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Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces

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Prior imaging studies have failed to show activation of the fusiform gyrus in response to emotionally neutral faces in individuals with autism spectrum disorder (ASD) [Critchley et al., Brain 124 (2001) 2059; Schultz et al., Arch. Gen. Psychiatry 57 (2000) 331]. However, individuals with ASD do not typically exhibit the striking behavioral deficits that might be expected to result from fusiform gyrus damage, such as those seen in prosopagnosia, and their deficits appear to extend well beyond face identification to include a wide range of impairments in social perceptual processing. In this study, our goal was to further assess the question of whether individuals with ASD have abnormal fusiform gyrus activation to faces. We used high-field (3 T) functional magnetic resonance imaging to study face perception in 11 adult individuals with autism spectrum disorder (ASD) and 10 normal controls. We used face stimuli, object stimuli, and sensory control stimuli (Fourier scrambled versions of the face and object stimuli) containing a fixation point in the center to ensure that participants were looking at and attending to the images as they were presented. We found that individuals with ASD activated the fusiform face area and other brain areas normally involved in face processing when they viewed faces as compared to non-face stimuli. These data indicate that the face-processing deficits encountered in ASD are not due to a simple dysfunction of the fusiform area, but to more complex anomalies in the distributed network of brain areas involved in social perception and cognition.

Keywords: Autism; Asperger disorder; Face perception; Fusiform gyrus; Visual processing

Introduction

Autism spectrum disorder (ASD) is a behaviorally defined neurodevelopmental disorder characterized by debilitating deficits in social-communicative skills and by restricted and repetitive interests and behaviors. Among the most characteristic social-communicative impairments in ASD is the failure to use information from faces, such as eye gaze, facial expression, and facial speech, to regulate social interaction. Given the crucial importance of face processing to social-communicative competence, it is critical to study how abnormalities in the perception of faces and the information they convey may contribute to the social impairment in ASD, and to identify which components of the face-processing system are deficient in ASD.

A number of behavioral studies have examined face processing in high-ability individuals with ASD, and have shown that they perform worse than non-ASD controls on tests of incidental face learning (Boucher and Lewis, 1992; de Gelder et al., 1991), memory for faces (Hauk et al., 1998), and recognition of familiar faces (Boucher and Lewis, 1992; Boucher et al., 1998; Langdell, 1978). Moreover, recognition of facial expressions of emotion has been found to be impaired in ASD (Adolphs et al., 2001; Braverman et al., 1989; Celani et al., 1999; Critchley et al., 2000; Davidson and Dalton, 2003; Hobson et al., 1988a,b; Ozonoff et al., 1990; Tantam et al., 1989; Teunisse and de Gelder, 2001). In electrophysiological studies, differences have been found in the amplitude of EEG signal during face perception between individuals with ASD and normal controls (Dawson et al., 2002; Grice et al., 2001). Behavioral studies have also suggested that individuals with ASD encode faces in an abnormal way (Klin et al., 2002), evidenced by a more feature-based strategy for face recognition (Teunisse and de Gelder, 1994) and a diminished face inversion effect (Hobson et al., 1988b; Langdell, 1978). Abnormal face perception processes have also been suggested by studies indicating reduced attention to the eyes and an increased focus on mouths in children and adults with ASD (Joseph and Tanaka, 2003; Klin et al., 2002; Langdell, 1978). Several recent studies have shown that visual scanning of faces is abnormal in individuals with autism, characterized by a tendency to look less at the inner features of the face, particularly the eyes (Davidson and Dalton, 2003; Klin et al., 2002; Pelphrey et al., 2002). These findings raise the question of

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whether evidence of abnormality in face processing in autism reflects inadequate attention to faces driven, for example, by a lack of interest or an affectively based aversion to looking at faces, rather than a more primary perceptual deficit.

In summary, there is substantial evidence that individuals with autism are impaired in processing information from people's faces. Such evidence is of particular interest because it would be reasonable to expect impairments in face processing to be closely related to many of the social and communicative symptoms that define autism as a diagnostic entity. However, the exact nature and the neural substrates of the face-processing impairment(s) in autism remain to be clarified.

