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Typical and atypical neurodevelopment for face specialization: An fMRI study

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Abstract

Individuals with Autism Spectrum Disorder (ASD) and their relatives process faces differently from typically developed (TD) individuals. In an fMRI face-viewing task, TD and undiagnosed sibling (SIB) children (5–18 years) showed face specialization in the right amygdala and ventromedial prefrontal cortex (vmPFC), with left fusiform and right amygdala face specialization increasing with age in TD subjects. SIBs showed extensive antero-medial temporal lobe activation for faces that was not present in any other group, suggesting a potential compensatory mechanism. In ASD, face specialization was minimal but increased with age in the right fusiform and decreased with age in the left amygdala, suggesting atypical development of a frontal-amygdala-fusiform system which is strongly linked to detecting salience and processing facial information.

Keywords

Face processing; typical development; Autism Spectrum Disorder; undiagnosed siblings; fMRI

Typical and atypical neurodevelopment for face specialization: An fMRI study An essential characteristic of Autism Spectrum Disorder (ASD) is difficulty processing emotional and non-verbal social signals in faces (Schultz 2005). Neuroimaging studies have shown that

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Ethics statement

All procedures were approved by the university's Institutional Review Board and have been performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. All persons gave informed consent or assent prior to inclusion in the study.

Conflict of interest statement

The authors declare that they have no conflict of interest.

components of the typical face processing brain network are not activated to the same degree or in the same manner as in typically developing (TD) controls. Most notably, the fusiform gyrus and fusiform face area (FFA; Kanwisher et al. 1997) show hypoactivation to faces in ASD (Bolte and Poustka 2003; Corbett et al. 2009; Dalton et al. 2005; Grelotti et al. 2005; Humphreys et al. 2008; Perlman et al. 2011; Pierce et al. 2001; Pierce and Redcay 2008; Scherf et al. 2010; Schultz and al. 2000). Other components of the face processing system are also hypoactivated in ASD, such as the amygdala (Corbett et al. 2009; Grelotti et al. 2005; Hadjikhani et al. 2007; Kleinhans et al. 2011; Kleinhans et al. 2009; Perlman et al. 2011; Pierce et al. 2001), visual cortex (Dalton et al. 2005), inferior frontal / precentral cortex (Bookheimer et al. 2008; Kleinhans et al. 2010; Uddin et al. 2008), and superior temporal gyrus (Hadjikhani et al. 2007; Humphreys et al. 2008; Pierce et al. 2001; Scherf et al. 2010). The finding of hypoactivation suggests that faces may not be processed as a special category in ASD or that perceptual processing of faces is altered, which has also been found in ERP studies (Bailey et al. 2005; Dawson et al. 2002; Grice et al. 2001; McPartland et al. 2004; O'Connor et al. 2005). In fact, Minshew and Keller (2010) have suggested that people with autism analyze faces as objects.

However, not all neuroimaging studies have reported FFA hypoactivation in ASD (Bookheimer et al. 2008; Hadjikhani et al. 2007; Hadjikhani et al. 2004; Jemel et al. 2006; Kleinhans et al. 2009; Koshino et al. 2008; Perlman et al. 2011; Uddin et al. 2008) and some studies report no differences (Grelotti et al. 2005; Hall et al. 2010; Pierce et al. 2004; Pierce and Redcay 2008; Uddin et al. 2008) or hyperactivation (Dalton et al. 2005; Hubl et al. 2003; Humphreys et al. 2008; Koshino et al. 2008) in other components of the face network. Jemel et al. (2006) note that face processing deficits in ASD may be overestimated. FFA activation does emerge in ASD when stimuli are relevant, such as faces of family members, same-age cohorts or favorite cartoon characters (Grelotti et al. 2005; Pierce et al. 2004; Pierce and Redcay 2008). FFA activation in ASD also depends on whether certain aspects of a face are attended, such as the eyes (Dalton et al. 2005; Perlman et al. 2011). Hence, “hypo” or “hyper” activation of the face processing system is not an overall principle in ASD and the direction of activation differences may depend on whether a task involves aspects of social cognition (DiMartino et al. 2009).

fMRI response to faces has also been examined in unaffected relatives of individuals with ASD and findings indicate reduced face activation in siblings compared to controls (Dalton et al. 2007; Spencer et al. 2011) in core components of the face network such as the amygdala, fusiform gyri, temporal pole and temporo-parietal junction. However, Dalton et al. (2007) also reported that siblings activated the left fusiform gyrus similar to typical controls. Other visual tasks have also reported reduced activation in some brain regions in relatives (Baron-Cohen et al. 2006; Belmonte et al. 2010; Spencer et al. 2012) with spared function in other regions such as the ventromedial prefrontal cortex (vmPFC) and posterior lateral temporal lobe, suggesting a compensatory mechanism during development (Kaiser et al. 2010). Because only a few studies have examined fMRI response to faces in unaffected relatives and findings are mixed as to the degree of typical activation in unaffected relatives, the present study will examine fMRI response to faces in siblings of children with ASD.

Given that ASD is a developmental disorder and typical face processing is associated with neural reorganization at different points in development (Johnson et al. 2005; Scherf et al. 2012), a deeper understanding of typical developmental trajectories can provide an important contextual framework for interpreting face processing activation patterns in ASD. Some characteristics of atypical neural recruitment are also found in typical development. For example, hypoactivation of the FFA has been reported in typical development, especially in children 8 years or younger (Gathers et al. 2004; Golarai et al. 2007; Joseph et al. 2011; Passarotti et al. 2003; Scherf et al. 2007). Older children may activate the right FFA, but adults and adolescents are more likely to activate the left FFA in addition to the right FFA (Cantlon et al. 2011; Gathers et al. 2004; Joseph et al. 2011; Pelphrey et al. 2009; Scherf et al. 2007). Consequently, face network hypoactivation may reflect an immature neural profile that is delayed in ASD, rather than aberrant or atypical. In addition, evidence that FFA activation does emerge in ASD individuals under some conditions suggests that FFA hypoactivation may be subject to compensatory changes.

To deepen the current understanding of typical and atypical face processing neurodevelopment and potential compensatory mechanisms, the present study used fMRI to examine functional activation patterns in TD children, children with ASD and undiagnosed siblings of individuals with ASD (SIB). The task involved passive viewing of face, object and visual texture stimuli. The strategy was to establish typical developmental responses to faces using the larger sample of TD children (n = 42) then examine responses to faces and objects in the ASD and SIB groups within regions recruited by the TD group.

The present study uses a face localizer task to examine developmental trajectories of face processing, following Joseph et al. (2011). Although the youngest children (5 to 9.7 years) in that study showed face preferential responses in some regions of the face network (right fusiform, right inferior occipital, bilateral middle occipital) specialization for faces increased with age. In addition, some regions were recruited more generally for other object categories (natural and manufactured objects) in childhood but increased in face specialization with age. Consequently, we expect a similar finding to emerge in TD children in the present study: younger children will show lack of face specialization in some regions of the face network but specialization will increase with age. Because Joseph et al. (2011) only examined developmental changes from 5 to 12 years of age, the present study will use a wider age range (6 to 18 years) that includes early to late adolescence to examine developmental trajectories of face processing more closely. Based on prior findings (Cantlon et al. 2011; Gathers et al. 2004; Joseph et al. 2011; Pelphrey et al. 2009; Scherf et al. 2007), Hypothesis I is that several critical regions of the face network (bilateral fusiform, right inferior occipital, bilateral middle occipital, right inferior opercular and right middle cortex) will increase in specialization with age in TD subjects, shifting from an object preference or no preference for faces in childhood, to greater preference for faces by late adolescence.

Based on prior reports of hypoactivation in response to faces in ASD (summarized above), Hypothesis II is that some regions that are specialized for faces in the TD group, particularly regions implicated in social cognition (e.g., amygdala, superior temporal sulcus, right inferior frontal cortex, vmPFC) or face processing more generally (e.g., fusiform gyrus), will show an altered response in ASD. In particular, the present study will test whether these

regions show an object preference in ASD, as suggested by others (Grelotti et al. 2005; Minshew and Keller 2010). Hypothesis III is that siblings will show some atypical activation in regions of the TD face network (as summarized above; e.g., right fusiform gyrus, amygdala) but will also demonstrate typical profiles of activation (e.g., left fusiform, vmPFC), as reported by Kaiser et al. (2010) and Dalton et al. (2007).

Methods

Participants

Assent and consent were provided according to procedures approved by the university's Institutional Review Board. Typically developing children were recruited through outreach presentations, fliers, email advertisements, and word-of-mouth. Children with ASD and siblings of children with ASD were recruited through the university's Psychiatry Department and regional autism groups. Handedness was determined using the Edinburgh handedness inventory (Oldfield 1971). Children received a small toy prize after each visit and were compensated at the end of the study. The typically developing children in this study and siblings had no contraindications for MRI, and no major medical, neurological, psychiatric condition or learning disability by parent report. The ASD-matched control and sibling subjects had no first-order relatives with an ASD diagnosis.

