



Abnormal Anterior Cingulate Activity during Error Processing in Autism Spectrum Disorder



Thakkar KN¹, Polli FE¹, Barton JJS³, Cain MS¹, Joseph RM⁴, Hadjikhani N^{2,5}, Manoach DS^{1,5}

Depts. of ¹Psychiatry and ²Radiology, Mass. Gen. Hosp.; ³Dept. of Neurology, U. of British Columbia; ⁴Depts. of Anatomy and Neurobiology, Boston U. Med. School; ⁵Athinoula A. Martinos Center, Harvard Med. School



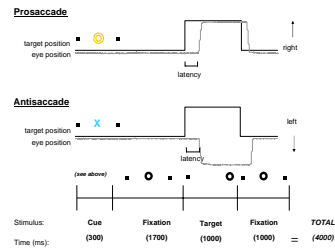
BACKGROUND & INTRODUCTION

- Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by impaired social interaction, restricted and repetitive patterns of behavior and interests, and behavioral perseveration—the persistence of inappropriate responses in spite of feedback.
- Perseverative behaviors in ASD may reflect deficient performance evaluation and remediation.
- Dorsal and rostral anterior cingulate cortex (dACC and rACC) are thought to participate in the cognitive and affective evaluation of performance, respectively.
 - Both structures show increased activity following errors.
 - dACC is also hypothesized to play a role in modifying prepotent stimulus-response mappings in response to error feedback (Holroyd & Coles, 2002).
 - rACC is thought to mediate affective appraisal of error responses (Nieuwenhuis et al., 2002).
- Structural and functional ACC abnormalities have been found in ASD (Haznedar et al., 1997; Barnea-Goraly et al., 2004)
- We examined performance evaluation in ASD by evaluating rACC and dACC activity following error versus correct responses using an antisaccade paradigm.
- We expected to find:
 - increased antisaccade errors in ASD participants relative to healthy controls, consistent with our previous findings (Manoach et al., 2004)
 - decreased rACC and dACC activation in error vs. correct responses in ASD participants reflecting deficient performance evaluation

METHODS

Saccadic Task

- A random series of antisaccade (AS) and prosaccade (PS) trials (~200 trials of each)
- PSs require a saccade *towards* a suddenly appearing target
- ASs require inhibition of the prepotent PS and the generation of a novel response: a saccade *away* from a suddenly appearing target



Participants

- 14 Healthy and 10 ASD participants
- Matched for parental SES, handedness, age, and sex
- ASD participants were diagnosed using the ADI-R and ADOS and diagnoses were confirmed by an expert clinician.

Data Acquisition

Behavioral Data

- ISCAN records eye movements during scanning

fMRI Data

- 20 5mm slices parallel to the AC-PC plane (3.13 X 3.13 X 5mm)
- BOLD contrast and gradient echo T2* weighted sequence (TR/TE/Flip=2000ms/30ms/90°) with prospective acquisition correction (PACE) for head motion

Analysis

Behavioral Data

- Eye tracking data manually scored to determine directional accuracy and latency of correct saccades

fMRI Data

- Off-line motion correction, intensity normalization, spatial smoothing
- Cortical surface segmentation and inflation
- Registration of functional and structural scans in individuals
- Inter-subject registration using surface-based coordinate system based on sulcal-gyral pattern (Fischl et al., 1999)
- Freesurfer FS-fast software
- Finite Impulse Response (FIR) models provide unbiased estimates of the hemodynamic responses for each trial type: correct and erroneous PS and AS trials.
- ACC divided into dorsal and rostral regions using a line drawn at the anterior boundary of the genu of the corpus callosum that was perpendicular to the intercommisural plane.
- rACC and dACC activity examined within and between groups
- Random effects model, $p < 0.01$ uncorrected

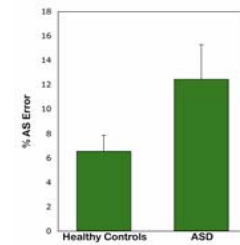
RESULTS

Behavioral

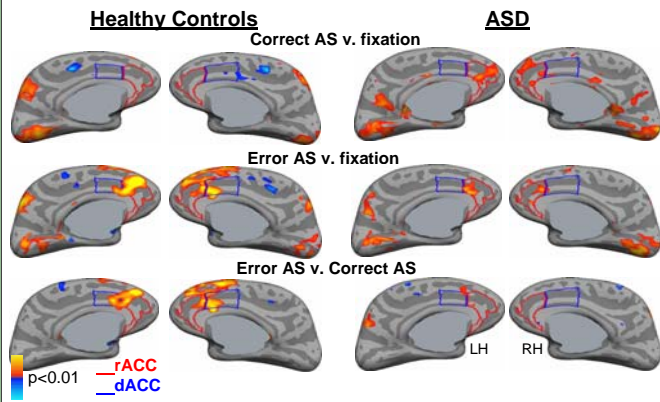
- AS Errors: ASD > Controls: $t(22)=2.05$, $p = 0.05$.

