Psychiatry Research: Neuroimaging 173 (2009) 196–205

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

A functional and structural study of emotion and face processing in children with autism

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ARTICLE INFO

Article history:
Received 28 February 2008
Received in revised form 9 July 2008
Accepted 12 August 2008

Keywords:
fMRI
Fusiform gyrus
Volume
Socioemotional
Coupling
Anxiety
Amygdala

ABSTRACT

Children with autism exhibit impairment in the processing of socioemotional information. The amygdala, a core structure centrally involved in socioemotional functioning, has been implicated in the neuropathology of autism. We collected structural and functional magnetic resonance images (MRI) in children 8 to 12 years of age with high-functioning autism ($n=12$) and typical development ($n=15$). The functional MRI experiment involved matching facial expressions and people. Volumetric analysis of the amygdala was also performed. The results showed that children with autism exhibited intact emotion matching, while showing diminished activation of the fusiform gyrus (FG) and the amygdala. Conversely, the autism group showed deficits in person matching amidst some FG and variable amygdala activation. No significant between-group differences in the volume of the left or right amygdala were found. There were associations between age, social anxiety and amygdala volume in the children with autism such that smaller volumes were generally associated with more anxiety and younger age. In summary, the data are consistent with abnormalities in circuits involved in emotion and face processing reported in studies of older subjects with autism showing reductions in amygdala activation related to emotion processing and reduced fusiform activation involved in face processing.

1. Introduction

Individuals with autism often demonstrate impaired processing of emotions (Celani et al., 1999; Macdonald et al., 1989), abnormal perception of faces (Adolphs et al., 2001; Ashwin et al., 2006; Baron-Cohen et al., 1999; Critchley et al., 2000; Dalton et al., 2005; Davies et al., 1994; Schultz et al., 2000), increased stress and anxiety (Amaral and Corbett, 2003; Corbett et al., 2006; Corbett et al., 2008; Muris et al., 1998), impaired gaze (Spezio et al., 2007) and impaired judgment of gaze direction and mental state (Courchesne, 1997). Thus, it is not surprising that the amygdala, a brain structure involved in the processing of emotions (Adolphs et al., 2002), novelty (Schwartz et al., 2003), stress (Tsigos and Chrousos, 2002), anxiety (Davis, 1992), eye gaze (Spezio et al., 2007), orienting (Moses et al., 2002; Wright et al., 2003), and empathy (Spinella, 2002; Vollm et al., 2006) would be implicated in the neuropathology of autism.

The amygdala is part of a network of brain regions that form the neural substrate for social cognition, subsequently referred to as the "social brain," which includes the amygdala, orbital frontal cortex (OFC), and the superior temporal sulcus and gyrus (STS/G) (Brothers, 1990). Individuals with autism demonstrate impairment in social cognition that includes the identification of facial expression, face recognition, discrimination of faces, and memory for faces (Adolphs et al., 2001; Adrien et al., 1991; Celani et al., 1999; Green et al., 1995; Hauck et al., 1998; Hobson et al., 1988; Macdonald et al., 1989; Yirmiya et al., 1989), although some studies do not report emotion or face processing deficits (Castelli, 2005; Hadjikhani et al., 2004). The amygdala is also important in acquisition, consolidation, and retrieval of emotional information, especially fear (Adolphs and Tranel, 1999; Aggleton, 2000; Aggleton et al., 1992; Davis, 1992; LeDoux, 1994, 1996; McGaugh et al., 1996).

There is converging evidence implicating the amygdala in the neuropathology of autism from several areas of neuroscience including postmortem (Bauman and Kemper, 1985; Kemper and Bauman, 1998; Schumann and Amaral, 2006), structural magnetic resonance imaging (MRI), and functional MRI (fMRI) studies. Volumetric studies have revealed both increased (Abell et al., 1999; Howard et al., 2000)

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doi:10.1016/j.pscychresns.2008.08.005

and decreased (Aylward et al., 1999; Pierce and Courchesne, 2000) amygdala volume in subjects with autism. A study of very young children with autism spectrum disorder (ASD), which includes autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS), showing bilateral amygdalar enlargement found an association between the amygdala and the core symptoms early in development (Sparks et al., 2002). Further, a longitudinal study reported that a larger right amygdala at 3 to 4 years of age was associated with poorer clinical outcome (Munson et al., 2006). Schumann reported amygdalar enlargement in 8-to-12-year-old children with ASD compared with typically developing peers (Schumann et al., 2004). Recently, positive correlations have been reported between amygdala volume and level of anxiety (Juranek et al., 2006) and social impairment (Nacewicz et al., 2006) in ASD. Similar volumetric differences have also been observed in the unaffected siblings of children with autism (Dalton et al., 2007). These data suggest that discrepancies between increased or decreased amygdala volume might be related to the age, level of clinical impairment, and extent of underlying anxiety or stress in the particular sample of subjects studied.

Functional imaging studies have also reported differences in amygdala activity between those with autism and control participants (e.g., Critchley et al., 2000). A recent fMRI study of adult males with ASD reported that activity was abnormal within the "social brain" network, with less activation of the amygdala and the OFC, and increased activity and greater reliance on the superior temporal cortex and anterior cingulate cortex (ACC) during a social perception task (Ashwin et al., 2007). Similarly, individuals with ASD showed significantly less amygdala activation than control subjects during a judgment task (Baron-Cohen et al., 1999). In an emotion matching and labeling task, children with ASD recruited different neural networks and utilized different strategies during the automatic processing of socioemotional information despite relatively unimpaired cognitive assessment of basic emotions (Wang et al., 2004). The familiarity of the stimulus also appears to be an important consideration in activation of the amygdala in adults with autism (Pierce et al., 2004). Additionally, activation in the amygdala and the fusiform gyrus have been shown to be positively associated with the time spent fixating on another's eyes in children with autism (Dalton et al., 2005) and their unaffected siblings (Dalton et al., 2007).

These data suggest that when typical subjects are carrying out tasks that require social evaluation, the amygdala is activated; however, this activation is decreased in individuals with autism. Such findings lend support for the "amygdala theory of autism" proposing that early dysfunction of the amygdala may be responsible, in part, for impairment in socioemotional functioning in autism (Baron-Cohen et al., 2000; Castelli, 2005).