There are now many studies of normal individuals showing that static neutral faces activate the fusiform and inferior occipital gyri (e.g., Hadjikhani and de Gelder, 2002; Halgren et al., 1999; Haxby et al., 2000, 2002; Kanwisher et al., 1997; Rossion et al., 2003). Further, in viewing emotionally expressive faces, or faces that vary in direction of eye gaze, normal individuals activate other parts of the neural circuitry involved in face recognition, including the amygdala, the superior temporal sulcus, the superior temporal gyrus, the prefrontal cortex, the anterior cingulate cortex, and the premotor cortex (Adams et al., 2003; Adolphs, 1999, 2002a,b; Baron-Cohen et al., 1999; Haxby et al., 2000, 2002; Hoffman and Haxby, 2000; Morris et al., 1998, 1996; Vuilleumier et al., 2001).

Nonetheless, there remains considerable debate over the brain bases of face processing, and several functional models of face processing have been proposed. In the modular model proposed by Kanwisher et al. (1997), a small region of the medial–lateral fusiform gyrus called the fusiform face area (FFA) is specialized for face perception. This model has been challenged by Gauthier (2001), Gauthier et al. (1998, 1999), who argue that FFA mediates the perception of objects that are identified as distinct exemplars of a particular category or, in other words, at the level of the individual objects. As such, FFA mediates visual expertise in general; it is specialized not simply for faces, but for discriminating within any homogenous category of objects. Finally, building upon Bruce and Young's model, (Bruce and Young, 1986), Haxby et al. (1994, 1996, 2000), Hoffman and Haxby (2000), see also De Gelder et al. (2003), have proposed a distributed representation model, in which different areas of the brain respond to different attributes of faces, such as identity (fusiform gyrus, inferior occipital gyrus), gaze (superior temporal sulcus), and expression and/or emotion (orbitofrontal cortex, amygdala, anterior cingulate cortex, premotor cortex). From this perspective, faces are complex and multidimensional stimuli that engage a distributed network of brain areas involved in identifying other individuals, assigning them affective significance, and interpreting the nonverbal signals they convey. Accordingly, the face-processing abnormalities observed in autism could originate at any of the nodes of this complex network or in the interaction between these nodes.

Two published fMRI studies (Pierce et al., 2001; Schultz et al., 2000) have demonstrated a lack of FFA activation in response to emotionally neutral faces in individuals with ASD. Schultz et al. (2000) found that individuals with ASD instead exhibited heightened activation of the inferior temporal gyri (ITG) during a face discrimination task, which was the same area that they and normal controls activated when comparing non-face objects. These findings have led to suggestions that individuals with ASD do not develop cortical face specialization, possibly due to reduced social interest or to a deficit in attention to faces (Dawson et al., 2002; Grelotti et al., 2002; Pierce et al., 2001). Yet, individuals with ASD do not exhibit the severe face perception deficits that are found in prosopagnosia, and the clinical presentation of autism is doubtlessly much more complex than a basic deficit in face identification, as others have already suggested (e.g., Grelotti et al., 2002).

Our goal in the present study was to assess further the pattern of ventral temporal and occipital cortical activation in response to face and non-face objects in individuals with ASD as compared to IQ-matched normal controls. Given the recent findings of abnormalities in the way individuals with ASD visually attend to faces (Klin et al., 2002; Pelphrey et al., 2002), we were particularly interested in the pattern of activation that would be found under passive viewing conditions in which participants would be continuously cued to direct their attention to faces as well as to the comparison stimuli.

