2.01, p = 0.05; prosaccades: 268 ± 99 vs. 240 ± 68 ms, t(28) = 1.41, p = .17) that did not differ significantly by task (F(1,28) = 1.08, p = .31).

A prior antisaccade vs. prosaccade slowed the latency of the current trial (F(1,28) = 11.51, p = 0.002). As in our prior study (Barton et al., 2005), group membership did not affect the magnitude of the prior antisaccade effect (F(1,28) = 0.94, p = 0.34). Contrary to our expectations, we did not detect significant prior antisaccade effects two trials later (t + 2) in patients.

3.2. fMRI data

3.2.1. Amplitude at 4 s

Relative to controls, patients showed significantly reduced activation in the left FEF in the contrast of antisaccades vs. prosaccades at 4 s (−26, 2, 46; cluster size = 722 mm³; CWP = 0.0001). There were no other significant group differences.

3.2.2. HDR timing

Significant Group by Task by Time interactions were observed in the left FEF (Fig. 2; −23, −1, 46; cluster size = 1183 mm³; CWP = 0.0001) and the right supplementary eye field (SEF; 9, 2, 48; cluster size = 853 mm³; CWP = 0.001).

To understand these interactions, we calculated the HDR parameters for each trial type in the FEF, SEF, and in a comparison region, primary visual cortex (V1), which is activated by the task but is not involved in ocular motor control. As we did not expect lateralized differences, we examined the HDR parameters in both hemispheres. Within our region of interest mask, we used anatomical criteria to define these regions. We restricted the FEF to vertices in and around the precentral sulcus and gyrus, excluding the medial surface (Paus, 1996), the SEF to the medial surface, dorsal to the cingulate sulcus, posterior to the V1 line and anterior to the precentral sulcus (Grosbras et al., 1999), and V1 to the calcarine sulcus. Three patients were missing data for prosaccades in the SEF because no peak was detected.

The groups did not differ in peak amplitude in any region for antisaccades or prosaccades. However, patients showed a significantly later time-to-peak in bilateral FEF and SEF for antisaccades, but not for prosaccades (Table 2, Fig. 2). In addition, in bilateral FEF, the HDRs for patients were significantly prolonged for antisaccades, but not prosaccades, as indexed by the full-width half-max. Patients also showed prolonged HSRs bilaterally in the SEF for prosaccades, but this finding was limited by the fact that no peak was detected in the SEF for prosaccades in three patients. There were no group differences in HDR parameters in V1.

3.2.3. Relations of FEF HDR parameters with performance

Time-to-peak did not correlate with antisaccade latency, and this did not differ by group. In the left FEF we observed a significant correlation of the prior antisaccade effect (t + 1) with the full-width half-max (Fig. 3, t(27) = 2.05, p = .05) that did not differ by group (t(27) = −0.07, p = .94). A similar, non-significant effect was seen in the right FEF. Finally, we examined whether FWHM predicted the magnitude of the prior antisaccade effect two trials later (t + 2) in schizophrenia. We observed a trend in the right FEF (t(16) = 1.65, p = .10) and a weaker relation in left FEF (t(16) = 1.20, p = .22). There were no relations in controls (p's > .8).

3.2.4. Control analyses

Please see Supplementary data for details. The groups did not differ in mean motion. Neither age nor antipsychotic medication dosage was significantly related to any FEF HDR parameter.

4. Discussion

Schizophrenia patients showed abnormally delayed and persistent HDRs in the FEF during antisaccades. This suggests that the processes necessary for successful antisaccade performance are implemented more slowly and are more persistent. That the HDR was delayed, but ultimately of similar amplitude in schizophrenia, underscores the importance of evaluating the temporal dynamics of neural activity to understanding the basis of cognitive dysfunction. If slower, more prolonged neural responses to cognitively demanding tasks are a more general feature of schizophrenia, it may be difficult to rapidly adjust behavior in response to the demands of the moment. Such dynamic adjustments are fundamental to adaptive, flexible behavior and impairments may contribute to perseveration.

As in prior studies, we observed similar significant prior antisaccade effects on saccadic latency for patients and controls — an antisaccade slowed responses in the subsequent trial (Manoach et al., 2002; Barton et al., 2005). This effect correlated with more prolonged FEF HDRs, which along with the findings of our paired MEG and fMRI studies (Manoach et al., 2007; Lee et al., 2011), suggests that persistent activity of the FEF following an antisaccade contributes to inter-trial effects on latency. In the present study, we failed to replicate our behavioral finding of a more prolonged prior antisaccade effect on latency in schizophrenia (i.e., that an antisaccade slowed latency two trials later, Barton et al., 2005), and this ‘t + 2’ effect only weakly correlated with the more prolonged HDRs for antisaccades (i.e., trend in right FEF, n.s. in left). This failure to replicate the behavioral finding may reflect the inferior temporal resolution of the scanner-based eye tracking system of the present study (60 vs. 1000 Hz), which may have been inadequate to detect a small effect on latency (i.e., 20 ms in the prior study). A higher resolution eye tracker may be necessary to evaluate the hypothesis that the more prolonged HDR in the FEF during antisaccades in schizophrenia is a neural correlate of the behavioral perseveration that we previously observed (Barton et al., 2005, 2006a).

Patients also showed a later peak of activation in the FEF for correct antisaccades. This might reflect less efficient implementation of inhibition and/or slower activation of the antisaccade task goal (e.g., Reuter et al., 2007), both of which have been proposed to account for impaired antisaccade performance in schizophrenia. The present findings cannot discriminate between these possibilities.