In addition to processing emotion elicited by faces, face processing itself is often impaired in autism (e.g., Critchley et al., 2000; Pierce et al., 2001; Piggot et al., 2004; Schultz et al., 2000; Wang et al., 2004) with some exceptions (Hadjikhani et al., 2004). Face perception is mediated by a distributed cortical network that includes the FG, an extrastriate visual cortical region located in the inferior temporal lobe identified as being selective both for faces (Allison et al., 1994; Haxby et al., 1994; Kanwisher et al., 1997; Kanwisher et al., 1999; McCarthy et al., 1997; Sergent et al., 1992) and for a variety of non-face object classes in which one makes a subordinate level judgment and has obtained a level of perceptual expertise (Gauthier et al., 2000; Kanwisher et al., 1997; Kanwisher et al., 1999).

The aforementioned studies provide the rationale for evaluating the role of the amygdala and fusiform regions in autism using functional and structural MRI. However, many of the studies investigated a heterogeneous sample of individuals across a broad autism spectrum and age span. For the present fMRI study, a homogeneous sample of children with autism and a narrow age range were employed. Due to the mixed results in previous studies of emotion perception (Baron-Cohen et al., 1999; Castelli, 2005; Hobson, 1986; Hobson et al., 1988; Howard et al., 2000), and the rather simple nature of the matching task, it was hypothesized that children with autism would show a comparable performance to the children with typical development. However, as in Schultz et al. (2000), we hypothesized that children with autism would demonstrate more difficulty with face perception. We predicted that the amygdala would show decreased activation to explicit emotion processing. We expected reduced fusiform activation to facial stimuli in autism. In regards to the volume of the amygdala, we predicted that children with autism would show bilateral amygdala enlargement, which would further be correlated with age, anxiety and social functioning.

2. Methods

2.1. Experiment 1: fMRI investigation

2.1.1. Participants

Two groups of children, 8-to-12 years of age, participated in this study: 12 with high-functioning autism and 15 with typical development. The demographic information for the groups is presented in Table 1. Despite the subjects being of average intelligence, independent samples *t*-tests revealed a significant IQ difference between the groups, based on the Wechsler Abbreviated Intelligence Scale (Wechsler, 1999), $t(25) = 4.89$, $P < 0.001$.

Inclusion criteria for all participants consisted of having an IQ > 80, and an absence of fragile X or other serious neurological, psychiatric, or medical conditions. The majority of the diagnostic participants were recruited from the University of California, Davis M.I.N.D. (Medical Investigation of Neurodevelopmental Disorders) Institute Subject Tracking System (STS) and already had a confirmed diagnosis from the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1999) and the Autism Diagnostic Interview-Revised (Lord et al., 1994). For children who were not already evaluated ($N = 3$), the following diagnostic procedures were conducted. A strict diagnosis of autistic disorder was based on DSM-IV criteria (American Psychiatric Association, 1994) and established by all of the following: 1) a previous diagnosis of autism by either a psychologist, psychiatrist or behavioral pediatrician with autism expertise, 2) an extensive clinical interview, and 3) confirmation of current autism symptoms by the ADOS Module 3 (Lord et al., 1999). To obtain a more homogeneous sample, only children with autistic disorder were enrolled.

Some research participants responded to announcements placed in various schools, recreational facilities and websites. The University of California, Davis Institutional Review Board (IRB) approved the study. Prior to inclusion, the child's parent completed written informed consent and the child assented to participate in the study.

Table 1
Demographics.

GROUP	*N*	Age	Gender	IQ	SCQ	MASC-T	MASC-SA
Autism	12	9.01 (1.60)	12 Male 0 Female	90.71 (13.82)	22.43 (5.92)	42.57 (17.50)	9.36 (5.95)
Typical	15	9.17 (1.44)	13 Male 2 Female	115.73 (15.76)	3.08 (3.62)	37.73 (10.34)	9.20 (4.42)
	27	$t = -0.34$	$\chi^2 = -0.53$	$t = 4.89$**	$t = -10.15$*	$t = -1.07$	$t = -0.08$

Note: *$P < 0.05$, **$P < 0.01$. IQ = Intelligence Quotient based on the WASI (Wechsler, 1999), broad average range from 85 to 115; SCQ = Social Communication Questionnaire (Rutter et al., 2003), scores > 15 are suggestive of autism; MASC = Multidimensional Anxiety Scale for Children (MASC; March et al., 1997), MASC-T = Total score; MASC-SA = Social Anxiety score.

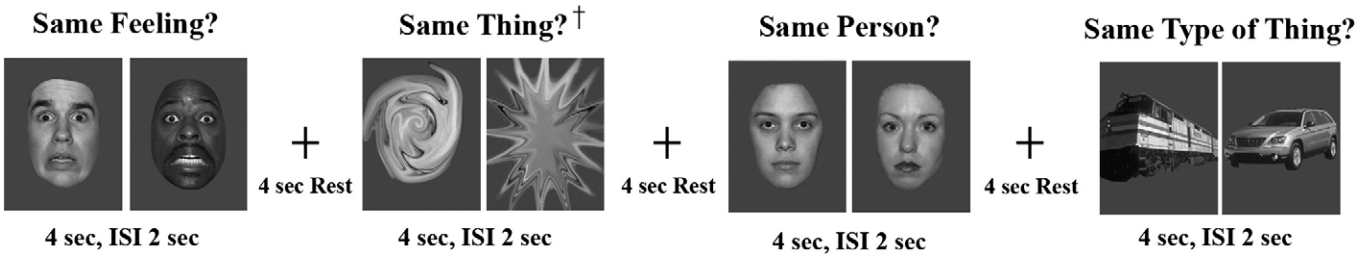

Fig. 1. Emotion Person Matching Task. Subjects were required to indicate whether the two images were the same feeling, same thing (control), same person or same type of thing. Sec = seconds, ISI = inter-stimulus interval. † = The "Same Thing" control condition follows each of the experimental conditions, "Same Feeling," "Same Person," and "Same Type of Thing." The entire series is run twice with a 30-second rest between each series.