Materials and methods

Sample

ASD participants were 11 high-functioning adult males who met a clinical diagnosis for autism, Asperger disorder, or pervasive developmental disorder not otherwise specified (PDD-NOS) from current clinical presentation and developmental history. The diagnoses were confirmed using the Autism Diagnostic Interview-Revised (ADI-R; (Lord et al., 1994)) and the Autism Diagnostic Observation Schedule (ADOS; (Lord et al., 2000)), which were administered by personnel who were trained to the standards of research reliability on both instruments. According to criteria recently developed by the NIH Collaborative Programs for Excellence in Autism for ADI-R/ADOS-based DSM-IV (American Psychiatric Association, 1994) diagnosis of autism and other ASDs (Lord and Risi, 2003), four participants met DSM-IV criteria for autism, four participants met criteria for Asperger disorder, and one participant met criteria for PDD-NOS. A reliable ADI-R informant was not available for two of the participants; however, both of these participants met criteria for autism on the ADOS as well as on the basis of clinical impression, and were therefore included in the study.

Control participants were 10 males selected from among a larger group of normal recruits to match the ASD sample as closely as possible on age as well as full-scale, verbal, and performance IQ. Individuals who were outside the age and IQ range of the ASD group were excluded from the control group. A screening was conducted to rule out any history of psychiatric or neurological disorder among the control participants.

IQ scores were obtained for all participants using the Wechsler Abbreviated Scale of Intelligence (WASI, 1999). As shown in Table 1, all the participants were in the normal range or above

Table 1
Participants characteristics

	ASD (n = 11) M (SD), range	Control (n = 10) M (SD), range
Age (years)	36 (12), 18–52	26 (6), 20–43
Full Scale IQ	119 (8), 105–128	119 (5), 112–129
Verbal IQ	120 (8), 105–131	118 (7), 107–131
Performance IQ	114 (10), 95–125	115 (10), 96–129

average, and the groups were well matched on full-scale, verbal and performance IQ scores. Although the ASD group was somewhat older, $t(19) = 2.3$, $P < 0.05$, the age ranges in the two groups were comparable. Table 2 displays the age and IQ scores for each individual in each group as well as the ADI-R and ADOS scores for the individuals in the ASD group.

Measures

Informed written consent was obtained for each participant before the scanning session, and all procedures were approved by the Massachusetts General Hospital Human Studies Committee under Protocol # 1999-P-010976/12.

High-resolution (1.0 × 1.0 × 1.3 mm) structural images were obtained with a magnetization-prepared rapid acquisition with gradient echoes (MP-RAGE) sequence, (128 slices, 256 × 256 matrix, echo time (TE) = 3.44 ms; repetition time (TR) = 2730 ms; flip = 7°) on a 1.5-T Sonata MR scanner (Siemens, Munich, Germany). This specific sequence at 1.5 T gives the best white-gray matter contrast and optimizes our segmentation processing. Images were then segmented, reconstructed, inflated, and flattened using Freesurfer http://surfer.nmr.mgh.harvard.edu) following standard procedures used at MGH and described previously (Dale et al., 1999; Fischl et al., 1999a).

MR images of brain activity were collected in a high field Allegra 3.0-T high-speed echoplanar imaging device (Siemens) using a quadrature head coil. Subjects lay on a padded scanner couch in a dimly illuminated room and wore foam earplugs. Foam padding stabilized the head. Functional sessions began with an initial sagittal localizer scan, followed by autoshimming to maximize field homogeneity. To register functional data to the three-dimensional reconstructions, a set of high-resolution (22 to 28 coronal slices, 3 to 4 mm thick, perpendicular to the calcarine sulcus, 1.5 × 1.5 mm in-plane no skip) inversion time T1-weighted echo-planar images (TE = 29 ms; TI = 1200 ms; TR = 6000 ms; number of excitations (NEX) = 4) was acquired, along with T2 conventional high-resolution anatomical scans (256 × 256 matrix, TE = 104 ms; TI = 1,200 ms; TR = 11 s, NEX = 2). The co-registered functional series (TR = 2000 ms, 22 to 28 coronal slices, 3 to 4 mm thick, 3.125 mm by 3.125 mm in plane resolution, 128 images per slice, TE = 30 ms, flip angle 90°, FOV = 20 × 20 cm, matrix = 64 × 64) lasted 256 s. Slices covered the entire occipital lobe, the parietal lobe, and the posterior and middle portions of the temporal lobe.