To confirm ASD diagnosis or neurotypical status, all ASD, SIB, and matched control children (TD-A: TD children matched to the ASD group; TD-S: TD children matched to the SIB group) were tested using the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2007). Parents completed the Social Responsiveness Scale (SRS, Constantino et al. 2003) and the Autism Diagnostic Interview – Revised (ADIR, Rutter et al. 2005) (one parent of an ASD participant did not complete the ADIR, but we have ADOS measures on this subject). The ADOS and ADIR were videotaped and results were confirmed via reliability testing by a speech-language pathologist. In addition, the Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn 1997) and Wechsler Block Design and Vocabulary subtests (Wechsler 2003) were administered (1 TD-S subject did not complete the PPVT).

Typically developing (TD) group—23 TD children (all right-handed except 1 ambidextrous subject), recruited as part of an ongoing study, completed the Peabody Picture Vocabulary Test (Dunn and Dunn 1997) and scored in the normal range (Table 1).

ASD group—18 children with a prior ASD diagnosis volunteered for the study and participated in at least one visit. Five participants did not complete all visits and data from one participant was not usable due to excessive head motion. The final ASD group consisted of 12 subjects (1 female; 7–18 years of age; M =13.5, SD = 3.3; 1 left-handed; Table 1). ASD participants were asked to stop any medications on the day of functional scanning.

SIB group—Nine children (8 females) with a sibling with ASD volunteered for the study and participated in at least one visit.

ASD and SIB matched control subjects—Of 22 subjects originally recruited as control subjects for the ASD or SIB groups, data from two subjects were removed due to

excessive head motion and one participant was not neurotypical according to the ADOS/ADIR, leaving 19 control children. Twelve of these children were matched to the ASD subjects on handedness (with one subject being ambidextrous), age and sex (TD-A group) and nine of these children were matched to the SIB subjects on the same variables (TD-S group). This means that two of the subjects were assigned to both the TD-A and TD-S groups for purposes of statistical analyses, but importantly, the TD-A and TD-S groups are never directly compared to each other and are only compared to the ASD and SIB groups, respectively. Table 1 describes the demographics for each of the subject groups.

SIB, TD-A, TD-S children had a mental age equivalent score of at least 6.2 years of age on at least one of the three standardized tests. Two ASD subjects did not have a mental age equivalence of at least 6.2 years. We address this wider range of IQ in the ASD group by including IQ as a covariate in the fMRI analysis of the ASD group. All subjects had normal visual acuity and color vision. As shown in Table 1, there were no significant differences in age [$t(22) = .38$, $p = .71$] or PPVT full scale IQ [$t(22) = -.1.3$, $p = .19$], between the ASD and TD-A groups. The ASD and TD-A groups were, however, different in WISC full scale IQ [$t(22) = -2.1$, $p = .04$], SRS [$t(18) = 8.5$, $p = .0001$] and all ADIR scores [preoccupations: $t(21) = 14.3$, $p = .0001$; verbal: $t(21) = 9.4$, $p = .0001$; social: $t(21) = 11.9$, $p = .0001$; non-verbal: $t(21) = 7.8$, $p = .0001$]. The SIB and TD-S groups were not different in age [$t(16) = -.37$, $p = .71$], PPVT full scale IQ [$t(15) = .99$, $p = .34$], WISC full scale IQ [$t(16) = .52$, $p = .611$], SRS [$t(16) = -1.2$, $p = .25$)] or ADIR scores [preoccupations: $t(16) = -.85$, $p = .406$; verbal: $t(16) = 0.0$, $p = 1.0$; social: $t(16) = .4$, $p = .694$; non-verbal: all scores were 0].

TD-combined group—The TD (n=23) and matched control subjects (n=19) were combined into a single group (TD-combined; n=42) for some analyses, as explained more below.

Procedure for TD group

On Visit 1 subjects completed initial screenings, practiced the face localizer task outside of the scanner, and received training inside the practice scanner. Recorded noises from the MRI scanner were gradually introduced into the practice session while the child watched a movie. Head tracking data were recorded using SmartNav3 (Naturalpoint, Corvallis, OR) and head movement feedback was provided to the child in the form of a game that rewarded points for keeping still (i.e. keeping a cursor within the center of a target). During training, all of the children were able to keep their heads still for 5 minutes continuously, which was the length of the functional runs). If the subject was comfortable with the scanner environment and head movement was minimal during mock scanner training, the subject then completed anatomical scans while watching a movie in the 3T MRI scanner. On Visit 2, the subject completed the fMRI tasks (one other task, not reported here, was also part of the fMRI protocol).

Procedure for ASD, SIB, TD-A, and TD-S groups

On Visit 1 potential subjects completed initial screenings. Eligible participants received a social story book that illustrated details of the research experience, which the parent(s) and child read in preparation for the next visit. Children were re-assented for each visit. On Visit

2 subjects completed the ADOS while the parent completed the ADIR and SRS. On Visit 3, subjects practiced the experimental tasks on a computer. If the subject did not appear to understand the task initially or after repeated instruction, they were discontinued from the study.

On Visit 4, subjects received training inside the practice scanner following the same procedure as the TD group. All participants were compliant after 2 visits of training. If the subject was comfortable with the scanner environment and head movement was minimal, the subject then completed anatomical scans while watching a movie in the 3T MRI scanner.

On Visit 5, participants re-visited the mock scanner to practice the tasks for approximately 15 minutes. Stimuli used during the practice sessions were not the same stimuli used during fMRI scanning. After this short practice session children completed the fMRI portion of the study.

fMRI Tasks and Stimuli

For the face localizer task (4.5 minutes) subjects passively viewed blocks of faces, objects, or textures, but pressed a button at the onset of each stimulus to ensure active participation. Stimuli consisted of 30 grayscale photographs each of unfamiliar high-school yearbook faces (15 female and 15 male), objects (e.g., tools, household objects), and textures constructed by blurring and scrambling the face and object photos. The face stimuli were head shots, mostly consisting of Caucasian individuals (3 faces were either Asian or Hispanic) with smiling (73% of the faces) or neutral expressions. No faces had facial hair or glasses. Although the images were cropped to capture only the internal features of the face while excluding the complete external contour, hairstyles and collars were partially visible. Each stimulus was presented individually in the center of the screen (vertical visual angle of 5.8 degrees). In each of 9 task blocks (3 each of face, object, texture), 10 stimuli appeared for 1 second each, followed by a fixation cross for 750 msec. Nine rest blocks consisted of 12.5 seconds of a fixation cross.

MRI Data Acquisition

A 3T Siemens Trio MRI scanner equipped for echo-planar imaging (EPI) was used (TR=2500ms, TE=30ms, flip angle=80°, 38 axial slices, FOV=224×224mm, $3.5mm^3$ voxels; 109 volumes). A high-resolution T1-weighted anatomical scan (MPRAGE; TE=2.56ms, TR=1690ms, TI=1100ms, FOV=256×224mm, $1mm^3$ voxels, flip angle=12°, 176 contiguous sagittal) and a 1-minute field-map scan were also collected. 3D shim adjustments were conducted before each functional run.

fMRI Data Preprocessing

Using FMRIB's FSL package (www.fmrib.ox.ac.uk/fsl), images in each participant's time series were motion corrected with MCFLIRT. Functional runs were discarded when uncorrected head motion exceeded a full voxel (3.5 mm). Images in the time series were spatially smoothed with a 3D Gaussian kernel (FWHM = 7.5 mm), and high-pass filtered (cutoff=100s) and corrected for geometric distortions using FUGUE. Three customized square waveforms (on/off) were generated for each condition (face, object, texture) and

convolved with a double-gamma hemodynamic response function. Six confound explanatory variables (EVs) that represented head motion were also added to the analysis for each subject. For 7 of the TD subjects, a single EV that modeled time points with relative head motion greater than 1.75 mm was also used. We used this option rather than multiple EVs (one for each aberrant time point) in order to preserve as many degrees of freedom for detecting effects of interest (i.e., activation for faces, objects or textures). We also opted not to use a scrubbing approach (Power et al., 2012; 2013) because that would remove more than just the aberrant time points from analysis thereby reducing degrees of freedom even further. For each participant, hemodynamic parameters for three different EVs (face, object, texture) were estimated.