Participants received minimal financial compensation and a summary of assessment results from standardized measures.

2.1.2. Behavioral procedures

Diagnostic, neuropsychological measures and questionnaires were completed during the course of one visit. The behavioral protocol used in the scanner consisted of a block design with alternating paired stimuli across two categories; facial expression and facial identity (based in part on Schultz et al., 2000). The stimuli consisted of black and white photographs (Tottenham et al., 2002) of actors displaying basic emotions (happy, sad, angry, afraid, neutral). Pictures were cropped to remove the outline of hair so matching was predominantly dependent on facial features. We were interested in determining whether we would see expected patterns of brain activation while the children were making same/different emotion judgments and same/different person judgments. Object stimuli ("Same type of thing?") were also presented, but the data did not contribute to the focus of the study and therefore were not included. The forced-choice matching of facial expressions (Emotion) was designed to measure emotion recognition. The participant saw a pair of faces and was required to indicate with a button press whether the two faces displayed the same emotion or not. Half of the trials were matching emotions and half were non-matching emotions. The forced-choice matching of faces (Person) was designed to measure facial identification. The stimuli consisted of two photographs of actors' faces displaying neutral expressions and displaying either the same person (a match) or slightly dissimilar persons (no match). After each block of experimental trials (Emotion, Person, Object), a corresponding block of Control trials (Thing) was displayed consisting of the same images distorted to look like abstract geometric patterns. Prior to the presentation of stimuli, prompts of "Same Feeling?" or "Same Person?" or "Same Thing?" were shown to identify the task to be performed in the next block. Behavioral responses were recorded using a fiberoptic response pad with two choices (1 = "Yes", 2 = "No"). A series consisted of three experimental blocks and three corresponding control blocks with five trials within each block. The series was followed by a 30-second rest and repeated once. Each stimulus was presented for 4 s, with an interstimulus interval (ISI) of 2 s, and each block was followed by a 4-s rest period. The total scan duration was approximately 8 1/2 min (including 6 s at the beginning and end of the run). The contrasts for the matching task included: emotion versus control (Emotion > Control) and person versus control (Person > Control). See Fig. 1.

2.1.3. Instruments

The Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1999) is composed of semi-structured interactive activities conducted with a child to assess specific current behaviors indicative of autism. Module 3, designed for children and adolescents with fluent speech, was used.

The Wechsler Abbreviated Intelligence Scale (WASI) (Wechsler, 1999) is a measure of general intelligence, which includes Vocabulary, Similarities, Block Design and Matrix Reasoning subtests administered to obtain an estimated IQ.

The *Social Communication Questionnaire* (SCQ) (Rutter et al., 2003) was used as a screening tool to ensure the absence of symptoms of autism in the typically developing children.

The *Multidimensional Anxiety Scale for Children* (MASC) (March et al., 1997) was used as a parent and self-report measure of anxiety.

2.1.4. fMRI data acquisition

Functional and structural MRI images were collected during the same scan session. Scanning was performed at the University of California, Davis Imaging Research Center. Children were familiarized with the imaging environment by use of an MRI simulator and trained on the fMRI task immediately before scanning.

Images were acquired on a 1.5 T GE Signa scanner with Echospeed gradients and a standard GE whole head coil. A single-shot gradient recalled echo-echo planar imaging (GRE-EPI) sequence was used to acquire functional images (TR 2000 ms, TE 32 ms, flip angle 90 degrees, FOV 22 cm, 4 mm slice thickness, 1 mm slice gap, 64×64 matrix, 27 slices, 1.00 NEX, and 62.5 KHz bandwidth and coronal orientation). We also acquired a high resolution T1-weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence. The tasks were programmed using Presentation™ software www.neurobs.com. The Initiation of the scan and the task was synchronized using a TTL pulse delivered to the control software at the onset of the first scan. The images were back-projected onto a translucent screen placed near the end of the MRI gantry and viewed through a periscopic prism system attached on the head coil.

2.1.5. Preprocessing and statistical analysis

Image processing and data analysis were conducted using the general linear model (GLM) in Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). Brain slices were realigned to the first image to correct for movement across the session, and then normalized to a standard stereotaxic space (Montreal Neurological Institute (MNI) template). We excluded participants who moved more than 3 mm in any direction during a single volume acquisition, which resulted in 4 of the

Table 2
Emotion>Control Matching Task.

VOI	Cluster Coordinate *x, y, z* (Talairach)	Brodmann areas	Cluster size	VOI *P* value	VOI *t* value
Within group					
Typical group					
Amygdala	−18, −9, −10		15	0.01	2.27
Fusiform†	−29, −35, −16		58	0.01	−3.35
	32, −40, −13	20,37	73	0.0002	−3.35
Autism group					
Amygdala	No suprathreshold activation				
Fusiform	No suprathreshold activation				

Notes: Cluster activation corrected $P<0.05$, which includes the number of voxels reported for each volume of interest (VOI). † = deactivation.

Table 3
Person > Control matching task.

VOI	Cluster coordinate *x*, *y*, *z* (Talairach)	Brodmann areas	Cluster size	VOI *P* value	VOI *t* value
Within group					
Typical group					
Amygdala	−22, −5, −10		36	0.003	3.24
	20, −6, −12		85	0.001	3.82
Fusiform	−36, −50, −16	37	53	0.001	3.21
	42, −53, −16	37	99	0.001	3.72
Autism group					
Amygdala	No Suprathreshold Activation				
Fusiform	40, −49, −19	37	129	0.004	2.62
Between group					
Typical > Autism					
Amygdala	−22, −8, −10		103	0.046	2.73
Fusiform gyrus	30, −32, −14	36,37	13	0.03	1.91

Notes: Cluster activation corrected $P<0.05$, which includes the number of voxels reported for each volume of interest (VOI).

original 16 children with autism (one female) and 2 of the original 17 typically developing children being dropped from the study and subsequently not included in the current analyses. Further, we performed univariate analysis of variance (ANOVA) of scan-to-scan movement for all the subjects to ensure there were no significant differences in motion across the groups, $F(1,27)=2.71$, $P=>0.1$. Functional data were then smoothed with a 4-mm Gaussian kernel.

