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

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Introduction

Impaired antisaccade (**AS**) performance is one of the most consistent cognitive findings in schizophrenia (**SZ**).

Patients have increased AS error rates and correct ASs have longer latencies and *more persistent effects on subsequent trials*.

Specifically, while both healthy and SZ participants demonstrate a ***'prior AS effect'*** -- saccades have longer latencies when preceded by an AS rather than a prosaccade (***Fig 1C***) -- only in SZ does this effect last two trials, reflecting perseveration of the ocular motor system (Barton et al., 2005).

To understand the basis of this abnormality, we examined the **temporal dynamics** of the hemodynamic response (**HDR**) to ASs.

We focused on activity in the frontal eye field (**FEF**), which is essential to both saccadic inhibition and the generation of volitional saccades.

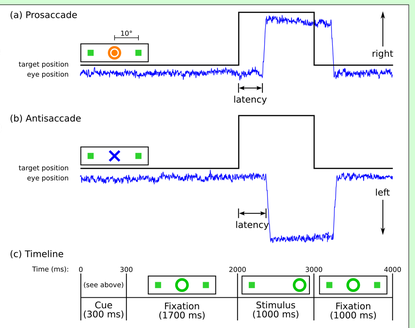
Evidence from both magnetoencephalography (Lee et al, 2010) and fMRI (Manoach et al, 2007) suggests that activity in the FEF also mediates the prior AS effect.

We hypothesized that the slower performance and more persistent effects of correct ASs in SZ would be paralleled by a longer time to peak and a more prolonged HDR.

Methods

Saccadic Paradigm for fMRI

- A pseudorandom series of prosaccade trials antisaccade trials, and a fixation baseline condition
- Prosaccade (PS): **prepotent** response of looking towards a suddenly appearing visual stimulus
- Antisaccade (AS): **inhibition** of the prepotent PS & generation of the novel behavior of looking *away* from a stimulus



Participants

- 15 Healthy controls, 11M, 37±10 yrs
- 18 Chronic outpatients treated with atypical antipsychotics,13M, 42±11yrs
- Groups did not differ significantly in sex, age, or parental SES.

fMRI acquisition and analysis

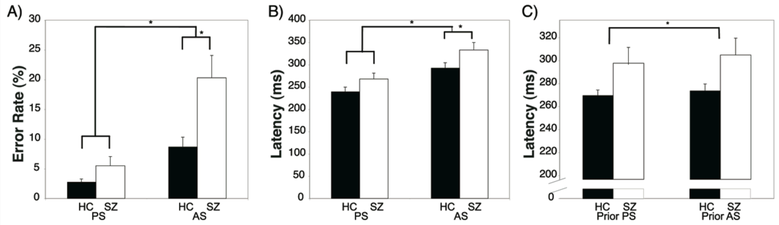
- 3T Siemens Trio with concurrent recording of eye position
- Inter-subject registration using a surface-based coordinate system
- Finite Impulse Response (FIR) models to provide unbiased estimates of the event-related HDR for correct ASs and PSs at each time point

To determine whether groups differed in the timing of the HDR, and whether differences were greater for ASs, we conducted an ANOVA

- A Group X Task (AS, PS) X Time (0, 2, 4, 6, 8, 10 s) interaction (***Fig. 2***) was seen in the left FEF and the right supplementary eye field (SEF).
- In **FEF**, **SEF**, and a control region activated by the task, **V1**, we used sinc interpolated HDR functions to calculate for each task & participant:
  Time to peak
  Peak amplitude
  Full-Width Half-Max (FWHM)
- These parameters were compared between groups and correlated with the prior AS effect on latency, defined as the difference in saccadic latency for a trial preceded by an AS vs. a PS, regardless of the identity of the current trial.

Results

1) Behavior: Compared to controls, patients showed (A) an increased AS error rate and (B) longer latencies of correct ASs. (C) Compared to a PS, an AS in the prior trial slowed response latency, and this did not differ by group. We also tested whether this effect was more persistent in SZ, lasting for two trials instead of one, as we previously reported (Barton et al., 2005). There was no significant effect on latency of the task two trials back, and no interaction with group, which may reflect the limited temporal resolution of our scanner-based eye tracking system (60 Hz).



2) HDR Timing: Groups did not differ in peak amplitude for either ASs or PSs. Patients showed a significantly later time to peak and a more prolonged HDR in FEF for ASs but not PSs. Similar effects for ASs were seen in SEF, but not in V1.

