Autism Eye Gaze Behavior Depends on Functional Amygdala Connectivity with the Superior Temporal Area

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Introduction:
Autism is a neurodevelopmental disorder with impairments in the behavioral, social, and communicative domain. The avoidance of eye contact when viewing human faces is a diagnostic feature of impaired social interaction in autism. Based on prior work in this laboratory which determined that gaze behavior in autism depends on the extent to which focal regions in a network of gaze processing circuitry are activated, we hypothesized that altered communication within this network contributes to autism eye gaze behavior. In this 3.0 Tesla functional MRI study using an emotional face processing task, we hypothesized a priori that, in autism, the functional connectivity of the amygdala with the superior temporal gyrus (STG) in the superior temporal area (STA) is dysfunctional and is associated with aberrant eye gaze behavior based on: (1) the role of the STA in facial emotion processing (Narumoto, Okada et al. 2001), in gaze perception (Pageler, Menon et al. 2003), and in integration of an observer's gaze direction with gaze processing (Akiyama, Kato et al. 2006); (2) reduced grey matter (Boddaert, Chabane et al. 2004) and reduced diffusion tensor imaging measures of fractional anisotropy (Barnea-Goraly, Kwon et al. 2004) in autism STA; and, (3) the known anatomical connections between the amygdala and STA (Amaral and Price 1984). We quantified the strength of the functional interaction in this circuit using a seed voxel correlation approach based on each individual's anatomically defined amygdala region of interest. In addition, we assessed the relationship between eye gaze behavior and the functional connectivity of the amygdala-superior temporal circuit in autism and controls.

Methods:
Twelve male control subjects with a mean age (+/- SD) of 17.0 (+/- 2.86) and twelve males with autism or Asperger's disorder aged 16.75 (+/- 4.52) years were recruited from a list of available autism volunteers maintained at the University of Wisconsin-Madison Waisman Center. Criteria for diagnosing autism and Asperger's Disorder included DSM-IV and confirmation with the Autism Diagnositic Interview Revised (ADI-R). Subjects participated in an event-related fMRI study using a facial emotion recognition task. In total 40 faces, 16 neutral and 24 emotional (8 happy, 8 fear, 8 anger), from the Karolinska Directed Emotional Faces Set (Lundqvist 1998) were presented for 3 seconds each with a jittered inter-trial interval ranging from 5 to 7 seconds. Subjects were instructed to decide if the face displayed an emotion (happy, fear, anger) or was neutral and to indicate their choice with a button box press. We recorded eye position during the scan session with the iView infrared eye tracking system and calculated total face and eye fixation for all subjects except one control subject. Image acquisition consisted of 409 gradient recalled echo-planar images using BOLD contrast (TE = 30 ms; TR = 2 sec; FOV = 240x240 mm, 64x64 matrix, voxel size= 3.75 x 3.75 x 5mm) acquired sagittally (30 slices; 4mm thick with 1mm gap) with a 3.0 Tesla GE SIGNA Scanner (Waukesha, WI). Axial T1-weighted 3D SPGR images were also acquired (TE = 8 ms, TR = 35 ms, FOV = 240x240 mm, 256x192 matrix, 124 axial slices, slice thickness = 1.1-1.2 mm, NEX = 1, flip angle = 30 degrees).

Analyses were carried out using AFNI (Cox 1996) and software developed in house. Echoplanar images were filtered in the spatial frequency domain, reconstructed, motion corrected, and registered to anatomical data. Voxel-wise whole brain functional connectivity maps seeded by each amygdala served as a metric for the spatial extent and degree of functional connectivity, or functional integrity, between the STA and the amygdala (Fig. 1). Whole brain correlation maps were entered into a three-way ANOVA (Group x Hemisphere x Subject) with Group and Hemisphere fixed and Subjects nested and randomized within Group. Tests of significance were restricted to the STA using a Talairach-defined region of interest. We tested for significant group differences in the relation of amygdala-STA connectivity with eye-gaze behavior using multiple regression with R (version 2.1.1) and SPSS 12.0 (SPSS Inc., Chicago).

