**ARCHIVAL REPORTS**

**Fusiform Function in Children with an Autism Spectrum Disorder Is a Matter of “Who”**

Karen Pierce and Elizabeth Redcay

**Background:** Despite the importance of face processing for normal social development, no functional magnetic resonance imaging studies of face processing in autism have focused exclusively on the childhood years. To fill this gap, 45 children aged 6–12 participated in practice scans. After exclusion due to motion, 11 children with an ASD and 11 age-matched normal control subjects were included in final analyses.

**Methods:** Stimuli consisted of pictures of a familiar adult, familiar child, stranger adult, stranger child, and objects. During the scan, children pressed a button in response to an identical face shown on two consecutive trials. On the basis of our prior research, masks of four anatomic regions of interest (ROIs) including the fusiform gyrus, amygdala, and anterior and posterior cingulate were created for each subject and manually edited for anatomic precision. Following deconvolution analyses, the number of voxels significantly active and percent signal change values that fell within each ROI mask were calculated for each subject.

**Results:** Analyses revealed normal fusiform activity in children with autism when viewing a face of their mother or other children. In contrast, looking at stranger adult faces initiated profound deficits in that the mean number of significantly active voxels in the fusiform bilaterally was approximately 25% of that shown in typically developing children.

**Conclusions:** A selective fusiform deficit in response only to the faces of adult strangers may be the result of reduced attention and interest during those conditions. Face processing abnormalities found in autism beyond the fusiform likely exist.

**Key Words:** Autism, children, face processing, fusiform face area, fMRI, pediatric imaging, stranger faces

Although face processing is one of the most widely studied aspects of autism using functional magnetic resonance imaging (fMRI), virtually every experiment has used adults or adolescents as the mean age of study (1–16). This period of life, however, represents a relative endpoint on a neurodevelopmental continuum. New neurobiological research has revealed a striking profile of deviant brain growth that changes considerably across the life span of the disorder. This growth pattern can be generally summarized by three phases: early brain overgrowth during the first years of life, arrest of growth during late childhood and preadolescence, and decline during adolescence and adulthood (see 17,18 for reviews). The dramatically changing landscape of neural development across ages in autism raises the caveat that results from functional brain imaging studies in autism should be placed in a developmental context.

In the three fMRI studies of face processing in autism that did include younger ages (4,7,9), the age range in those samples extended up to 25, 17, and 23 years, respectively, and age-related effects were not specifically analyzed. As such, there is a large gap in knowledge regarding the brain response to faces in autism prior to the onset of the purported neural decline.

Although there have been exceptions (8,10,12), the vast majority of research on face processing leads to a general conclusion: the middle lateral aspect of the fusiform gyrus, the brain region highly involved in face processing in normal subjects, is hypoactive in adults with autism (1–5,7,9,14,19–21). If there is developmental continuity in autism and if hypoactivity of the fusiform is a fundamental and biologically defining feature of the disorder, then fusiform defects should be similar or perhaps even stronger at younger ages.

On the other hand, considering the triphasic brain growth trajectory in autism described earlier, it is equally reasonable to predict the opposite—namely, that dysfunction in the fusiform may not be as severe in children with autism because they have not yet undergone the phase of cell loss or volume reduction typical of the adult phase.

Although there are no fMRI studies of face processing exclusively in children with autism, a few studies using other imaging modalities have been conducted. Using event-related potential (ERP) technology, Webb and colleagues (22) found a 10-msec delay, but no amplitude differences, in the neural response to faces between 3- and 4-year-old children with autism and control subjects. A magnetoecephalography study with 7 to 12 year olds found no differences from normal in the N140 response thought to be similar to the adult N170 over extrastriate areas in children with autism (23). The authors concluded that face processing in children with autism follows a similar trajectory to that seen in normal development, with minor deviations. Taken together, these two studies raise the possibility that defects in the fusiform may be less severe, or at least have a different profile, than previously reported with adults with the disorder.

Because autism is fundamentally a disorder of sociability, it is important to consider the type of faces that are used to test social perception. With three exceptions (4,8,15) virtually every fMRI/face study of autism has used the faces of strangers (1–3,5–14,16). It has long been known that contact with strangers often induces distress and reduces social interaction in people with autism. Thus, although how the brain responds to stranger faces is essential to study in autism, it is but one aspect of face processing. The inclusion of faces that might hold more interest for people with autism, such as faces that are personally meaningful, may have a powerful impact on functional brain responding in this population (8).