Face Localizer group-level analyses in TD-combined group

The TD, TD-A and TD-S groups were combined into one large comprehensive TD-combined group. This provided a larger sample (n=42) and wider age range to isolate regions of interest (ROIs) and test for correlations with age. The group contrast of Face > Texture was used to isolate ROIs ($z=2.81$, $p < .0025$, uncorrected) in which specific hypotheses about face or object specialization were tested in each subject group (as described more in the "Regions-of-Interest (ROIs)" section below). An uncorrected threshold was used in order to isolate ROIs that sampled typical face network regions reported in other studies. Although the ROIs isolated by the Face > Texture contrast would be expected to yield a significant difference in fMRI signal for faces versus textures in the TD-combined group, the ROIs could also show a greater response to faces versus objects, objects versus faces or objects versus textures. However, given that the ROIs were defined by the Face > Texture contrast, they could be more biased toward face- than object-specialization. Therefore, isolating ROIs based on the Face > Texture contrast is not a completely independent approach to test for face-specialization in the TD-combined group. However, because the Face > Texture ROIs were isolated only in the TD-combined group, the ROIs are independent from the data used to test face and object specialization in the ASD and SIB groups (Kriegeskorte et al. 2009). We also examined another approach to isolate ROIs that was based on the average response to faces and objects versus textures to address any concerns that the Face > Texture contrast is biased more toward face specialization (see Appendix).

Regions-of-interest (ROI) analyses

Within each ROI from the Face > Texture contrast, FSL's featquery was used to extract percent signal change for each condition (Face, Object, Texture, v. baseline) and each subject. In each ROI and for each subject, a face specialization index (FSI) was computed. Zhu et al. (submitted) explored different formulas for FSI and OSI. Based on their distributional properties and better face validity, the following FSI and OSI formulas were used:

$$\mathrm{FSI}=\frac{Face_{adj}-(Object_{adj}+Texture_{adj})/2}{\mathrm{Max}(Face_{adj},Object_{adj},Texture_{adj})}$$

Where

$$Face_{adj}=F_{pc}+|minimum(F_{pc}, O_{pc}, T_{pc})|;$$
$$Object_{adj}=O_{pc}+|minimum(F_{pc}, O_{pc}, T_{pc})|;$$
$$Texture_{adj}=T_{pc}+|minimum(F_{pc}, O_{pc}, T_{pc});$$

and Fpc, Opc , Tpc are percent signal change for faces, objects, or textures, respectively, relative to baseline. Similarly,

$$\text{OSI}=\frac{Object_{adj}-(Face_{adj}+Texture_{adj})/2}{\text{Max}(Face_{adj}, Object_{adj}, Texture_{adj})}$$

These formulas are a modification of the one used by Joseph et al. (2011) with an adjustment for negative values described by Simmons et al. (2007) which avoids overinflation of difference scores and avoids extreme values for the FSI and OSI, while preserving the relative differences in percent signal change. The formulas above scale the face- (or object-) preferential response to the maximum value of Fpc, Opc, and Tpc which addresses potential group differences in BOLD signal magnitude. The index can range from −1 (e.g., object and texture preference for FSI) to 1 (e.g., complete face preference for FSI). One-sample t-tests determined whether FSI and OSI in each region were significantly different from 0 in each subject group (TD-combined, ASD, SIB). In addition, FSI and OSI for ASD were compared to TD-A (and SIB v. TD-S) using non-parametric independent samples t-tests which are used in cases where assumptions about probability distributions are difficult to make (i.e., for small sample sizes). FSI and OSI in each region were also correlated with age in each of the subject groups separately using Pearson correlations for the TD-combined group given the larger sample, but Spearman rank correlations for the ASD and SIB groups due to the smaller sample sizes.

Additional analyses

As secondary analyses, Face>Texture, Face>Object and Object>Texture contrasts were determined in the TD-combined, ASD, TD-A, SIB and TD-S groups using a cluster-corrected p value of .05 and $z > 2.33$. These additional analyses isolate regions recruited for face or object processing in the different subject groups that were not necessarily captured by the ROIs from the Face>Texture contrast in the TD-combined group at an uncorrected threshold. We also included age as a covariate for these contrasts for the TD-combined, TD-A, SIB and TD-S groups to explore developmental increases in fMRI response for the various contrasts. For the ASD group, we included both age and IQ as covariates, with age as a covariate of interest (to explore developmental changes) and IQ as a covariate of no interest given the wide range of IQ scores in the ASD group. Finally, we also explored correlations between FSI and OSI and autism severity (Social Responsiveness Scale, SRS, raw total score, as used by others; e.g., Kaiser et al. 2010) in the ASD group using Spearman rank correlations. Correlations significant at $p < .05$ were then submitted to a bootstrapping procedure as a non-inferential approach to assess statistical significance (implemented in IBM statistics v. 21, Chicago, IL) using simple sampling with total number of bootstrap

replications of 1000 to estimate 95% confidence intervals (CI). If the 95% CI included 0, we conclude that correlation is not significant.

Results

Behavioral Results

The only behavioral response required in the present task was a button press at the onset of each picture to monitor attention to the stimuli. Average percent of button presses was 80% in the ASD group, 95% in the SIB group, and 87% in the TD-combined group. Two ASD subjects made minimal button presses (0% and 34%) as did two TD-combined subjects (0% and 4%). These children were included in the study because it was difficult to determine whether the lack of responses was due to inattention, an incorrect button press or failure to remember to press a button.

Face Localizer results for TD-combined group

The Face > Texture contrast yielded a network of regions (which served as ROIs) that were distributed throughout occipital, temporal, and frontal areas as depicted in Figure 1 and described in Table 2. Because the right occipital cluster was large and included both the FFA and occipital face area (OFA), that region was further masked by the AAL atlas (Tzourio-Mazoyer et al. 2002) right fusiform region to yield a right FFA. The remainder of the right occipital cluster is referred to as the right OFA.

ROI analyses

Percent signal change in each region for face and object conditions versus baseline is plotted in Figure 2a–b for each group. One-sample t-tests revealed that fMRI signal was different from 0 for faces, objects, or both, in most of the regions (except the right precentral gyrus) for at least one subject group, indicating significant levels of activation. This analysis was important to show that the ASD group activates many of the same regions that the TD-combined group activates above a baseline level.

One-sample t-tests revealed that SIBs showed face-preferential responses in bilateral amygdala and vmPFC, the TD-combined group showed face-preferential responses in the right amygdala and vmPFC and the ASD group showed no face-preferential responses (Figure 2c–d). All groups showed a significant OSI in the left OFA and the SIB group showed a significant negative OSI in the vmPFC. There was a significant group difference for FSI in the right FFA: according to a non-parametric Median Test, the right FFA showed a lower FSI in the ASD compared to the TD-A group (Fisher exact significance = .039). There were no group differences in OSI in any region.

Correlations with age

Two regions showed a significant or marginal correlation between age and FSI in the TD-combined group: the left FFA ($r = .29$, $p = .057$), and right amygdala ($r = .44$, $p = .003$), as shown in Figure 3. The right FFA FSI did not show a significant correlation with age ($r=.24$, $p=.12$), but the trend was positive (Figure 3). Two regions also showed a significant

correlation with age in the ASD group: the left amygdala (rho = −.69, p = .003) and right FFA (rho = .67, p = .017), also shown in Figure 3.

Additional analyses

The Face > Texture contrast isolated regions in the TD-combined, SIB and TD-S groups (at a cluster corrected threshold of z > 2.33, p<.05; Table 3) but not the ASD or TD-A groups. All group maps with activation that survived the corrected threshold showed extensive occipito-temporal activation, but the SIB group also showed extensive right medial and anterior temporal lobe activation (Figure 4a). Interestingly, the age covariate map for the Face > Texture contrast in the ASD group yielded several right hemisphere clusters of activation at a cluster corrected threshold (z > 2.33, p<.05) with one cluster in the right FFA (Figure 4b, Table 3).

The Object > Texture contrast yielded significant clusters in all subject groups except TD-A (Table 4). The TD-combined and SIB groups showed extensive occipito-temporal and posterior parietal activation, but the SIB group showed more extensive activation in the amygdala bilaterally and posterior parietal cortex compared to the TD-combined group. The Face > Object contrast did not yield any significant clusters using a corrected threshold in any subject group.

Correlations with SRS

No correlations were significant.

Discussion

The present study examined neural substrates for face and object viewing in typical children, children with ASD and unaffected siblings of individuals with ASD. Several hypotheses were tested regarding typical, atypical, and endophenotypic (SIB group) face processing. In general, the present findings are consistent with prior reports of atypical face development in ASD and these findings are interpreted with respect to both typical and endophenotypic responses.

Hypothesis I

Hypothesis I was that several critical regions of the face network would increase in specialization with age in the TD-combined group, shifting from an object preference or no preference for faces in childhood, to greater preference for faces by late adolescence. This hypothesis was confirmed for the left fusiform gyrus and right amygdala, with the right fusiform showing a non-significant trend.