During the scanning, participants were shown grayscale pictures of faces, objects, and Fourier scrambled versions of these pictures in an AB-blocked presentation, with 16-s epochs for each stimulus type. The stimuli were the same as those used by Hadjikhani and de Gelder (2002) and consisted of 64 different faces and objects, each with its own scrambled version. A large number of different stimuli were chosen to minimize a reduction in attention that might be produced by the repeated presentation of the same object or face. Each stimulus had a red fixation cross in the center, was contained within a circle 480 pixels in diameter to control for retinotopic differences, and occupied 20° of visual angle (Fig. 1). Each stimulus was presented for 1800 ms followed by a blank interval of 200 ms. The participant's task was to fixate the center of the visual stimulus throughout the

Table 2
Individual participant characteristics

	Age	IQ			ADI-R			ADOS		
		FSIQ	VIQ	PIQ	Communication	Social	Repetitive behaviors	Communication	Social	Diagnosis
ASD group										
1	18; 1	120	117	119	7	15	5	1	5	Asperger
2	18; 5	128	131	119	12	17	5	2	7	Autism
3	26; 8	112	119	103	10	18	8	2	6	Autism
4	26; 8	105	105	104	14	26	6	2	8	Autism
5	29; 5	128	127	124	8	16	6	3	5	Autism
6	39; 7	118	122	109	12	15	2	2	6	Asperger
7	40; 10	119	119	114	7	15	2	1	5	Asperger
8	43; 6	112	130	95	–	–	–	5	11	Autism
9	46; 7	125	119	125	–	–	–	6	8	Autism
10	49; 3	126	122	124	5	13	1	2	9	PDD
11	52; 7	113	106	118	13	12	2	3	8	Asperger
Control group										
1	20; 11	129	127	126						
2	21; 7	114	117	107						
3	22; 7	114	131	96						
4	23; 3	117	119	110						
5	24; 1	112	117	105						
6	24; 11	116	108	121						
7	24; 2	123	121	118						
8	24; 8	119	107	129						
9	25; 5	120	117	119						
10	43; 0	124	119	121						

Threshold scores for a diagnosis of autism on the ADI-R are 8, 10, and 3 for communication, social, and repetitive behavior symptoms, respectively. Threshold scores for a diagnosis of autism on the ADOS are 3 and 6 for communication and social symptoms, respectively. Threshold scores for a less severe diagnosis of ASD on the ADOS are 2 and 4 for communication and social symptoms, respectively.

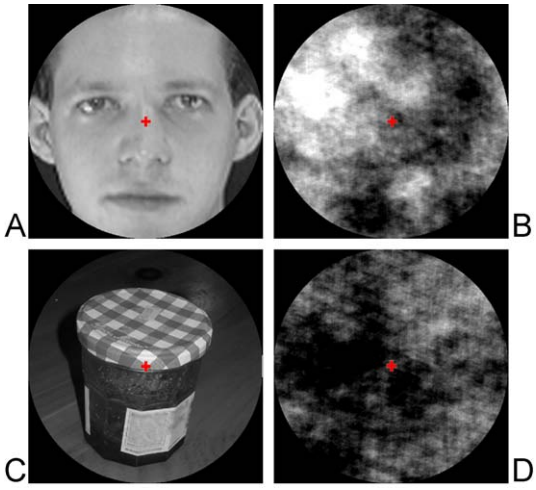

Fig. 1. Example of the stimuli used. Panel A shows a face contained within a circle, and Panel B shows the Fourier-scrambled version of the same face. Panel C shows an object contained within the same circle, and Panel D shows its Fourier scrambled version. Each stimulus was scrambled individually. A red fixation cross was continuously present in the center, and the participants' task was to fixate this red cross.

period of scan acquisition. The stimuli were presented for passive viewing to minimize movement artifacts that are more likely to occur during an active task. The instructions were to focus on the red fixation cross so as to maximize the possibility that the participants would attend to the central part of the face. To be able to compare our results with those obtained in previous imaging studies, we chose to compare faces and scrambled faces, faces and objects, and objects and scrambled objects in different runs.