In addition to the delayed peak of the HDR, correct antisaccades were performed more slowly in patients. This is consistent with prior reports of delayed HDRs in the context of slower manual reaction times (Ford et al., 2005a; Velanova et al., 2007; Yarkoni et al., 2009).
Prior fMRI studies of schizophrenia have reported both delayed activation in several regions during a visual oddball task (Ford et al., 2005a) and normal HDR peak times in primary sensorimotor and supplementary motor regions during a flashing checkerboard (Barch et al., 2003). Our findings of normal HDRs in V1 and delayed HDRs in ocular motor regions are consistent with both of these reports. The shape of the HDR has been shown to vary across brain regions, stimulus types, individuals, and groups (Miezin et al., 2000; Duann et al., 2002; Ford et al., 2005a; Velanova et al., 2007). Thus, whether HDR timing abnormalities are observed in schizophrenia may depend on both the region and the type of cognitive demand. Greater demand may lead to delayed and prolonged neural responses in higher order regions and, consequently, to slower, more perseverative responses.

The finding of delayed HDRs in schizophrenia resonates with numerous reports of delayed cognitive event-related potentials. The relative dearth of prior reports of delayed HDRs may reflect that most standard fMRI analysis techniques assume a shape to the HDR and only test for group differences in amplitude. Had we limited our

Fig. 2. Statistical map of the Group by Time by Task interaction on the inflated medial and lateral cortical surfaces. Clusters in left FEF and right SEF survived correction for multiple comparisons. HDR time course graphs (with standard errors) are displayed for each condition (prosaccades and antisaccades) relative to the fixation baseline for bilateral FEF and SEF, as well as the control region V1. Red lines represent patient data, black lines represent healthy control data. Time in seconds is on the x-axis and percent signal change relative to the fixation baseline is on the y-axis. Significant group differences in 'time-to-peak' and full-width half-max are denoted by asterisks (*). Trends are denoted by the symbol †.
investigation to amplitude at the time peak of the HDR in the combined group as is standard, we might have erroneously concluded that patients showed significantly reduced FEF activation. Instead, this reduction reflected a delayed peak in patients, and, at later time points (i.e., 8 and 10 s) patients actually showed significantly greater activation than controls, which reflected more prolonged activation rather than increased amplitude. This suggests that a failure to consider the timing of the HDR may lead to erroneous conclusions and contribute to inconsistent findings concerning fMRI activation differences in schizophrenia.

A limitation to the present study is that all of the patients were chronically ill and taking antipsychotic medications. Although controlling for dosage did not alter the findings, this does not exclude a confounding effect of medications. Even if the abnormalities observed were due to medication, progression, or epiphenomena of long-term illness, they remain relevant since the vast majority of patients with schizophrenia are chronic and medicated.

In summary, we propose that delayed and prolonged HDRs in the FEF during antisaccades in schizophrenia contribute to slower and more perseverative ocular motor responses. If delayed and prolonged neural responses to cognitively demanding tasks are a more general feature of schizophrenia, they may contribute to cognitive slowing and to responses that are unduly influenced by the recent past at the expense of more immediate demands.

Role of funding source
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Table 2
Means, standard deviations and group comparisons of peak amplitude, time-to-peak, and full-width half-max (FWHM) of HDRs to antisaccades and prosaccades by region and hemisphere.

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<th>ROI</th>
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<td>LH</td>
<td>.26±.06</td>
<td>.28±.08</td>
<td>−0.42</td>
<td>.68</td>
<td>5.93±.72</td>
<td>6.26±.63</td>
<td>−1.39</td>
<td>.17</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>RH</td>
<td>.27±.10</td>
<td>.27±.07</td>
<td>0.08</td>
<td>.94</td>
<td>5.84±.77</td>
<td>6.23±.60</td>
<td>−1.61</td>
<td>.12</td>
</tr>
</tbody>
</table>

⁎ In three patients no peak was detected in the SEF for prosaccades, one in both hemispheres, one in the right hemisphere, and one in the left hemisphere.

Fig. 3. Scatter plots of the relations of the full-width half-max (FWHM) in left and right FEF with prior antisaccade effects on latency by group with regression lines. Healthy controls are represented by filled black circles and solid lines, and schizophrenia patients are represented by open circles and dashed lines.

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Contributors
Dr. Dyckman, Lee, and Agam contributed to data collection, analysis, and manuscript preparation. Dr. Vangel provided statistical consultation. Dr. Goff provided patient characterization, assisted with recruitment, and consulted regarding the findings. Dr. Barton participated in task design and the conceptualization of the findings. Drs. Manoach oversaw and participated in all aspects of the study. All authors contributed to and have approved the final manuscript.

Conflict of interest
Dr. Manoach reports having received research funding from Springer, Inc. Dr. Goff reports having served as a consultant or advisor to: Xyris, Forest Labs, Pfizer, Indevus Pharmaceuticals, H. Lundbeck, Schering-Plough, Lilly, Takeda, Biovial, Solvay, Hoffman-La Roche, Cypress, and Dianippon Sumitomo. He served on a DSMB for Otsuka and Wyeth. He received research funding from Pfizer, Janssen, Novartis, and GlaucosSmithKline. Drs. Dyckman, Lee, Agam, Vangel, and Barton reported no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at doi:10.1016/j.schres.2011.07.026.

References