Given that our study’s focus was on the childhood years, another face type that may influence fusiform function is child...
faces. Indeed, there is a strong developmental drive for infants and children to prefer to attend to the faces of other children (24). For example, when given the choice, the mean number of seconds an infant spends looking at child faces is significantly higher than the mean number of seconds spent looking at adult faces (25).

The fusiform, however, is but one structure within a larger “social brain” network that plays a role in evaluating faces in normal individuals, particularly when emotional or personally meaningful faces are used. Other structures such as the amygdala and the anterior and posterior cingulate play key roles in evaluating the social and emotional significance of faces.

Overall we aimed to investigate face processing in a younger and narrower age sample than previous studies and to vary systematically the type of face on two important dimensions: whether a face was familiar or a stranger and whether the face was of a child or an adult. Functional imaging data collected during the early and middle childhood years are much closer to the time of symptom onset and as such may provide a clearer picture of basic phenomenon that are related to abnormal social development.

Methods and Materials

The study was approved by the University of California—San Diego Human Research Protection Program. All parents of participants gave informed consent.

Subjects

Forty-five autism spectrum disorder (ASD) and typical children between the ages of 6 and 12 years participated in a series of pre-fMRI training procedures before the final experiment (see Supplement 1, Methods).

Final ASD Group. Eighteen children with an ASD passed through all phases of training and participated in the final experiment. Children with movement exceeding motion criteria were not included in the final analyses, leaving a final sample size of 11 children with an ASD (9 autistic disorder, 1 pervasive developmental disorder—not otherwise specified, and 1 Asperger’s disorder) (see Supplemental Figure 1 and Table 1).

Final Normal Control Group. When possible, typical children were matched on a one-to-one basis to each autistic child based on sex, chronological age, and handedness. The mean age difference between each pair was 9 months. Autistic and typical children were not matched according to IQ, and the typical group had a significantly greater IQ score (mean 91 vs. mean 109, t(20) = -3.4, p < .05). After elimination due to motion and other factors, 11 typical children were included in final analyses (see Supplement 1, Methods).

Stimuli

Three stimulus sets, “familiar,” “stranger,” and “object,” were used for each participant and contained pictures of their mother, their friends, unknown adults, unknown children, and objects. Overall, a total of 130 nonrepeating pictures were used (see Supplement 1, Methods).

Behavioral Testing

During Scan—N-1 Back Task. To facilitate continuous attention to the stimuli during the scan, subjects pressed a button when the identical image was presented consecutively, also known as the N-1 back task (26).
Postscan—Face Processing Behavioral Tasks. A behavioral task was designed to evaluate relationships between face recognition ability and neurofunctional activation to familiar and unfamiliar faces. The task was based on previous studies showing shorter reaction times to familiar faces (27,28). The test sheet contained a “target face” at the top, followed by rows of faces, totaling 48 faces. The task was to scan the array and cross out the target face wherever it appeared (Supplement 1, Methods).

Postscans—Face Identity Task. To verify that subjects could identify each photograph as a familiar person, subjects were asked to name verbally each familiar photograph shown on a printed page immediately following the scan.

Experimental Procedure and Image Processing

Procedures were similar to our previously published report that used a rapid event-related fMRI design (8). Children viewed photographs of faces of and objects interspersed among trials that presented a fixation cross. The experimental run contained 188 trials. In 130 of the trials, photographs were presented for 2000 msec followed by 500 msec of a white screen. The remaining 58 trials presented the fixation cross for 2500 msec (null trials).

MRI Data Acquisition. Imaging data were collected on a 1.5-T Siemens (San Diego, California) Symphony magnetic resonance scanner. All of the image registration and functional analyses were conducted using Analysis of Functional Neuroimages (AFNI) software (29) (see Supplement 1).

Motion Analysis. Images were corrected for motion using the AFNI program 3DVolreg. An independent samples t test was used to compare the motion indices between the final group of autistic and typical children. No significant between-group differences were found (Supplement 1).

fMRI Data and Whole Brain Analyses. After motion correction, the functional image time series were smoothed with a Gaussian filter (6 mm) and resampled into Talairach coordinates using AFNI. Individual subject analyses were performed using a deconvolution approach (3dDeconvolve program) (Supplement 1).