Data analysis

Each functional run was first motion-corrected with tools from the AFNI package (Cox, 1996), then spatially smoothed using a three-dimensional Hanning filter with full width at half maximum of 8 mm. The mean offset and linear drift were estimated and removed from each voxel. The spectrum of the remaining signal was computed using the FFT at each voxel. The task-related component was estimated as the spectral component at the task fundamental frequency. The noise was estimated by summing the remaining spectral components after removing the task harmonics and those components immediately adjacent to the fundamental. For individual and fixed-effects group analyses, an F statistic was formed by computing the ratio of the signal power at the fundamental to the total residual noise power. The phase at the fundamental was used to determine whether the BOLD signal was increasing in response to the first stimulus (positive phase) or the second stimulus (negative phase).

Cortical surface analysis

Each participant's fMRI scan was registered to a high-resolution T1. The real and imaginary components of the Fourier transform of each participant's signal were re-sampled from locations in the cortex onto the surface of a template sphere to bring them into a standard space. The techniques for mapping between an individual volume and this spherical space are detailed by Fischl et al. (1999a,b). A group average significance map for the cortical surface was computed, using a GLM analysis to perform a fixed (Fig. 5) and a random effects (Fig. 4) average of the real and imaginary components of the signal across subjects on a per-voxel basis. The significance of the average activation was determined using an F statistic and mapped from the standard

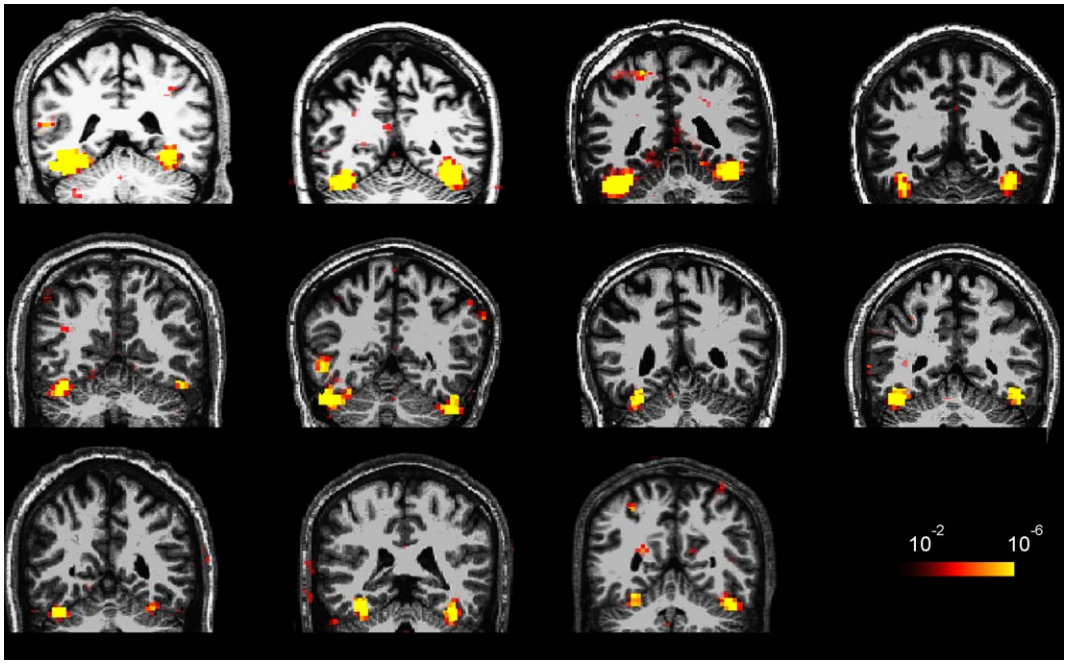

Fig. 2. Coronal views taken between $y = 49$ and $y = 60$ of the brains of the 11 participants with ASD. Regions shown in red ($P < 0.01$) to yellow ($P < 0.000001$) responded more to faces than to scrambled faces. Activation of the fusiform gyrus can be seen in all the participants, and is bilateral in all but one. The threshold used is shown in the lower right corner.