Each task condition was modeled and convolved with the canonical hemodynamic response function (HRF) in SPM. A first level, single subject analysis using random-effects, voxel-wise *t* statistics for each contrast using the GLM was performed on the functional data. Since our hypotheses were restricted to the amygdala and the fusiform, analyses were limited to these regions. Masks were established for the amygdala and fusiform based on anatomical features and using coordinates from previous investigations in autism (Ashwin et al., 2007; Maldjian et al., 2003). The resulting volume of interest (VOI) was extracted while controlling for multiple comparisons using a random field approach, thresholded at $t>2.5$, $P<0.05$ corrected (Brett et al., 2003; Worsley et al., 1996). The amygdala was defined by published coordinates in autism: L *x*, *y*, *z* = −21, −3, −16; R *x*, *y*, *z* = −19, −5, −14, and the radius was 8 mm (Ashwin et al., 2007); while the fusiform was established by a published atlas-based mask (Maldjian et al., 2003). We report activation in the selected brain regions which were converted to and confirmed using Talairach coordinates (see Tables 2 and 3) (Talairach and Tournoux, 1988).

Although the scope of the investigation was restricted to the amygdala and fusiform, within-group whole brain analysis was conducted (see Table 4, $P<0.001$ uncorrected). Further, a between-group, exploratory voxel-wise random effects whole brain analysis was conducted to provide an overall estimation of brain activity. Nontask-related regions were excluded by imposing a combined mask of significant regions of activity from the Typical and Autism group (Yoon et al., 2008). Thresholding of statistical maps followed the procedure for determining voxel-level significance using the false discovery rate (FDR) (e.g., Benjamini and Hochberg, 1995; Genovese et al., 2002). Activations surviving FDR at $P<0.05$ are presented in Table 4.

3. Results

3.1. Behavioral data

We conducted separate 2 (Condition: Emotion vs. Control and Person vs. Control) × 2 (Group: Autism vs. Typical) repeated measures ANOVAs for accuracy and response time (RT) data for the emotion and person matching task. The results revealed a difference in Accuracy between Emotion vs. Control condition (Thing) $F(1,27)=10.57$, $P=0.003$, indicating that facial expressions were more difficult to match than the abstract figures. Similarly, performance was worse for Person vs. Control Accuracy $F(1,27)=12.27$, $P=0.002$. However, there was also a significant Group difference, $F(1,27)=17.93$, $P=0.001$, and a significant Person×Group interaction, $F(1,27)=7.65$, $P=0.01$, indicating that children with autism had notable difficulty matching the facial stimuli. In regards to RT, there were significant differences in Emotion RT, $F(1,27)=4.44$, $P=0.044$, and Person RT, $F(1,27)=47.06$, $P=0.001$, compared to the Control condition such that the experimental conditions resulted in longer reaction times.

3.2. Functional MRI data

The results for within- and between-group VOIs are presented in Tables 2 and 3. Whole brain activation analyses with FDR correction are presented in Table 4.

3.2.1. Emotion > Control

3.2.1.1. Within-group analyses: VOI. In the typical group, significant left amygdala activity was observed in the Emotion>Control contrast. In this contrast, the fusiform gyrus was significantly deactivated bilaterally. The autism group showed no suprathreshold activations for the amygdala or fusiform (Fig. 2).

3.2.1.2. Between-group comparison: VOI. There were no significant positive differences in activation between the groups that survived correction.

Table 4
Within- and between-group whole brain analysis.

	Typical*		Autism*		Typical > Autism			Autism > Typical		
	Region	*xyz*	Region	*xyz*	Region	*xyz*	*P* value	Region	*xyz*	*P* value
Emotion > Control	MFG	49, 12, 33	MFG	−37, −1, 52	FG	24, −38, −14	FDR <0.05	SPL	−62, −30,2	FDR <0.01
	FG	36, −49, −20	MTG	−62, −32, 4				PG, MFG	−33, −12, 60	0.01
	PHG	−18, −12, −6	STG	−57, −57, 11				PG	−61, −15, 31	0.01
	FG†	−21, −36, −11						SPL	−35, −64, 49	0.02
	Culmen†	−18, −34, −14						BA 9, MFG	−50, 8, 38	0.02
	MOG†	−47, −60, −9						BA 40	−54, −52, −32	0.02
Person > Control	FG	36, −56, 19	MFG	36, 43, 11			FDR >0.05			FDR >0.05
	Amyg	19, −8, −5	STG	−36, 8, 14						
	FG	−30, −78, −20	MOG†	34, −86, −5						
	IOG	23, −86, −20								

Note: * Within-group results presented at $P<0.001$ uncorrected. MFG = Middle Frontal Gyrus, PHG = Parahippocampal Gyrus, STG = Superior Temporal Gyrus, FG = Fusiform Gyrus, MOG = Middle Occipital Gyrus, MTG = Middle Temporal Gyrus, IOG = Inferior Occipital Gyrus, BA = Brodmann Area, PG = Precentral Gyrus, SPL = Superior Parietal Lobe, SFG = Superior Frontal Gyrus, Medial FrG = Medial Frontal Gyrus , CG = Cingulate Gyrus, † = deactivation, FDR = False Discovery Rate.