For group analyses, linear contrast scores for each participant obtained from the deconvolution analysis were included in a three-way analysis of variance (ANOVA) using face and object conditions as factors. Separate analyses were conducted for ASD and normal control children. Correction for multiple comparisons was established using a voxel-cluster threshold technique (30) for an overall corrected level of significance (alpha) of .05 (individual voxel $p < .01$, two-tailed; minimum cluster threshold required = 800 mm$^3$). General linear tests (glt) were conducted to compare the blood oxygen level–dependent activation from the first to the fourth acquisitions following stimulus presentation (2.5–10.0 sec) for conditions of interest.

Region of Interest (ROI) Analyses. The fusiform gyrus, amygdala, and anterior and posterior cingulate were ROIs identified a priori for specific analyses. Each ROI has been shown to be functionally active in response to personally meaningful faces in our previous work (8). Briefly, ROIs were traced using a combination of automated and manual procedures, and only voxels within the mask that exceeded a significance threshold of $p < .01$, two-tailed, were included in analyses (Supplement 1).

Correlation Analyses

Fusiform, Amygdala, and Face Processing Task. Pearson correlation coefficients were computed to examine associations between the number of voxels active in the fusiform and amygdala and behavioral performance on the face processing task.

Fusiform and Other ROIs. Pearson correlation coefficients were computed to examine the relationship between the number of voxels active in the fusiform in relation to the remaining three ROIs in each group.

Table 1. Subject Characteristics

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ASD, autism spectrum disorder; ADI-R, autism diagnostic interview—revised; ADOS, autism diagnostic observation schedule; Restr & Rep, restricted and repetitive behavior; Comm, communication.
Results

Behavioral Testing

During Scan—N-1 Back Task. Although all 22 subjects performed the N-1 back task during the scan, technical issues prevented a computer generated logfile for four subjects (two ASD, two control). Of the remaining 18 subjects, no differences in reaction time [normal 907 msec vs. ASD 984 msec, \( t(16) = -0.69, p > .05 \)] or accuracy [normal correctly identified 13.6 targets vs. ASD 12.5 targets, \( t(16) = .93, p > .05 \)] between groups was found.

Postscan—Face Processing Behavioral Task. There were no significant differences between groups in reaction time, number of false alarms, or misses in response to mother’s face. Children with ASD were significantly slower than typical children to identify the stranger female face (mean 31.9 sec vs. 45.8 sec, \( t = -1.9, p < .05 \)) and had more misses (mean 1.36 misses vs. 4.37 misses, \( t = -2.34, p < .05 \)) in this condition (Figure 1).

Postscan—Face Identity Task. Following the scan, all children were able to identify the familiar faces used during the experiment.

ROI Analysis: Number of Voxels Active

There were no statistically significant between-group differences in the amygdala or anterior cingulate. Statistically significant fusiform and posterior cingulate findings follow.

Fusiform. A repeated-measures ANOVA for the right fusiform revealed a significant main effect of group \( F(1,20) = 3.158, \)
In response to unfamiliar faces, the predicted social network of the fusiform, amygdala, and other regions should be active in response to the stranger adult condition. Because fusiform hypoactivity to unfamiliar faces is consistent with the majority of previous research studies on adults with autism (31), we conclude that a selective fusiform abnormality in response to unfamiliar faces may well be persistent across ages from middle childhood to adulthood. In our current study, the number of active voxels in response to unfamiliar faces was approximately only 25% that of control subjects in both the right and left fusiform. In contrast, the fusiform response to unfamiliar faces such as mother, friend, or unknown child were similar between children with ASD and typical children. Behav-

**Correlations**

**Fusiform, Amygdala, and Face Processing Task.** No significant correlations between reaction time during the face processing task and number of voxels active or percent signal change in the fusiform were found for either group. However, significant amygdala correlations were found. First, results indicated a negative correlation between the number of voxels active in the amygdala and reaction time to identify stranger faces (r = -0.66, p < 0.04), indicating that children with fewer active amygdala voxels took longer to identify stranger faces. Second, there was also a trend for reduced left amygdala percent signal change to be associated with a slower reaction time to identify stranger faces (r = -0.53, p < 0.09).