As shown in Figure 3 for the left FFA, the majority of FSI responses under age 9 in the TD-combined group reflected no preference for faces followed by a shift toward a positive FSI after age 9 and into adolescence. The finding that the left FFA showed a more pronounced increase in face specialization with age than the right FFA was also reported by Joseph et al. (2011). Golarai et al. (2010) also reported that the left FFA increased in specialization with age (like the right FFA) during adolescence. In addition, several other studies report that

adults or older children show face-specific activation in the bilateral fusiform gyrus but younger children only show this in the right fusiform gyrus (Cantlon et al. 2011; Gathers et al. 2004; Joseph et al. 2011; Pelphrey et al. 2009; Scherf et al. 2007) or not at all (Aylward et al. 2005). Moreover, although Scherf et al. (2011) reported face specialization in the fusiform gyrus bilaterally in adolescents, only the left fusiform showed fMRI adaptation to faces. Younger children did not show face selectivity in either fusiform region. Collectively, these findings support the idea that the left fusiform gyrus is less specialized for faces in childhood, but increases in specialization with age. In contrast, the right fusiform did not show a significant increase in specialization with age but showed a positive trend. Given prior reports of only right (but not left) fusiform activation in children in response to faces (Cantlon et al. 2011; Gathers et al. 2004; Joseph et al. 2011; Pelphrey et al. 2009; Scherf et al. 2007), it seems that the right FFA likely matures earlier than the left FFA in terms of a face preference.

Why would the left FFA show later development than the right FFA and what is its role in face processing? Based on findings that the left fusiform is associated with making fine distinctions among faces or visually homogenous categories of objects (Joseph and Gathers 2003; Joseph and Farley 2004; Liu, Steinmetz et al. 2008; Haist, Lee et al. 2010), we suggest that later development of this area relative to the right hemisphere homologue is related to greater demands on differentiating individual faces as a person develops. In support of this, Scherf et al. (2011) showed that adolescents and adults exhibited category-level fMRI adaptation in the bilateral fusiform (i.e. individuating faces versus non-faces) but individual-level adaptation (i.e. individuating specific faces) only in the left fusiform. Adults also showed individual-level adaptation in the right fusiform, but children showed no category- or individual-level adaption to faces in the fusiform. Hence, the left fusiform gyrus appears to be a critical locus for individuation of faces during development. Because an individual's social network greatly expands during adolescence demands on individuating specific persons would necessarily increase.

The right amygdala also showed a significant increase in face preference with age in the TD-combined group. The importance of the amygdala in face processing is well documented but findings are mixed as to whether children and adolescents show less (Ebner et al. 2013), more (Guyer et al. 2008; Hoehl et al. 2010; Killgore and Yurgelun-Todd 2007; Vasa et al. 2011) or comparable (Lobaugh et al. 2006) levels of activation to faces than adults. Most of these studies used group comparisons of children and adults rather than examined changes with age over a developmental time window or used correlations with age, as in the present study. However, Todd et al. (2011) examined age trends and also found that bilateral amygdala activation for emotional faces versus scrambled images increases with age. Pagliaccio et al. (2013) reported amygdala activation in children, but the amygdala response was undifferentiated with respect to different emotion categories. This differentiation did not emerge until adolescence. As suggested by Marusak et al. (2013), face stimuli or particular kinds of facial information, including emotional content, may increase in salience with age, thereby implicating the amygdala which plays an important role both in detecting salient stimuli (Santos et al. 2011) and in processing emotional information in faces.

Hypothesis II

Hypothesis II was that some regions that are specialized for faces in the TD group would show generalized object processing in ASD. In particular, regions implicated in social cognition (e.g., amygdala, superior temporal sulcus, right inferior frontal cortex, vmPFC) are more likely to show an object preference in ASD than in TD. Two regions that showed a significant FSI in the TD-combined group did not show a significant FSI in ASD (vmPFC, right amygdala). However, these regions also did not show a significant OSI in ASD, as would be predicted by Hypothesis II. Nevertheless, others have reported altered responses to faces in some of these regions in ASD. The right amygdala has shown greater (Dalton et al. 2005; Monk et al. 2010; Tottenham et al. 2013; Swartz et al. 2013; Weng et al. 2011), weaker (Baron-Cohen et al. 1999; Corbett et al. 2009; Domes et al. 2013; Kaiser et al. 2010) or no differences (Pierce et al. 2004; Zurcher et al. 2013) in activation in ASD compared to controls in response to faces. For the most part, the studies that report amygdala hyperactivation in ASD required processing emotional or social aspects of faces but the studies that report amygdala hypoactivation used perceptual discrimination or theory of mind tasks. For example, Tottenham (2013) showed that the elevated amygdala response in ASD was related to threat ratings (even though the faces themselves were neutral) and Dalton et al. (2005) used an emotion discrimination task. In contrast, Baron-Cohen et al (1999) asked subjects to make judgments about another person's thoughts based on the information in the eyes, and amygdala activation was lower in ASD. The present study used yearbook faces, the majority of which had a happy expression, but subjects only passively viewed the faces and were not required to make any type of discrimination (perceptual or emotional). Therefore, similar to those studies that used tasks that did not require emotional face processing, hypoactivation in ASD emerged in the present study. The lack of significance for the FSI measure may be due to the greater variability in the ASD group with respect to face specialization. It is probably the case that a wide range of social cognition and face processing capacities are present in the ASD group (Weigelt et al. 2012) and this heterogeneity is responsible for the lack of face specialization in the right amygdala. In other words, some ASD subjects show a face preference in this region whereas others do not. This is clearly illustrated in Figure 3, where half of the ASD subjects show a negative FSI and half show a positive FSI.

Altered response to faces or biological stimuli in the medial PFC in ASD has also been reported (Hubl et al. 2003; Kaiser et al. 2010; Pierce et al. 2004; von dem Hagen et al. 2013), but again, the direction of this effect (hypo- or hyper-activation in ASD) varies across studies. Zurcher et al. (2013) reported reduced vmPFC activation when attending to the mouth rather than the eyes whereas von dem Hagen et al. (2013) reported reduced vmPFC activation when viewing direct rather than averted eye gaze compared to controls, but the opposite was true for averted gaze. As the present study did not require attention to any particular region of the face or eye gaze direction, we do not know where participants were attending. However, other studies that have used eye tracking methodology report that people with ASD may focus on different aspects of faces than do typical controls (e.g., Pelphrey et al., 2002). Therefore, lower vmPFC face preference in the ASD group in the present study may reflect attending different aspects of the faces compared to the TD subjects.

Hypothesis III

Hypothesis III was that siblings would show reduced activation to faces in some regions of the TD face network (as reported by others) but would also demonstrate typical profiles. This hypothesis was not confirmed: for the most part, the SIB group showed more evidence for face specialization than either the TD-combined or ASD groups. Similar to the TD-combined group, SIBs showed a significant FSI in the vmPFC and right amygdala, but SIBs also showed face specialization in the left amygdala, the same region where ASD subjects showed regressive changes with respect to face specialization. The SIB group also showed more extensive right amygdala and antero-medial temporal lobe activation according to the Face > Texture contrast at a corrected threshold (Figure 4a) compared to the other groups.

In contrast to the present findings, other fMRI studies of unaffected siblings have reported reduced activation in many face processing regions compared to controls and similar profiles of activation between ASD and sibling groups (Dalton et al. 2007; Spencer et al. 2011). Similar findings have been reported for other visual tasks (Belmonte et al. 2010; Kaiser et al. 2010; Spencer et al. 2012). One possible reason that the present study showed more activation or greater face specialization in SIBs compared to other groups is that the SIB sample in the present study was predominantly female whereas SIB samples in other studies have had more male representation. Female children are more sensitive to facial expression, according to a meta-analysis of studies from infancy through adolescence (McClure. 2000); therefore, the more extensive face-related activation in the SIB group in the present study may simply reflect the greater female composition of this group. However, as noted in the results, the TD-S group was also predominantly female but did not show this extensive activation.

Another potential explanation for the more extensive activation in the SIB group compared to the TD-combined group could be that the SIB group was also older. Again, however, both the TD-S and TD-A groups were similar to the SIB group with respect to age and these groups did not show the same right anterior / medial temporal lobe activation. Nevertheless, the right amygdala did increase in face specialization with age in the TD-combined group. Therefore, at least some of the more extensive right temporal lobe activation in SIBs could be attributed to maturation.