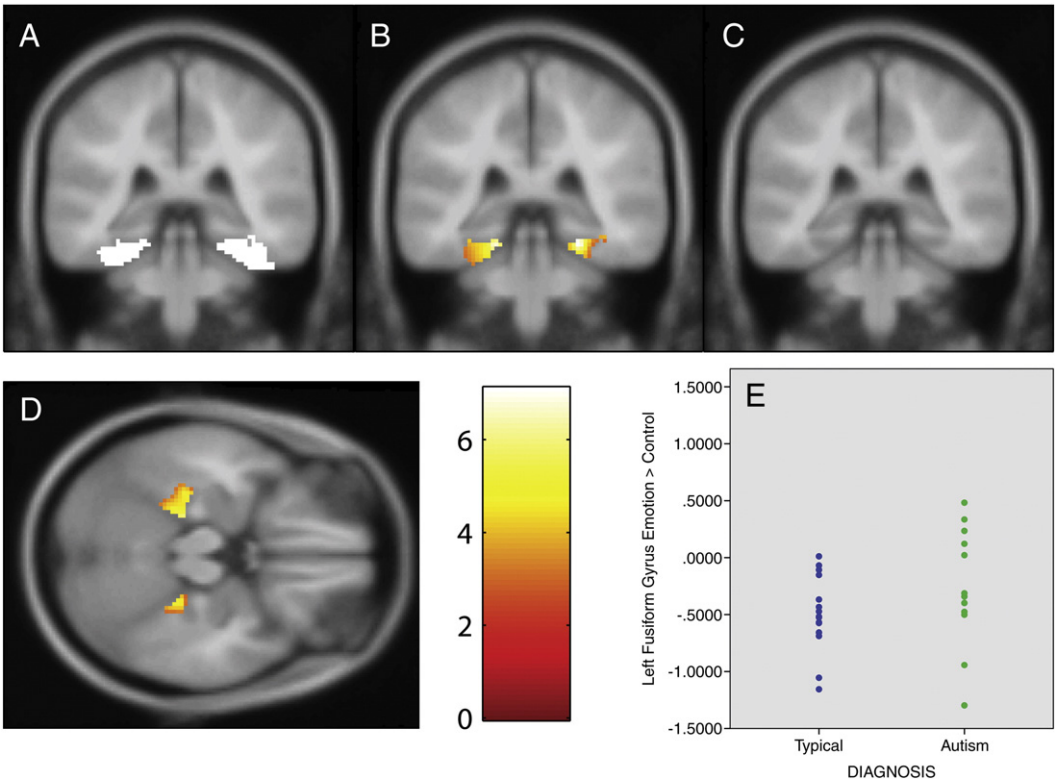

Fig. 2. Emotion > Control and beta values: fusiform gyrus. A. The mask for the left and right fusiform is presented. B. The left and right fusiform is significantly deactivated in response to Emotion faces versus Control images in the typical group shown in coronal view. C. A lack of fusiform activation in the autism group. D. The left and right fusiform is significantly activated in response to Emotion faces versus Control images in the typical group shown in axial view. E. Individual beta values are plotted for the Typical and Autism subjects. The resulting areas of activation and data plotted are characterized in terms of their peak values.

3.2.2. Person > Control

3.2.2.1. Within-group analyses: VOI. For the typically developing children, the left and right amygdalae were activated as well as the left and right fusiform. The autism group showed no suprathreshold activation for the amygdala; however, activation in the right fusiform gyrus approached significance: $P<0.08$. (See Table 3.)

3.2.2.2. Between-group comparison: VOI. There was a significant difference between the groups for the right fusiform gyrus (see Fig. 3) and the left amygdala (see Fig. 4).

3.2.3. Whole-brain analysis

The within-group and between-group whole brain analysis results are presented in Table 4. The within-group results (uncorrected $P<0.001$) show that some regions were activated in both groups, such as the middle frontal gyrus in Emotion > Control, although many differences were noted. Between-group whole brain analysis Typical > Autism for the Emotion > Control condition resulted in only the right fusiform gyrus surviving FDR correction ($t=7.09$, $P<0.05$). There were no activations that survived FDR correction in the Person > Control condition.

The between-group whole brain analysis Autism > Typical appears to be driven by the autism group recruiting other brain regions for emotion

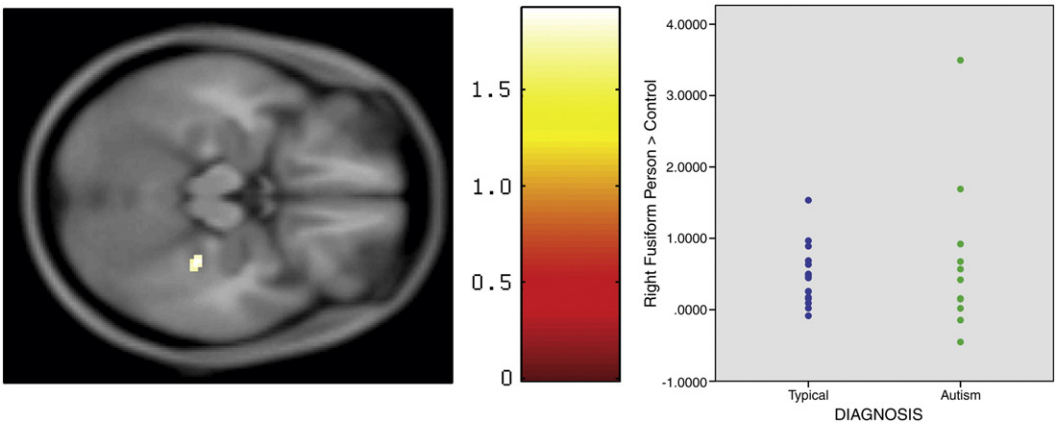

Fig. 3. Person > Control contrast and beta values: fusiform gyrus. Between-group contrast for Person > Control and beta values: right fusiform. The right fusiform gyrus is significantly more activated in the Person match condition than the Control match condition in the Typical group compared to the Autism group. The resulting areas of activation and data plotted are characterized in terms of their peak and maximum values.

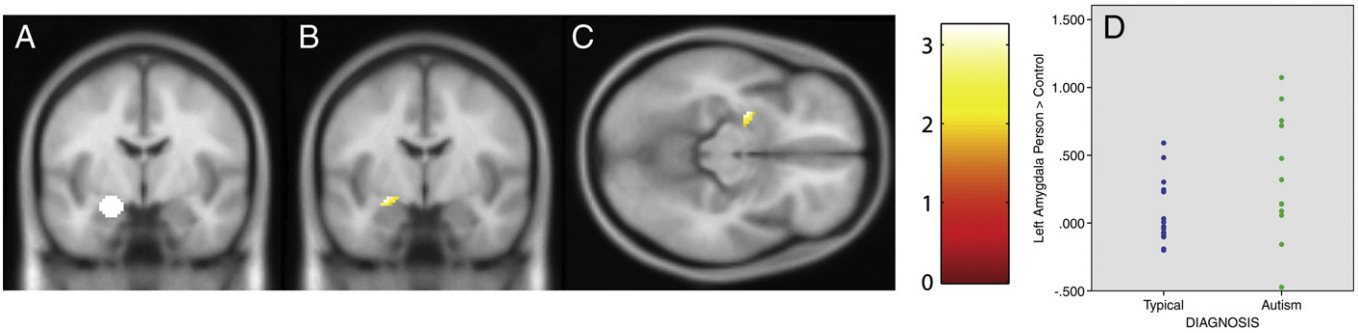

Fig. 4. Person > Control contrast and beta values: amygdala. A. The mask for the left amygdala is presented. B. The between-group contrast shows that the left amygdala is more active in the typical group than in the autism group shown in axial view and C. coronal view. D. Individual beta values are plotted for the typical and autism subjects. Although Beta values were extracted for the autism group for comparison, there was no suprathreshold activity observed even at significantly reduced values.