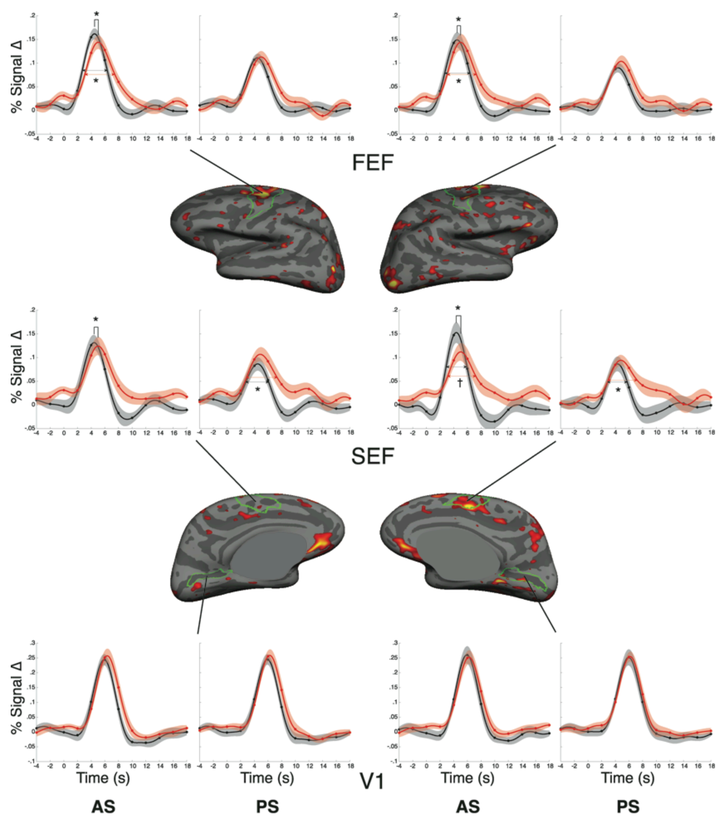
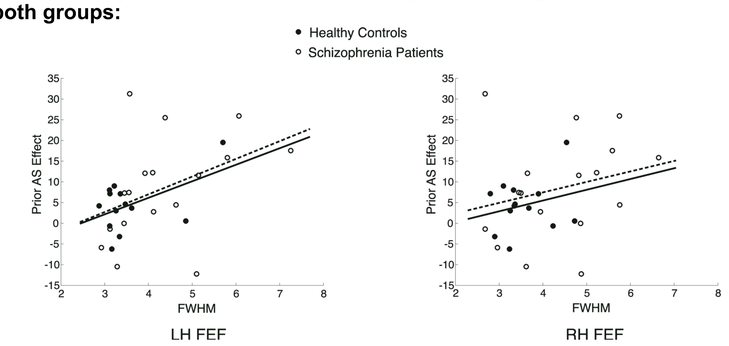
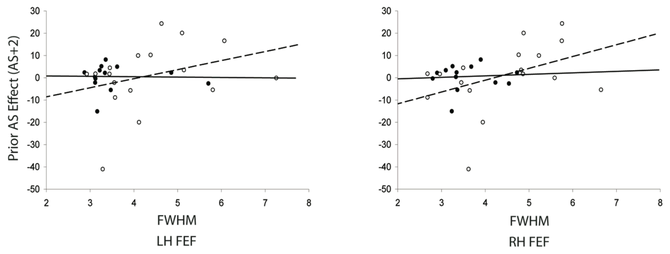


Figure 2. Statistical map of the Group X Time X Task interaction on the inflated medial and lateral cortical surfaces. Clusters in left FEF and right SEF survived correction for multiple comparisons. HDR time course graphs (with standard errors) are displayed for each condition (PSs and ASs) relative 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. Significant group differences in 'time to peak' and full-width half-max are denoted by asterisks (*). Trends are denoted by the symbol †.

3) More prolonged HDRs for ASs in the FEF predicted larger Prior AS effects in both groups:



4) In patients only, more prolonged FEF HDRs for ASs predicted larger Prior AS effects two trials later:



Discussion

Compared to controls, SZ participants showed abnormally delayed and prolonged HDRs in bilateral FEF for ASs but not PSs. Greater persistence of the HDR predicted larger prior AS effects on latency. This was true for both groups in the subsequent trial, but only for patients two trials later, suggesting that the abnormally prolonged HDR in SZ is a neural correlate of perseveration. We interpret the delayed and prolonged HDRs in SZ to reflect that the processes necessary for successful AS performance -- response inhibition and the generation of a volitional saccade -- are implemented more slowly and are more persistent, perseverating into subsequent trials and interfering with performance. That the HDR for ASs was delayed, but ultimately of similar amplitude in SZ underscores the importance of evaluating the temporal dynamics of neural activity to understand the basis of cognitive dysfunction. If slower, more prolonged neural responses during cognitively demanding tasks are a more general feature of SZ, this may make it more 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.

References, Support

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