Another potential reason for more extensive and specialized activation to faces in SIBs in the present study could be that prior studies have had varying levels of shared genetic variance in their samples, which could explain the degree of similarity between activation levels in siblings and ASD subjects. Notably, Spencer et al. (2011) reported the most shared variance (100%) and showed that activation in siblings was not different from the ASD group but was different from the control group in the majority of task-relevant regions. Dalton et al. (2007) reported less shared genetic variance (44%), with one region not differently activated by siblings and controls (left fusiform) and two other regions (right fusiform and right amygdala) activated less than controls. Kaiser et al. (2010) reported the least shared variance (~20%) and noted regions uniquely and more strongly activated in siblings compared to the ASD group. Consequently, when shared genetic variance between sibling and ASD subjects is high, activation patterns are also more similar. When shared variance is low, more differences between siblings and ASD subjects emerge, and more

similarities between siblings and controls are reported. The more extensive face preferential activation and greater face specialization in SIBs in the present study may reflect having learned compensatory strategies during development to overcome increased genetic risk for autistic behaviors (Kaiser et al. 2010). This possibility is especially compelling given that, in the present study, one region that showed strong face specialization in SIBs but not in the TD-combined or ASD groups was the left amygdala. This very same region also showed regressive changes with age in face specialization in the ASD group, suggesting compensatory development in this region in SIBs.

Correlations with Age

The exploratory analyses of age in the ASD and SIB groups revealed some surprising findings. Although the ASD group as a whole did not show strong face specialization in the right FFA (or other components of the face network), face specialization did increase with age in this region according to the ROI analysis. In light of the suggestion abive that the right FFA develops earlier than the left FFA in typical subjects, this age-related increase in activation in ASD could point to delayed development of the right FFA. Of note, other right hemisphere regions were also associated with age-related increases according to the age covariate map for the Face > Texture contrast. Another interesting finding was that face specialization in the left amygdala *decreased* with age in the ASD according to the ROI analysis. Comparing these two developmental trajectories in Figure 3 shows that older children or adolescents with ASD show slightly greater right FFA face specialization than younger ASD children but also show much less left amygdala face specialization. In other words, whereas the typical developmental trajectory is marked by increased face specialization in both the bilateral amygdala and fusiform gyrus, in ASD these regions show opposed developmental trends, with right fusiform face specialization modestly increasing and left amygdala face specialization decreasing with development. This finding fits in with the suggestion that the amygdala-fusiform system is disrupted in ASD (Schultz, 2005) and that the amygdala, in particular, shows aberrant development followed by a cascading effect on cortical areas. The present cross-sectional design cannot speak to the issue of whether atypical amygdala development precedes a cascading effect on cortical development. Nevertheless, the amygdala-fusiform system appears to be affected in ASD. As an example, Kleinhans et al. (2008) reported that reduced fusiform-amygdala connectivity is associated with greater social impairment in ASD. Although the present study did not find significant correlations with ASD severity, the amygdala-fusiform response to faces becomes more dissociated with age, which could potentially manifest as reduced connectivity between these regions.

Limitations of the Present Study

The primary limitation of the present study was the small number of subjects in the ASD and SIB groups. Although we used statistics appropriate for small sample sizes and the TD-A and TD-S groups were well matched to the ASD and SIB groups, respectively, the present findings should be interpreted with caution. We cannot conclude that the ASD group showed lack of face specialization based on null findings that the FSI was not different from 0. In smaller sample sizes variability is higher, so the failure to reject the null hypothesis

may be due to this greater variability. Nevertheless, we note that the SIB group was even smaller, and significant results were obtained for that group.

Another limitation was that the SIB group composition was mostly female thereby limiting the ability to generalize these results to siblings of children with ASD. Although the present study only compared the SIB subjects to age- and gender-matched controls, the present findings regarding SIBs may only apply to female undiagnosed siblings and not to males.

We also acknowledge that a passive-viewing task as used in the present study cannot guarantee that the stimuli were attended. We attempted to circumvent this by requiring participants to press a button each time a picture appeared. The majority of subjects did this the majority of the time, but two ASD and two TD subjects made fewer than 35% button presses. Although this could indicate lack of attention to the stimuli, it could also reflect not remembering the instruction to press a button or pressing the wrong button (but we did not record responses that were made with the wrong button). Importantly, both children with ASD and TD children fell into this category of not responding. Therefore, we do not think the present findings of differences between the ASD and TD-combined group can be explained by failure to press a button.

Conclusions

The present study extended the current understanding of typical and atypical developmental trajectories of face processing. The left fusiform gyrus and bilateral amygdala show the greatest typical developmental increase in face specialization from middle childhood to late adolescence. These developmental changes likely reflect the increasing salience and importance of faces during adolescence and the need to make finer discriminations among faces as an individual's social repertoire grows. With respect to atypical development, an important finding was that children with ASD did not show face specialization in the right amygdala and vmPFC, which were regions where typical controls and siblings showed face specializiation. In addition, ASD subjects showed decreasing face specialization with age in the left amygdala. These regions have been implicated in detecting salient stimuli (amygdala) and in attending to specific aspects of faces that relate to inferring mental states of others (vmPFC; such as attending to the eyes versus mouth or processing eye gaze direction). Such capacities are diminished in ASD (Schultz 2005). With respect to understanding genetic vulnerability to ASD and potential compensatory mechanisms, the SIB group showed responses on par with the typical controls with additional recruitment of antero-lateral temporal regions and the amygdala. This additional recruitment may reflect development of compensatory mechanisms to counter the genetic risk for autistic traits and behaviors.

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Appendix

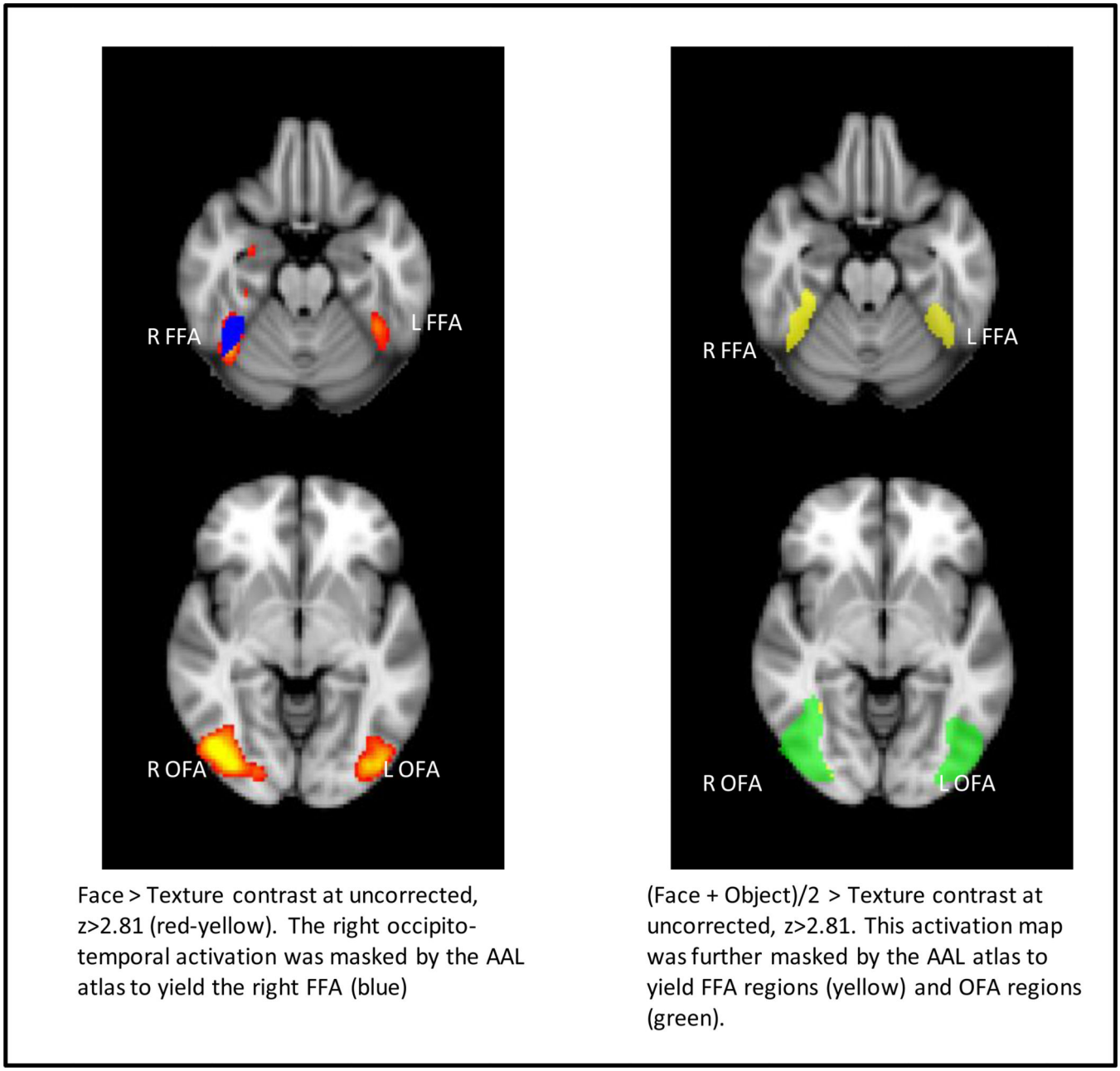
The Face > Texture contrast was used to isolate regions of interest (ROIs) in the present study, but this contrast may be biased to detect face preferential responses, thereby raising concerns about the independence of ROI definition and hypothesis testing. To address this concern, we also ran a (Face+Object)/2 > Texture contrast and applied the same uncorrected threshold ($z > 2.81$) that was used to create ROIs from the Face > Texture contrast. As shown in Figure A1, this contrast yielded 2 large occipito-temporal clusters that survive an extent threshold of 43 voxels. Forty-three voxels was used as a minimal extent threshold given that spatial smoothing used a 7-mm FWHM Gaussian kernel. Therefore, the resolvable element size was 343 μL. During spatial normalization the data were resampled to 2 mm^3 or 8 μL; therefore, 43 voxels in MNI space = 344 μL, which matches the minimum resolvable element.