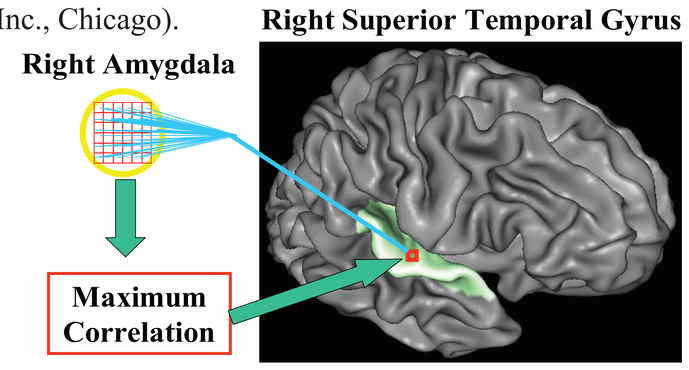

Figure 1: Functional Connectivity Method

Results:
We identified group differences in functional connectivity between the amygdala and STA (Fig. 2). The integrity of functional amygdala connectivity with the right STA is greater in autism [Right Amygdala: t(22)=2.06, p=0.052; Left Amygdala: t(22)=4.43, p=0.002] (Fig. 3). In autism, the integrity of connectivity between the right STA and both the right amygdala [Autism: t(10)=-4.81, p=0.001; Control: t(9)=-0.407, p=0.694] and left amygdala [Autism: t(10)=-3.24, p=0.009; Control: t(9)=1.27, p=0.236] predicts the percentage of time spent fixating the eyes when gazing upon emotional faces (Fig. 4). This relationship is significantly different between groups for right STA connectivity with the left [t(19)=-2.95, p=0.008], but not the right [t(19)=-1.828, p=0.083], amygdala.

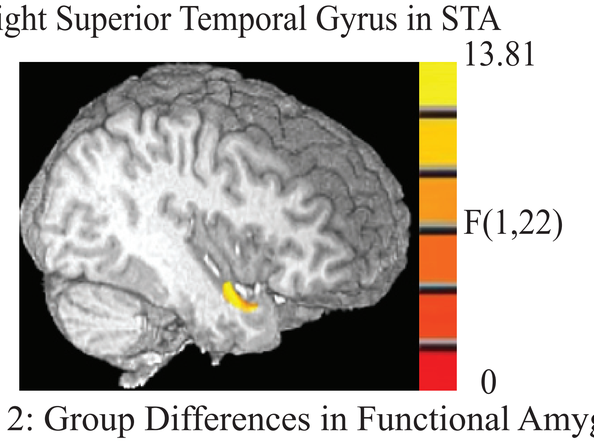

Figure 2: Group Differences in Functional Amygdala-STG Connectivity. Corrected for multiple comparisons and thresholded at F(1,22)=8.84.

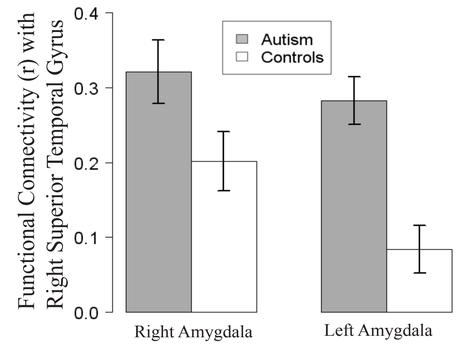

Figure 3: Functional Amygdala-STG Connectivity

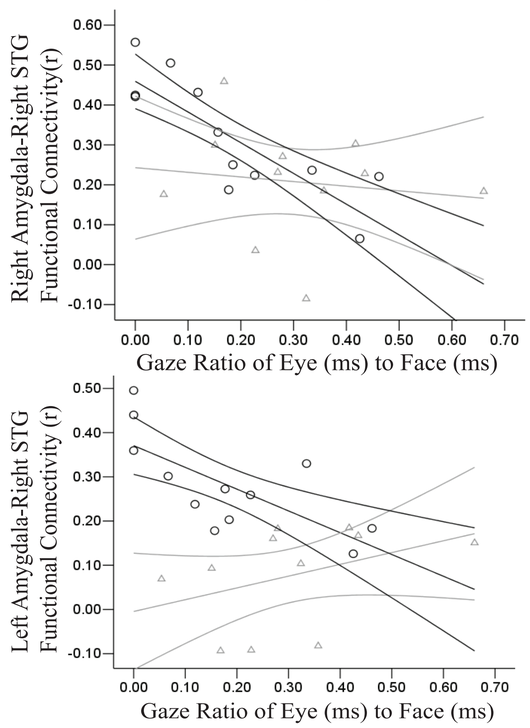

Figure 4: Connectivity versus Eye Gaze Behavior

Conclusions:
During emotional face processing, the amygdala-STA circuit is functionally overconnected in autism. The extent of this overconnectivity predicts the amount of time that individuals with autism spend looking at the eyes when gazing upon a face. This brain connectivity-eye behavior relationship is significantly different between groups for the left amygdala-right STG circuit. This study provides evidence that gaze avoidance in autism is associated with overcommunication between nodes involved in gaze processing (STA) and emotional face processing (amygdala). Future investigations are needed to determine if gaze avoidance is the cause or result of functional connectivity alterations in the amygdala-STA circuit.

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