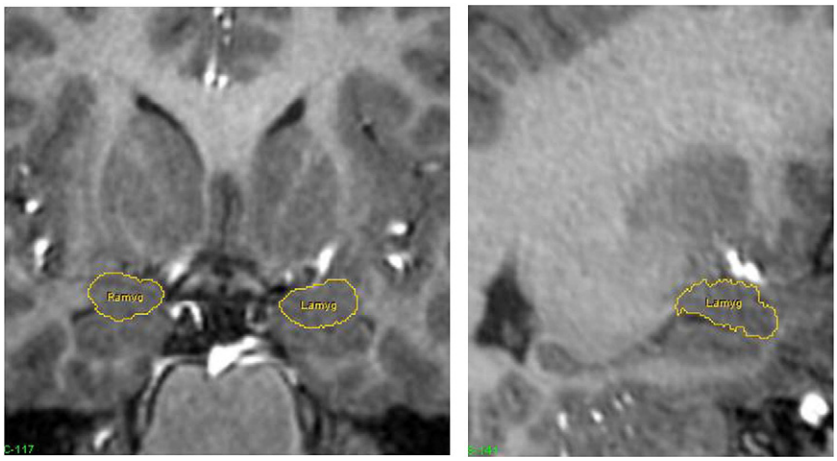

Fig. 5. Volumetric tracing protocol example: amygdala. Volumetric tracing protocol. Sample slices are shown in the coronal (left) and sagittal (right) view.

processing, such as the superior temporal gyrus. Thus, the distinction does not appear to be due to excessive activation in the autism compared with the typical group, rather from differential recruitment in the processing of socioemotional information.

3.3. Experiment 2: volumetric analysis

3.3.1. Image analysis

Following completion of MRI acquisition, images were transferred to the M.I.N.D. Institute Computational Neuroimaging Laboratory for volumetric analysis of the amygdala. Each coronal SPGR series was imported into ANALYZE (Robb et al., 1989), an MRI analysis program, and converted to cubic voxel dimensions of 0.469 mm using a cubic spline interpolation algorithm. Images were then reoriented and aligned along a horizontal axis drawn from the rostral tip to the caudal extent of the hippocampus. The amygdala was manually segmented on each coronal image based on a detailed set of tracing guidelines to ensure reliability. The precise protocol is outlined in detail elsewhere (Schumann et al., 2004). Two reliable tracers (>90% inter-rater reliability) were utilized and a random selection of scans were checked by the originator of the protocol (cms). See Fig. 5.

3.3.2. Statistical analysis

To compare the amygdala volumes and total cerebral volume, independent sample *t*-tests were conducted. In order to explore within-group effects of age, social impairment and social anxiety on amygdala and cerebral volumes, stepwise linear regression analyses were conducted in the autism group.

3.4. Right and left amygdala and total cerebral volume results

Mean volumetric results for the two groups are presented in Table 5. There were no significant differences for the total cerebral volume between the groups, $F(1,27) = 3.23$, $P = 0.09$. As can be seen in Fig. 6, there were no between-group differences for either the left, $F(1,27) = 0.242$, $P = 0.627$, or the right amygdala, $F(1,27) = 0.016$, $P = 0.901$.

We performed stepwise linear regression to predict the effects of age, IQ, social anxiety and social impairment on the right and left amygdala and total cerebral volume in the autism group. Social impairment was measured by the ADOS (Lord et al., 1999) and social anxiety was based on the MASC (March et al., 1997). For the right amygdala, $F(2,8) = 8.18$, $P = 0.01$, $R^2 = 0.67$, social anxiety was first to enter the model and was negatively correlated, $t = -3.09$, $P = 0.01$; whereas age was positively correlated, $t = 2.67$, $P = 0.03$. In other words, smaller right amygdala volume was associated with more anxiety and younger age. Social impairment and IQ were not

Table 5
Volumetric analysis.

Diagnosis	Age	Cerebral volume mm^3	Right volume mm^3	Left volume mm^3
Typical	9.69	1,247,046.91	1811.62	1811.43
$N = 15$	(1.47)	(79,912.32)	(201.91)	(222.43)
Autism	9.63	1,299,778.64	1797.38	1759.18
$N = 12$	(1.48)	(47,146.11)	(356.30)	(308.64)
Total	9.67	1,269,012.63	1805.35	1788.44
$N = 27$	(1.45)	(72,005.15)	(273.92)	(259.22)