These two large clusters were further broken down into FFA and OF A components using AAL atlas regions as masks (as we did for the ROIs from the Face > Texture contrast). The resulting ROIs are very similar, but not identical to, the FFA and OFA ROIs that we used in the paper. We then examined face-specialization index (FSI) and object-specialization index (OSI) in these 4 new ROIs to see if any of the results differed.

One difference was that SIBs showed a significant FSI (compared to 0) in the new right FFA which was marginally significant before. Another difference was that the comparison of ASD v. TD-A (via nonparametric Median Test) was not significant in the new right FFA. Also, the marginal correlation between age and FSI in the TD-combined group was not significant in the new left FFA. However, the correlation between FSI and age in the right remains significant in the new right FFA as well

Taken together, different results with the new ROIs apply to those situations where the effects were marginal or not as strong as in some other ROIs. However, the fundamental findings of the present study were not drastically changed by the two approaches to defining ROIs.

Figure A1. Comparison of two approaches used to define ROIs. The approach on the left was used for the main analysis and the approach on the right is an alternative approach that was explored.



Face > Texture contrast at uncorrected, z>2.81 (red-yellow). The right occipito-temporal activation was masked by the AAL atlas to yield the right FFA (blue)

(Face + Object)/2 > Texture contrast at uncorrected, z>2.81. This activation map was further masked by the AAL atlas to yield FFA regions (yellow) and OFA regions (green).

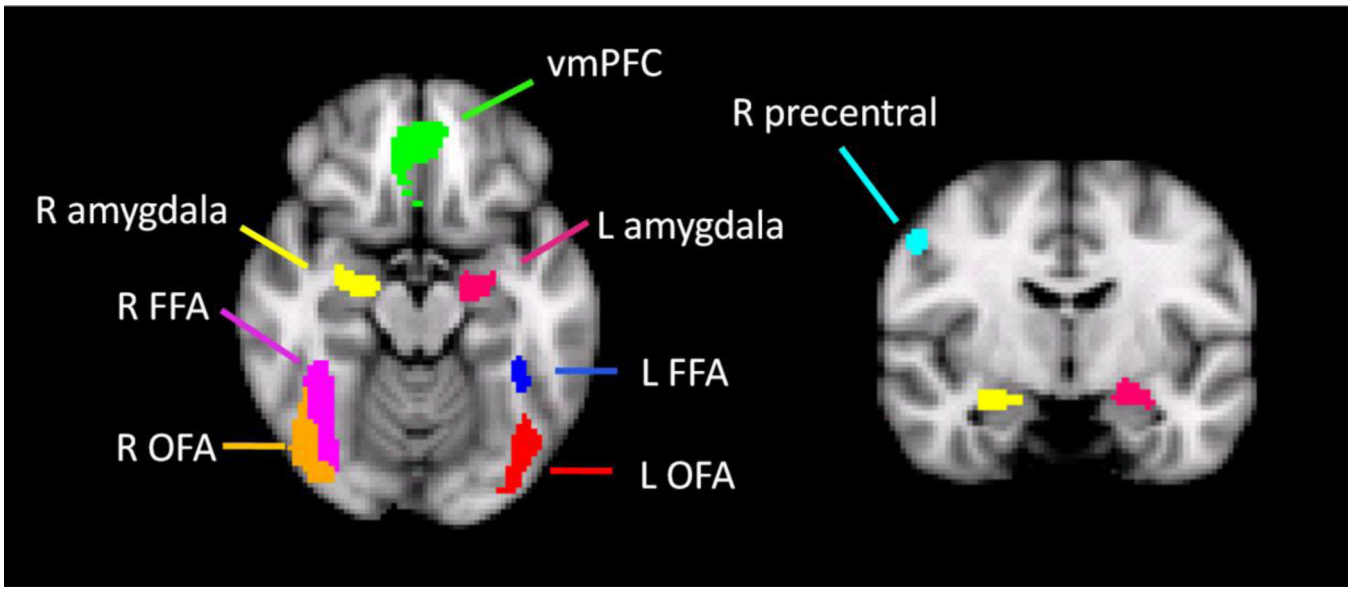
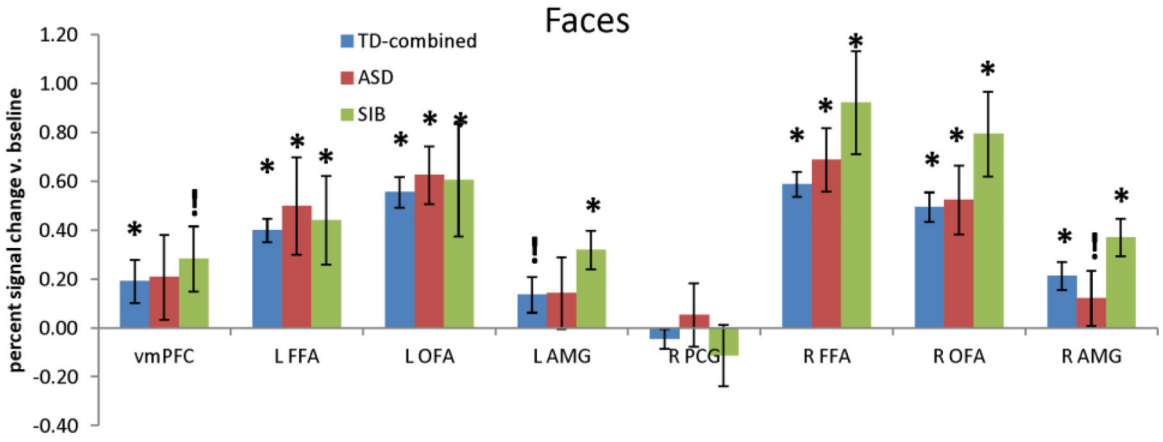


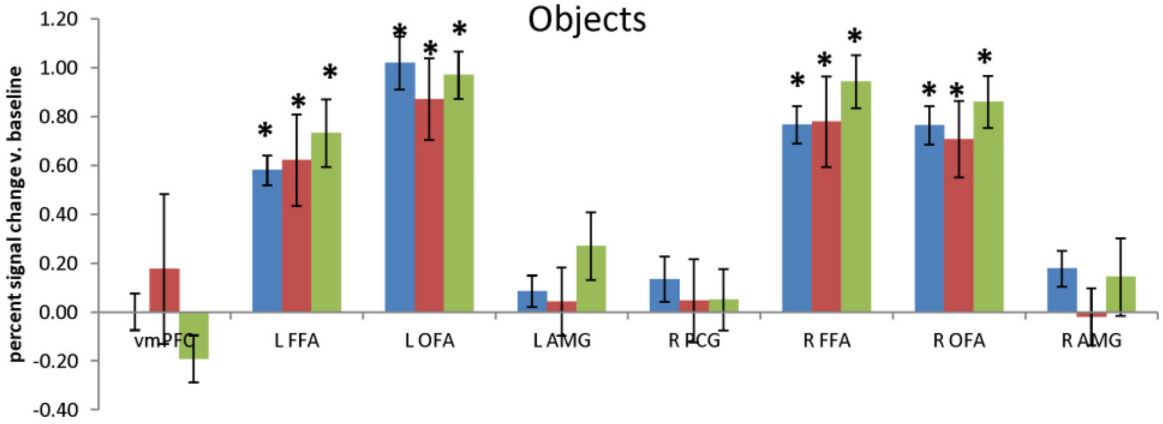
Fig. 1.

Regions of interest from the activation map for Face > Texture in the TD-combined group ($z > 2.81$, $p < .0025$, uncorrected). The right occipito-temporal region was further masked by the fusiform and inferior occipital regions of the AAL atlas to yield two separate ROIs for the fusiform face area (FFA) and occipital face area (OFA).