Table 3
Number of voxels in the fusiform gyrus

Hemisphere	ASD (n = 11) M (SD)	Control (n = 10) M (SD)	P
Right	178 (32)	190 (36)	0.41, n.s.
Left	153 (33)	170 (28)	0.21, n.s.

sphere to a target individual's cortical surface (Fischl et al., 1999b). Maps were visualized on a target individual's surface geometry, or by overlaying a group curvature pattern averaged in spherically morphed space (Fischl et al., 1999a,b).

ROI analysis

Regions of interest (ROIs) were defined by structural (anatomical) or functional constraints. The structural constraints were specified by labels corresponding to the areas produced by automatic cortical parcellation (Fischl et al., 2004) (Fig. 4). Each functional constraint was selected for voxels with a significance level of $P \leq 0.001$. Time courses were extracted from the ROIs. In addition, the peak at the fundamental value of the stimulus was computed for each voxel and averaged for the entire ROI by taking the square root of the sum of the squared real and imaginary signals.

Results and discussion

All 11 individuals with ASD showed bilateral activation of FFA and bilateral activation of the inferior occipital gyri (IOG) in response to faces, except for one participant who showed FFA activation on the right side only. Nine of the 10 controls showed bilateral FFA and IOG activation to faces, and one showed bilateral FFA activation, but no IOG activation to faces.

Because our slice prescription and number of slices were chosen to maximize resolution and signal in the FFA and IOG, we were not able to collect data from more anterior parts of the brain, such as the amygdala or the frontal cortex.

Fig. 2 shows fusiform activation in response to faces vs. scrambled faces for each participant with ASD. Activation of the fusiform gyrus is present in all ASD participants, and is bilateral in all cases except in one.

In Fig. 3, we present activation data for faces and for objects produced with the random-effects group averages of the ASD and control participants, and the location of the IOG, the fusiform gyrus (FG), and the inferior temporal gyrus (ITG), as defined by our automatic parcellation program (Fischl et al., 2004). In both populations, an area of activation specific to faces was seen in the FG, corresponding to the FFA. The FFA did not activate in response to objects in either group. Another area of the fusiform gyrus, medial to the FFA, which we refer to as the fusiform object area (FOA), activated in response to objects in both populations. No activation to faces was seen in more lateral parts of the brain, such as the ITG, in either group. These data are comparable to those from similar experiments with normal individuals (e.g., (Haxby et al., 2000)). The normal controls show less activation in the IOG than the ASD in this random-effect analysis. This might be because 1 out of 10 of our controls showed no IOG activation, and that of the remaining 9, there was a fair amount of variability, as expressed for the FFA activation in Table 5.

The *total volume* of the fusiform gyrus, measured by the number of voxels, was similar in the two populations (Table 3).

To compare the *level of activation* between groups, we measured the percentage of voxels of the fusiform gyrus (comprising both the FFA and the FG object area, see Fig. 3) activated at a threshold of $P < 0.001$ during the functional scans. A t test revealed no difference between groups in the face condition (ASD: M = 40, SD = 20; controls: M = 33, SD = 12; $P = 0.3$) and in the object