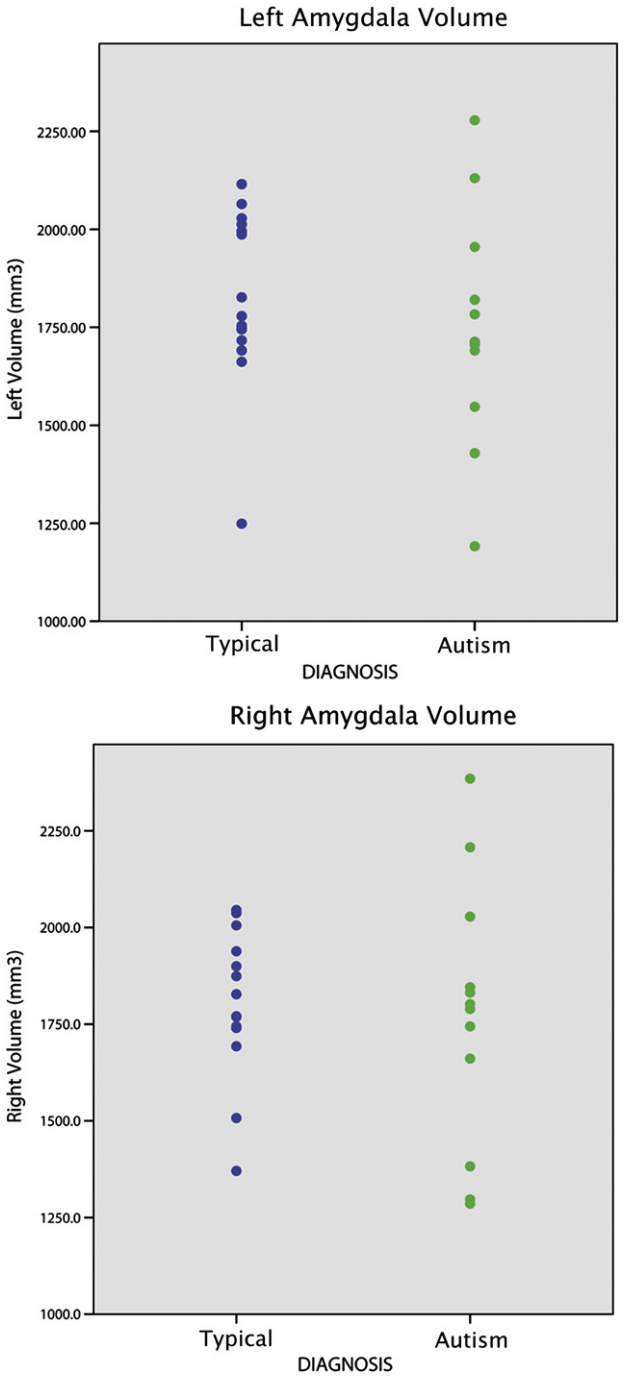

Fig. 6. Left and right amygdala volume. Volumetric analysis of amygdala. The left and right amygdala volumes were not significantly different in the children with autism compared to the typically developing children.

associated with right amygdala volume ($P>0.05$). For the left amygdala, $F(1, 10)=5.97$, $P=0.04$, $R^2=0.40$, there was a positive association with age, $t=-2.29$, $P=0.04$, but no correlation with social anxiety, social impairment or IQ (all $P>0.05$). For total cerebral volume there were no associations between overall brain volume and the independent variables (all $P>0.05$).

4. Discussion

In order to more thoroughly understand the role of the amygdala and the fusiform gyrus in autism, we conducted a comprehensive investigation using functional and structural MRI in a group of well-characterized children with high-functioning autism compared with typically developing peers of the same age.

For the fMRI study, we hypothesized decreased amygdala activation in the autism group. Consistent with this hypothesis, the behavioral results showed that the children with autism accurately matched the emotions, but revealed limited engagement of the amygdala while performing the task. This was in contrast to the typical group, which demonstrated recruitment of the amygdala during both the emotion (bilateral amygdala) and person (left amygdala) matching conditions. Ostensibly, the children with autism utilize different brain regions such as frontal and parietal regions as suggested by the pattern of results seen in the whole brain analysis for the appraisal of affective stimuli. A recent fMRI study also showed that ASD children utilized different strategies and recruited atypical neural networks during automatic emotion processing amidst intact emotion identification (Wang et al., 2004). The limited amygdala activation in the current investigation is consistent with previous fMRI studies in autism during the perception of fear faces (Ashwin et al., 2007), the implicit processing of emotions (Critchley et al., 2000) and emotion judgment (Baron-Cohen et al., 1999).

In regards to face processing (person matching condition), a different pattern emerged. The children with autism showed impairment in matching facial stimuli while showing some activation of the fusiform gyrus, albeit less than typical children. This supports the idea that the autism group were processing the face stimuli, but less efficiently and effectively than processing seen in the typical group, as shown in some previous reports (Critchley et al., 2000; Pierce et al., 2001; Schultz, 2005; Schultz et al., 2000). The presence of some fusiform activation suggests that the children with autism are encoding the facial stimuli albeit to a limited degree. Therefore, to some extent, the ASD group is recruiting brain regions important in the interpretation of facial information. However, activation of the fusiform gyrus alone is not sufficient for the processing of faces since individuals with prosopagnosia, a severe inability to recognize faces, recruit the fusiform gyrus (Avidan et al., 2005) despite their behavioral deficits. Thus, the atypical activation of the fusiform gyrus and the amygdala provides support for a dysfunctional neural network or pathway related to deficits in socioemotional processing in autism, especially identifying faces.

It was recently reported that activation in the amygdala and the fusiform gyrus was positively associated with the time spent fixating on the eyes, which may explain the observed hypoactivation often reported in these brain structures in autism (Dalton et al., 2005). Although we did not utilize an eye tracker in the current investigation to ascertain eye fixation or gaze duration, the adequate performance on the emotion matching task suggests that the children with autism were attending to the facial stimuli. The determination that subjects who look into the eyes activate the amygdala is provocative (Dalton et al., 2007, 2005) and the lack of eye tracking data could be seen as a weakness of the current study. It was recently shown that amygdala damage impairs eye-to-eye contact with an increase in gaze-to-mouth looking (Spezio et al., 2007), a finding previously reported in autism (e.g., Klin et al., 2002). Thus, it seems likely that the present results, with reductions in amygdala and FG activation in the amygdala and the fusiform gyrus during emotion and face processing, reflect a true neural correlate of an inherent deficit in ASD children.

The finding of relatively intact emotion matching abilities is consistent with some studies (Castelli, 2005), but not others (Adolphs, 2001; Baron-Cohen et al., 1999; Hobson, 1986; Hobson et al., 1988; Howard et al., 2000), which likely pertains to the complexity and diversity of the tasks across the studies (Castelli, 2005). The accurate emotion matching, despite altered amygdala and fusiform gyrus function, suggests that children with autism can distinguish basic emotions, but they may not be assigning the appropriate emotional and social significance. The failure to provide emotional salience may reveal a lack of automatic emotional processing provided by the amygdala (Dolan and Vuilleumier, 2003). A recent report showed a lack of affective priming for emotional faces in autism (Kamio et al., 2006). A

fundamental role of the amygdala is to rapidly provide the emotional salience of incoming sensory stimuli even preceding conscious awareness (Halgren, 1992; Vuilleumier et al., 2003). Although children in our investigation were able to identify emotions at a conscious level, they showed reduced amygdala recruitment during the detection of socio-emotional facial stimuli (Kamio et al., 2006; Wang et al., 2004).