(a)



(b)



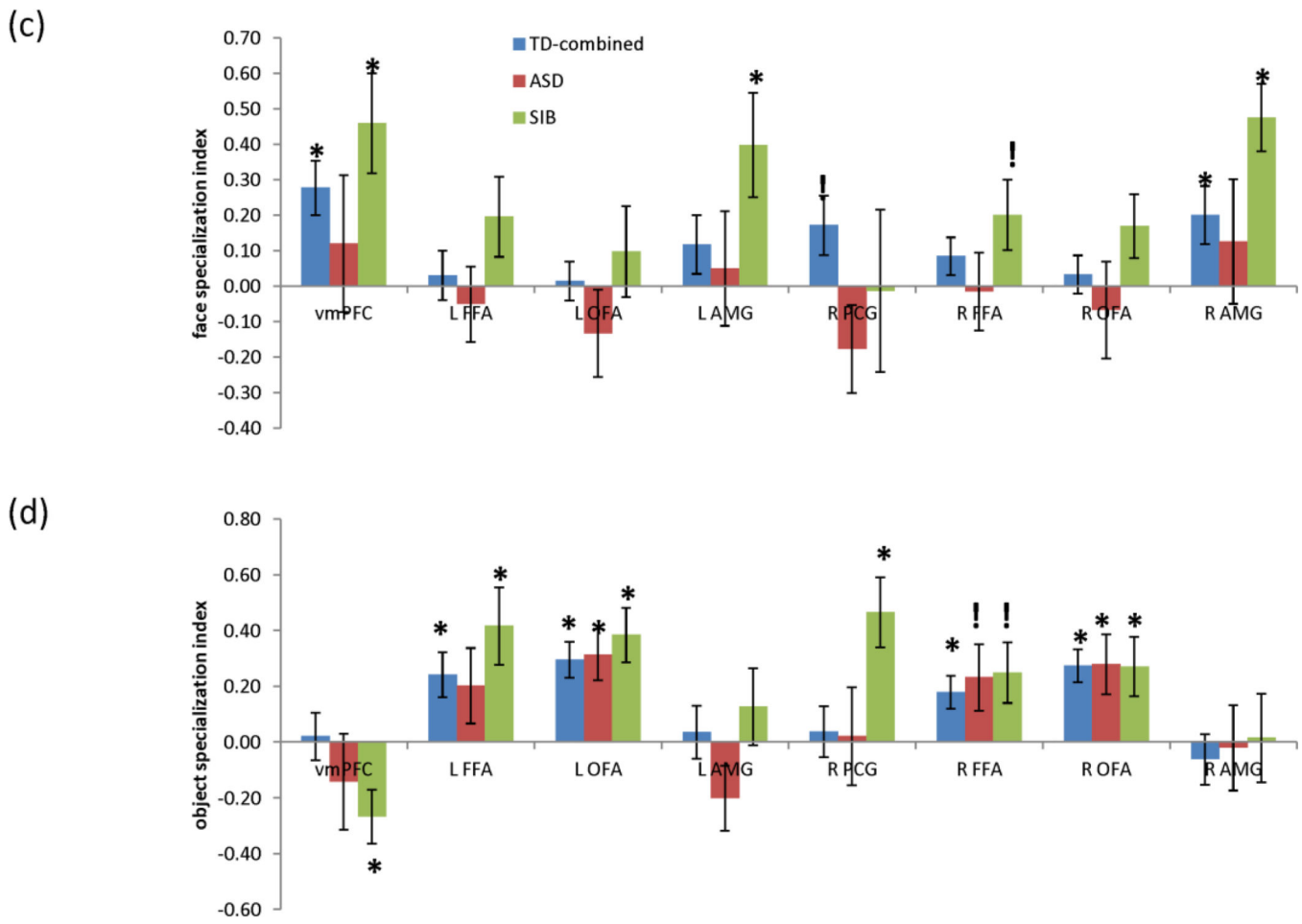


Fig. 2.

ROI results. ROIs based on the Face > Texture contrast in the TD-combined group. (A–B) Face and object percent signal change versus baseline in each ROI for each subject group. (C–D) Face and object specialization index in each ROI for each subject group. * indicates a significant difference from 0 at $p < .05$; ! indicates $p < .08$ according to one-sample t-test.

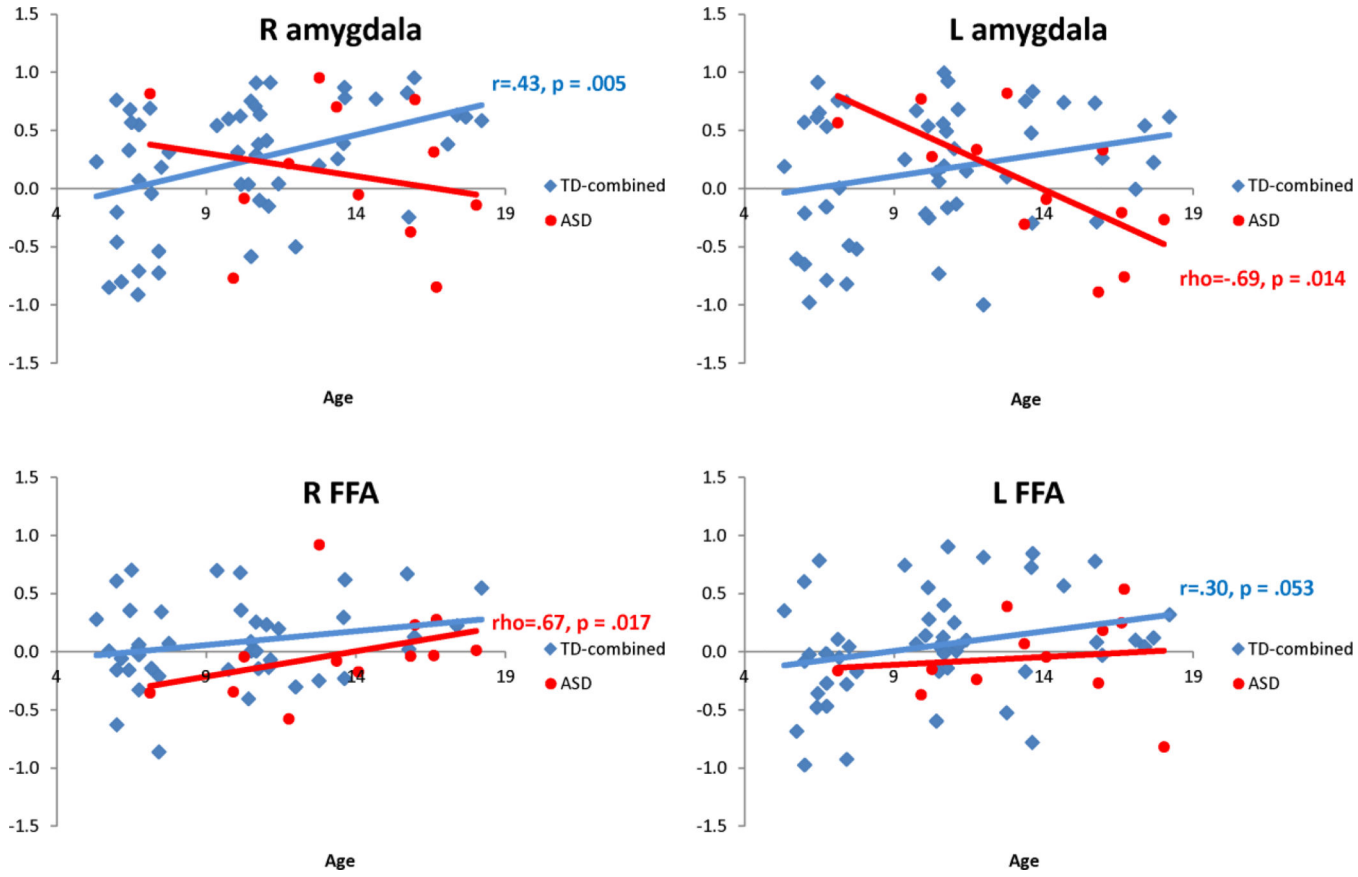


Fig. 3.

Correlations between face specialization index and age in TD-combined group (blue) or in the ASD group (red) in the bilateral amygdala and bilateral FFA.