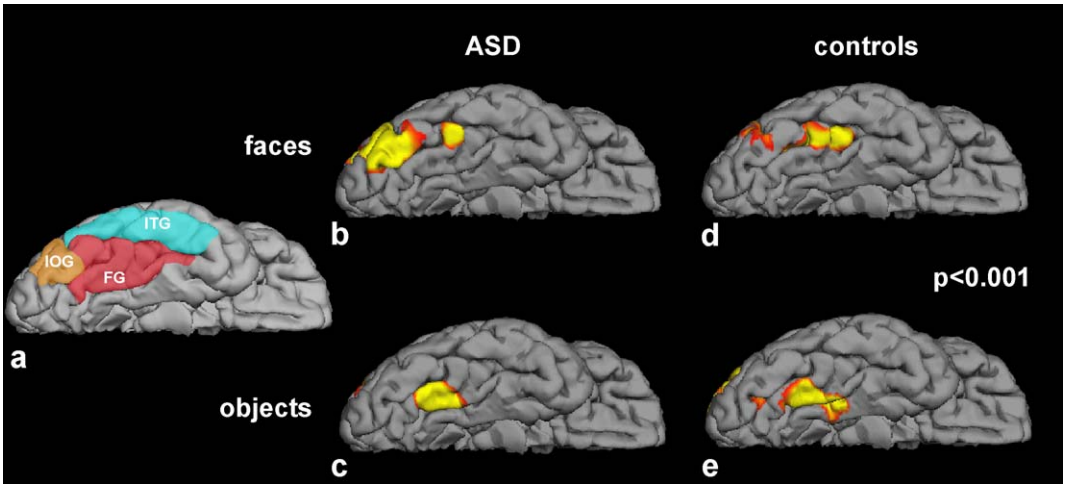

Fig. 3. Location of the regions of the right hemisphere that are involved in the visual analysis of faces and objects. Panel a shows the location of the IOG (orange), the FG (red) and the ITG (blue), as defined by our automatic parcellation system (Fischl et al., 2004). Panels b and c show the random-effects average for the ASD subjects, and panels d and e for the control population. Panels b and d show brain activation for faces in the ASD and control group, respectively, and panels c and e show brain activation for objects in the ASD and control group, respectively. The data displayed are for a statistical significance of $P \leq 0.001$. In both groups, activation for faces can be seen in the more lateral part of the FG that corresponds to the FFA. No activation for faces is seen in the ITG. Activation for objects can be seen in the more medial part of the FG (FOA) in both the ASD and in the control group. Activation for objects is also present in the lateral occipital gyrus in both groups (see Fig. 5). The activation for faces and objects is similar in the two groups.

Table 4
ANOVA of the time courses of the FFA response to faces in individuals with ASD

Source	*df*	Sum square	Mean square	*F*	P
Task	1	11.2215	11.2215	86.9136	3.49e−16
Subject	10	0.337	0.337	0.2611	0.9883
Interaction	10	0.8067	0.0807	0.6248	0.7906
Residuals	132	17.0426	0.1291		

Table 5
ANOVA of the time courses of the FFA response to faces in control participants

Source	*df*	Sum square	Mean square	*F*	*P*
Task	1	8.965	8.965	59.6791	3.75e−12
Subject	9	315.052	31.83	233.0307	2.2e−16
Interaction	9	1.704	0.189	1.2604	0.2655
Residuals	120	18.026	0.150		

condition (ASD: M = 44, SD = 30; controls: M = 51, SD = 26; $P = 0.6$). See Fig. 4.

Fig. 5 presents the *overall pattern of activation* obtained for the direct comparison of faces and objects in the ASD group, using fixed-effects analysis. These data confirmed the activation of the FFA, IOG and the superior temporal sulcus in response to faces in our ASD participants, and are similar to findings reported for normal individuals (Haxby et al., 2000).

To evaluate the *response to faces*, we defined an ROI in the FFA for all participants, and examined the time course of activation. The averaged results for each group are displayed in Fig. 6. Both groups of participants exhibited strong FFA activation in response to faces.

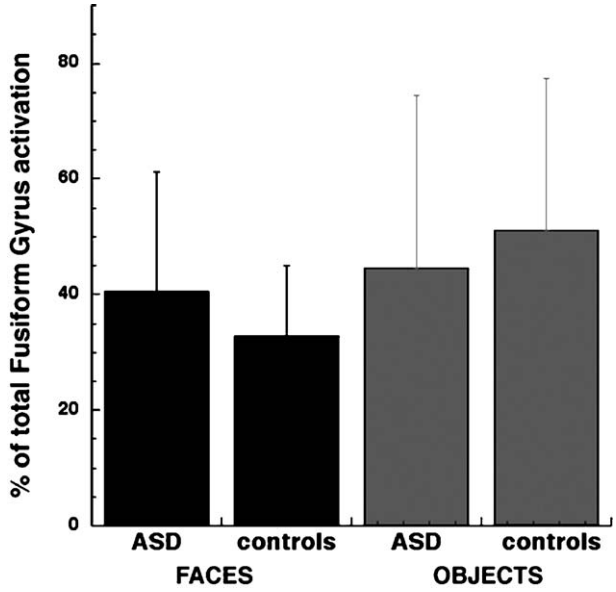

Fig. 4. Amount of activation in the entire fusiform gyrus (colored in red in Fig. 3) in ASD and control participants. The number of active voxels at a threshold of $P < 0.0001$ was computed for each individual, and related to the total amount of voxels in the fusiform gyrus. No significant group difference was found for either task.