fMRI

- Following the AS response:
 - Correct AS v. fixation:** > rACC activity in ASD than controls
 - Error AS v. fixation:** > subgenual rACC activity in ASD than controls. This region of rACC is not implicated in error-processing in healthy controls (Polli et al., 2005).
 - Error AS v. Correct AS:** < differential activity in dACC and rACC between error v. correct responses in ASD than controls.

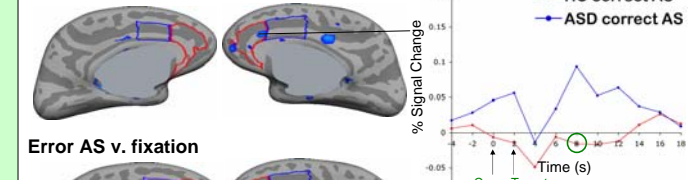


Within group analysis, 6s post-target

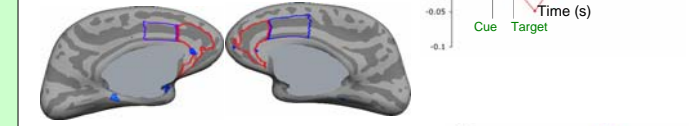


Between group comparison, 6s post-target

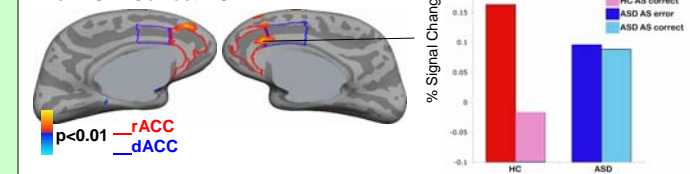
Correct AS v. fixation



Error AS v. fixation



Error AS v. Correct AS



DISCUSSION

- ASD subjects show less differentiated ACC activation following error v. correct responses. This is due to ASD subjects showing greater ACC activity following correct trials.
- Reduced discrimination between error and correct trials may compromise the modification of prepotent stimulus-response mappings in response to error feedback and consequently, perseverative behavior.
- Greater activation following correct trials in ASD participants may reflect increased response evaluation.
- This inappropriate evaluation of correct responses may divert resources away from ongoing performance.
- These ACC abnormalities found in ASD during error-processing may contribute to impaired AS performance and, more broadly, to the rigid and perseverative behaviors that characterize ASD.

REFERENCES

- Barnea-Goraly N, Kwon H, Menon V, Eliez S, Loshpech L, Reiss A (2004). White Matter Structure in Autism: Preliminary Evidence from Diffusion Tensor Imaging. *Biological Psychiatry* 55(3), 323-6.
- Fischl B, Sereno M, I. & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage* 9(2), 195-207.
- Haznedar M, Buchsbaum MS, Metzger M, Solimando A, Spiegel-Cohen J, Hollander E (1997). Anterior Cingulate Gyrus Volume and Glucose Metabolism in Autistic Disorder. *American Journal of Psychiatry* 154(8), 1047-1050.
- Holroyd CB & Coles MG (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological Review* 109(4), 679-709.
- Manoach DS, Lindgren KA, Barton JJS (2004). Deficient saccadic inhibition in Asperger's disorder and the social-emotional processing disorder. *Journal of Neurology, Neurosurgery, and Psychiatry* 75(17), 19-26.
- Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GP, Kok A (2001). Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. *Psychophysiology* 38(6), 752-60.
- Polli F, Barton JJS, Cain M, Thakkar K, Rauch S, Manoach D (2005). Rostral and dorsal anterior cingulate cortex make dissociable contributions during antisaccade error commission. *Proc Natl Acad Sci U S A* 102(43), 15700-5.

SUPPORT

NIMH R01 MH67720-02, MIND Institute—Mental Illness and Neuroscience Discovery DOE DE-FG02-99ER62764, and NCRR P41 RR14075