**Fusiform and Other ROIs.** To evaluate further the selective fusiform abnormality in response to the faces of stranger adults, correlations were performed between the number of active voxels in the right fusiform and the three remaining ROIs during this condition. Interestingly, there was a strong positive correlation between right fusiform and right amygdala activity (r = 0.62, p < 0.05) and right fusiform and right posterior cingulate activity (r = 0.82, p < 0.05) in children with ASD, but there were no significant correlations in response to stranger faces in the normal group.

**Discussion**

Our study revealed a striking selective deficit in fusiform function in children with an ASD when they viewed only one type of face: the face of an adult stranger. Because fusiform hypoactivity to unfamiliar faces is consistent with the majority of previous research studies on adults with autism (31), we conclude that a selective fusiform abnormality in response to stranger adult faces may well be persistent across ages from middle childhood to adulthood. In our current study, the number of active voxels in response to stranger adult faces was approximately only 25% that of control subjects in both the right and left fusiform, and percent signal change values were significantly reduced in the left fusiform. In contrast, the fusiform response to other face types such as mother, friend, or unknown child were similar between children with ASD and typical children. Behav-

**Whole Brain Analysis**

Whole brain functional activity in response to all faces combined as well as to familiar and unfamiliar faces separately was examined in each group. After the cluster volume correction, there was significant bilateral fusiform activation in response to all face types in typically developing children but predominantly right hemisphere activation in children with ASD. Furthermore, there was a weak bilateral fusiform response to stranger faces in children with ASD compared with typical children (Figure 4).

In response to familiar faces, the predicted social network of ROIs (fusiform, amygdala, anterior and posterior cingulate) were significantly active in the normal group. Within this social network, only the fusiform and amygdala were significantly active in the ASD group (Figure 5).

**ROI Analysis: Percent Signal Change**

Comparing only voxels that were significantly active for each ROI, there were no percent signal change differences between groups in any condition in any ROI, with the exception of the left fusiform in response to the stranger adult condition [mean percent signal change .78 normal vs. .49 ASD; t(1,20) = 1.9, p < .05; Figure 3].

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ioral results echoed the notion of a selective deficit in response to the faces of strangers in that children with an ASD were slower to perform the face task and made more errors when the face presented was an adult stranger. In contrast, reaction time and accuracy in response to mother’s face were not statistically different from normal. As such our findings provide direct evidence of what has been clinically obvious in autism for decades: individuals with this disorder have considerable abnormality, on both the behavioral and the neurologic level, in response to strangers (32–34).

Although the sample size was relatively modest and thus results should be interpreted with caution, the specificity of these findings raises an important question: what are the neurofunctional mechanisms that could be responsible for such a selective deficit in the fusiform in response to adult stranger faces?

Many possibilities may account for this finding, but abnormal signaling from interconnected and face-relevant structures such as the amygdala may play a role (30,35–38). Connectivity between the two structures has been demonstrated in both humans (39) and nonhuman primates (40). Feedback loops between the fusiform and amygdala have been hypothesized to play a role in evaluating emotion in faces, particularly those that appear threatening (41). Exaggerated amygdala activation has been reported in response to emotional human faces in a range of social anxiety disorders (42–44). Children with autism often display anxiety, and a recent study found a positive correlation between amygdala volume and symptoms of anxiety in children with the disorder (45). Although it may be plausible to speculate that the adult stranger faces shown in this experiment induced anxiety for children (and perhaps they did), hyperactivity of the amygdala was not observed. Instead, volumes of functional activity in the amygdala as well as percent signal change did not differ between groups. However, there was a significant positive correlation between the number of active voxels in the fusiform and amygdala during the stranger adult condition. Thus those who showed a weak or absent fusiform activity in response to stranger faces also showed a weak or absent amygdala response. Furthermore, there was a trend showing that those children who were slowest to identify stranger faces were also those who showed the smallest percent signal change in the amygdala. Taken together, results suggest amygdala involvement in the abnormal fusiform response to adult strangers.
Another possibility is that enhanced attention or motivation to attend to the mother and child faces selectively influenced fusiform activity particular to these conditions. Conversely, reduced attention during the stranger adult condition, particularly to the eye region of the face, may have directly influenced fusiform responding. Although this study did not use an eye tracker, enhanced face scanning particularly in the eye region is has been shown to correlate with fusiform activity in autism (4).