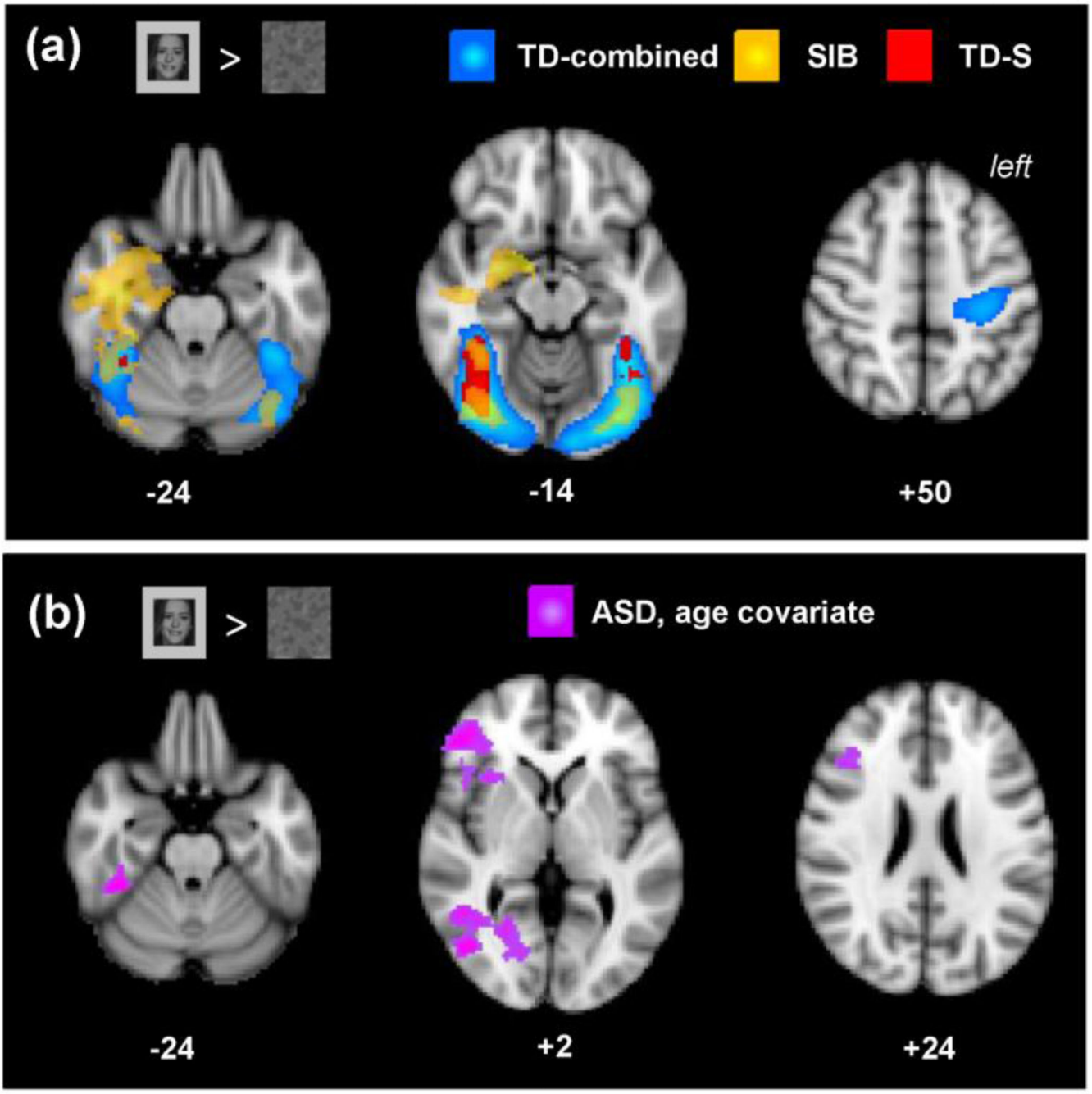


Fig. 4.

(A) Activation map for Face > Texture in the TD-combined (blue), SIB (yellow) and SIB-matched control (TD-S) groups. (B) Activation map for the age covariate for the Face > Texture contrast in the ASD group. Activations are significant at $z > 2.33$, $p < .05$, cluster corrected.

Table 1

Participant Characteristics

	ASD Mean (SD)	TD-A Mean (SD)	SIB Mean (SD)	TD-S Mean (SD)	TD-combined Mean (SD)
Total n (# males)	12 (11)	12 (11)	9 (1)	9 (2)	42 (21)
AGE (years)	13.5 (3.5)	13.0 (3.45)	12.5 (3.5)	11.9 (3.3)	9.88 (3.5)
PPVT FSIQ	101.7 (28.5)	114.8 (17.6)	117.3 (10.6)	110.8 (16.4)	117.9 (14.4)
WISC FSIQ	96.1 (26.5)[a]	115.8 (15.8)	112.3 (7.5)	109.9 (12.0)	n/a
SRS-Total	106.1 (26.7)[a]	22.2 (14.7)	12.7 (8.6)	18.56 (11.9)	n/a
ADIR-Preoccupations	6.5 (1.4)[a]	0.25 (0.45)	0.33 (0.71)	0.78 (1.4)	n/a
ADIR-Verbal	14.3 (4.9)[a]	0.17 (0.39)	0.22 (0.67)	0.22 (0.67)	n/a
ADIR-Social	20.4 (5.5)[a]	0.42 (.90)	0.33 (0.71)	0.22 (0.44)	n/a
ADIR-NonVerbal	7.5 (3.1)[a]	0.08 (0.29)	0.0 (0.0)	0.0 (0.0)	n/a

[a] Mean is different from TD-A group at $p < .05$

ADIR, Autism Diagnostic Interview – Revised. ASD, Autism Spectrum Disorder. FSIQ, Full-scale IQ. PPVT, Peabody Picture Vocabulary Test. SD, Standard Deviation. SIB, undiagnosed siblings. SRS, Social Responsiveness Scale. TD-A, Typically developing matched controls for the ASD group. TD-combined, Typically developing control subjects.TD-S, Typically developing matched controls for the SIB group. WISC, Wechsler Intelligence Scale for Children.

Table 2

Regions from the Face > Texture contrast in the TD-combined group (z > 2.81, uncorrected, cluster size > 43) that served as regions-of-interest

Region	Size (voxels)	Maximum z value x	MNI coordinates		
			y	z	
Left Amygdala	123	4.35	−22	−11	−15
Right Amygdala	124	4.35	25	−10	−16
Right Precentral Gyrus	127	4.06	52	−4	45
Left Fusiform Face Area	148	4.14	−39	−46	−21
Ventromedial prefrontal cortex	300	3.99	2	42	−15
Left Occipital Cortex	727	5.03	−39	−78	−9
Right Occipital Cortex	1745	6.37	40	−70	−10
Right Fusiform gyrus (FFA)	534	5.74	38	−59	−17
Right Occipital cortex (OFA)	1211	6.37	41	−75	−6

ASD, Autism Spectrum Disorder. SD, Standard Deviation. SIB, undiagnosed siblings. TD-A, Typically developing matched controls for the ASD group. TD-combined, Typically developing control subjects.TD-S, Typically developing matched controls for the SIB group.

Table 3

Regions from the Face > Texture contrast (z > 2.3, cluster corrected at p<0.05)

Group	Region	Size (voxels)	Maximum z value	MNI coordinates		
				x	y	z
ASD	none					
ASD, age covariate	Right occipital and fusiform cortex	1411	3.63	41	28	5
	Right inferior frontal Cortex	1158	3.53	35	−61	−4
TD-A	none					
TD-combined	Bilateral occipital and fusiform	10374	7.32	40	−78	−10
	Left precentral and central sulcus	1503	4.44	−38	−24	6
SIB	Right occipital. fusiform, temporal	4412	4.07	36	−52	−16
	Left lateral occipital	1146	3.54	−34	−80	−14
TD-S	Right occipital and fusiform cortex	1485	4.17	37	−72	−5
	Left occipital and fusiform cortex	922	3.86	−33	−80	−2

ASD, Autism Spectrum Disorder. SD, Standard Deviation. SIB, undiagnosed siblings. TD-A, Typically developing matched controls for the ASD group. TD-combined, Typically developing control subjects.TD-S, Typically developing matched controls for the SIB group.

Table 4

Regions from the Object > Texture contrast (z > 2.3, cluster corrected at p < 0.05)

Group	Region	Size (voxels)	Maximum z value	MNI coordinates		
				x	y	z
ASD	Right occipital and fusiform	1928	3.87	40	−76	−6
	Left occipital and fusiform	1150	4.00	−38	−62	−13
TD-A	none					
TD-combined	Left occipital and fusiform	9597	7.79	−35	−66	−6
	Right occipital and fusiform	8830	8.01	35	−66	−5
SIB	Left occipital, fusiform, amygdala	6528	4.05	−33	−56	−7
	Right occipital, fusiform, amygdala	6273	4.30	33	−51	−8
TD-S	Left occipital and fusiform	2355	3.94	−38	−64	−6
	Right occipital and fusiform	2014	4.39	39	−60	−9

ASD, Autism Spectrum Disorder. SD, Standard Deviation. SIB, undiagnosed siblings. TD-A, Typically developing matched controls for the ASD group. TD-combined, Typically developing control subjects.TD-S, Typically developing matched controls for the SIB group.