Alternatively, the diminished activation of the amygdala and fusiform gyrus observed in the children with autism across the fMRI contrasts may indicate limited functional connectivity between these interconnected brain regions. It has been shown that emotional faces increase effective connectivity between the amygdala and the fusiform gyrus through an enhanced, dynamic coupling resulting in increased brain activation and attentional resources (Fairhall and Ishai, 2006). Based on dynamic causal modeling, the authors proposed that the FG provides the primary causal input into extended brain systems, which in turn process the subsequent emotional and social characteristics of face stimuli.

These aforementioned interpretations are not mutually exclusive. Based on the pattern of activation in the amygdala and the fusiform gyrus in the children with autism, we hypothesize a dysfunctional connection between these structures, resulting in a failure to provide the emotional salience and social relevance, respectively. Schultz (2005) convincingly argued that deficits in the amygdala-fusiform network point to a fundamental causal mechanism in the social perception deficits in autism. Recently, Bachevalier and Loveland (2006) presented a model compatible with our interpretation that dysfunction of the orbitofrontal–amygdala circuit results in deficits in social and emotional cognition in autism. Additionally, it has been noted that deficits in face processing in autism are part of a dysfunctional distributed network (Hadjikhani et al., 2004), and thus extend beyond the dysfunction of any single brain region such as the amygdala (e.g., Baron-Cohen et al., 2000) or the fusiform gyrus (e.g., Schultz et al., 2000).

The typically developing children showed relative deactivation of the fusiform gyrus on the emotion matching condition. Although unexpected, a similar finding has been reported in another study of individuals with typical development compared to those with ASD, and interpreted to reflect modulations in the activation of the fusiform gyrus based on the varying intensities of the emotion stimuli presented in the task (Ashwin et al., 2007). Our task contained variable emotion stimuli, which may similarly have dampened the recruitment of the fusiform gyrus and contributed to the deactivation findings in the typical group.

Regarding the volumetric analyses, we did not observe structural differences in the right or left amygdala or total cerebral volume across the groups. Additional within-group analyses revealed that amygdala volume appeared smaller as a function of younger age. We also observed an association between reported social anxiety and the right amygdala in that greater anxiety was related to smaller right amygdala volume. The results may seem counterintuitive, however, since larger amygdala volumes in children and adolescents with generalized anxiety disorder have been reported (De Bellis et al., 2000); recently, smaller amygdala volumes have been shown in children with pediatric anxiety using voxel-based morphometry (Milham et al., 2005). The association between anxiety symptom severity, the size of the amygdala and age may support a complex interplay between these covariates (Juranek et al., 2006; Nacewicz et al., 2006; Schumann et al., 2004). Still, notable variability in amygdala volumes was observed as found in other investigations of amygdala volumes in autism (Salmond et al., 2003), highlighting the heterogeneity and complexity of the disorder.

Despite our careful recruitment of a homogeneous sample within a narrow age range and with strictly defined autism, significant variability of biological profiles remains and challenges the study of autism. Nevertheless, it has been shown in our studies and others that variability in and of itself remains one of the more consistent findings in autism (e.g., Corbett et al., 2006; Corbett et al., 2008). As such, examination of individual differences or subtypes may ultimately be a more meaningful exploration of brain and behavior relationships.

A potential limitation of the study is the significant discrepancy in IQ between the groups. We did not attempt to match on current IQ, since equating groups on inherent factors related to the diagnosis of autism may introduce systematic bias referred to as matching fallacy (Meehl, 1970). Instead, we selected subjects based on an IQ>80. Even though the mean IQ for the autism group was solidly in the average range, the mean of the control group was very high. It is possible that the IQ difference may contribute to differences in other cognitive processes beyond face and emotion perception. Another limitation of the fMRI portion of the study is the short duration of the scan which resulted in fewer time points and reduced power. Although this allowed the majority of our subjects to complete the scan, there is the possibility that some of our findings are the result of chance.

In summary, to the best of our knowledge, we conducted one of the first investigations employing both functional and structural MRI in 8- to 12-year-old children with and without autism to evaluate socio-emotional processing. Based on an explicit emotion and face matching fMRI paradigm, children with autism showed a lack of amygdala activation and reduced activation of the fusiform gyrus. We hypothesize that the amygdala fails to provide the socioemotional relevance and context to other brain regions, such as the fusiform gyrus, during basic and complex social situations that require higher-level cognitive interpretation. Further, whether the finding is attributed to an innate lack of social preference or entrainment to look in the eyes, we speculate that the limited engagement of the amygdala results in a dysfunctional connection or poor effective coupling between the amygdala and the fusiform gyrus in many children with autism. Despite the observed disruption in the amygdala and the fusiform gyrus, it is likely that the neuropathology extends well beyond these brain regions. Thus, it will be important for future studies to adopt a systems-based approach to better understand the complexity in regards to both the neural mechanisms and symptoms of autism.

Acknowledgements

This work was supported by a National Institute of Mental Health Career Development Award (5K08NMHO72958). Portions of these data have been presented at the Society for Neuroscience (November, 2006), International Neuropsychological Society (February, 2007) and the International Meeting for Autism Research (May, 2007). The authors thank David G. Amaral, Ph.D., for his participation in the preliminary pilot work that led to this project. Further, we appreciate the assistance of Cyndi Schumann, Ph.D., and Aaron Lee pertaining to the volumetric analysis, Niles Ryan for his assistance with figure reproduction, and Kami Kodewyn for her assistance in creating the visual stimuli. The authors are indebted to John Ryan, Scott Martin and Michael Buonocore, Ph.D., for their ever-present technical assistance. Most importantly, we express our sincere gratitude to the children and families that participated in our research.

Disclosure: Cameron Carter, M.D., has been a consultant to Pfizer, Roche and Lilly.

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