To date, six studies have reported normal levels of fusiform activity in adolescents and adults with autism, and all studies contained a feature that may have been particularly attention enhancing. The Pierce (8) and Kleinhans (15) studies used personally meaningful faces such as mother. Hadjikahni and colleagues (10,16) and Bird and colleagues (12) directed attention to the eye region of the face by the use of a red dot placed between the eyes, and Wang and colleagues (9) instructed subjects to label the face. Consistent with ours and others’ previous hypotheses (4,8,10,12), our present findings suggest abnormality in systems that modulate fusiform activity, rather than a defect in the fusiform per se.

The only other condition that showed reduced fusiform activity in children with autism was in response to common objects such as a hat or cup. Although children with autism are often preoccupied with objects, it is usually only those of unique interest to a specific child (e.g., maps). Indeed, children with autism do not show an interest in novel objects and often display reduced exploration of their environment (46). A reduction in fusiform activity in the object condition further suggests that reduced attention and interest may be responsible when findings of hypoactivity of the fusiform are observed.

The anterior and posterior cingulate are part of a newly defined system know as the “default network,” which consists of brain areas that are involved during internally focused tasks such as autobiographical memory and perceiving the mental states of others (47,48). A negative correlation between activity in the fusiform and posterior cingulate in a 2006 face-matching study by Bokde et al. (49) has been interpreted as a failure of particular control tasks to attenuate the default network. Although the default network is presumably always “on,” observed as deactivation during rest, Buckner and colleagues (47) pointed out that the default network is observed as positive activation during tasks of autobiographical memory retrieval, theory of mind, and the like. Theoretical discussions of the default network suggest that the development of this system may lie at
the core of human ability to engage in socially complex interactions (47) and may not be fully mature until after the childhood period (50). Consistent with circinate abnormalities detected in this study, abnormalities in the default network have recently been identified during rest in autism, suggesting a possible neural basis for observed abnormalities in introspective and social processing in the disorder (51).

Although face processing is right-hemisphere dominant, the cortex responds to faces bilaterally (52). Until recently, the role of the left fusiform in face processing in autism has not been highlighted. Bird and colleagues (12) showed that attention did not modulate fusiform activity in the left hemisphere in subjects with autism. Additionally, Webb and colleagues (22) found a slower ERP response to faces in the left hemispheres of children with autism but no latency differences from control subjects in the right hemisphere. In our present study, percent signal change values were considerably lower in children with autism in the left hemisphere in three of the four face conditions, although statistical significance was only reached in the adult stranger condition. Whole brain analyses also revealed weak left fusiform activity in the children with autism in all conditions. In normal development, many functions that show hemispheric dominance in adulthood exhibit a more bilateral and distributed pattern in childhood. The failure of children with autism to show strong patterns of bilateral fusiform activity raises the possibility that abnormal interhemispheric communication early in development may contribute to atypical patterns of functional activity, particularly between brain regions that are involved in continued processing of face stimuli. Deficits in white matter is a consistent finding in autism (53,54) including a thinning of the posterior region of the corpus callosum (55). Several research groups have theorized that autism is a disorder that results in increased local, but reduced long distance, connectivity (17,56–59).

Although precursors to the adult face processing system have been observed as early as 3 months in normal infants (60), a fully mature system may not be present until late childhood or preadolescence (61–63). For example, young children often do not show a bias for faces over objects within the classical fusiform face region (62–64). This less specialized response in typical children may allow for experience to play a greater role in the neural substrate underlying face processing in adulthood (64). Reduced experience with faces during the course of development in autism may also be a contributing factor as to why patterns of functional activity in the fusiform were inconsistent (e.g. stronger in response to some face types) and not fully elaborated as evidenced by a reduced extended network. Future pediatric imaging studies that use functional connectivity analyses will be pivotal for understanding such system development.

What makes interactions with strangers particularly challenging for individuals with autism remains a mystery. Here we show not only that children with autism have defects at the neurofunctional level in response to adult stranger faces in the fusiform but also that this same structure is capable of responding to preferred faces such as mother or other children. As such, it eliminates the fusiform as the primary site of face-processing defect in autism and instead suggests dysfunction in systems that modulate fusiform activity.

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