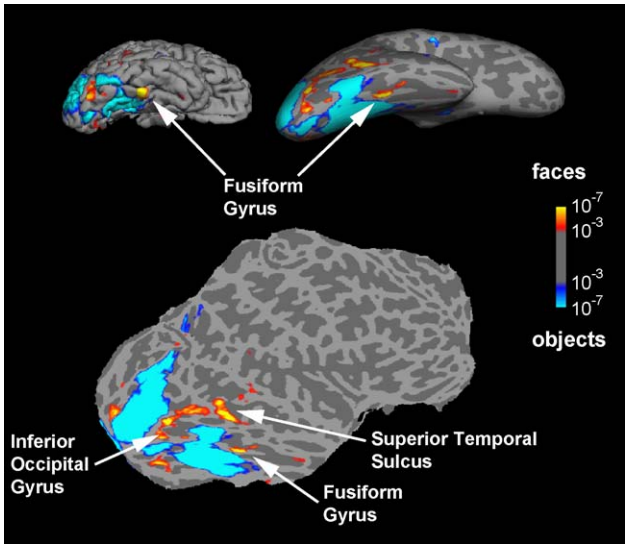

Fig. 5. Locations of regions involved in the visual analysis of faces vs. objects averaged for participants with ASD. The hemispheres have been inflated and flattened to show the sulci (darker shade of gray) and the gyri (lighter shade of gray). The upper images show ventral views of the right hemisphere. They are alternately folded and inflated, and both have been tipped 70° to show the ventral surfaces of the occipital and temporal lobes. The lower image is a flattened representation of the entire hemisphere. Areas that were activated by faces are displayed in red ($P < 0.001$) to yellow ($P < 10^{-7}$). Areas that were activated by objects are displayed in dark blue ($P < 0.001$) to cyan ($P < 10^{-7}$). Activation for faces was found in the fusiform gyrus, the inferior occipital gyrus, and the superior temporal cortex. Activation for objects was observed in the lateral occipital cortex, the inferior temporal cortex, and the lingual and fusiform gyri. However, in the fusiform gyrus, activations by objects and by faces were distinct.

To examine further the validity of our data, we used analysis of variance (ANOVA) to test for main effects of task (face vs. scrambled faces), and a task by group interaction in the fusiform gyrus for both the controls and the ASD groups. In both groups, the difference in activation due to the task was highly significant, with *P* values much less than 0.0001 (Tables 4 and 5).

For the control group, there was significant inter-subject variability ($P < 0.0001$), which was not the case for the ASD group ($P = 0.9$), suggesting that the group of participants with ASD was more homogenous in their response to the stimuli.

However, in both groups there was no interaction between the subject and the task effects, that is, the change in activation due to the task was generally uniform across individuals.

To examine whether there was a *difference between groups in fusiform activation*, we computed the percentage of signal change in the fusiform gyrus in response to faces relative to scrambled faces. As shown in Fig. 7, a two-tailed *t* test showed no difference between groups, $t(19) = 1.218$, $P = 0.2$.

We next examined the *specificity of FFA response to faces*, and whether other areas of the brain that are normally associated with object processing were recruited abnormally in the participants with ASD. Patterns of responses were examined in the FFA, defined as those voxels within the fusiform gyrus that maximally responded to faces vs. objects, and in the FOA, defined as those voxels within the fusiform gyrus that maximally responded to objects vs. faces, at a threshold of $P < 0.001$. It is known from research with normal individuals (Haxby et al., 2001) that the representation of faces and objects is distributed and overlapping in

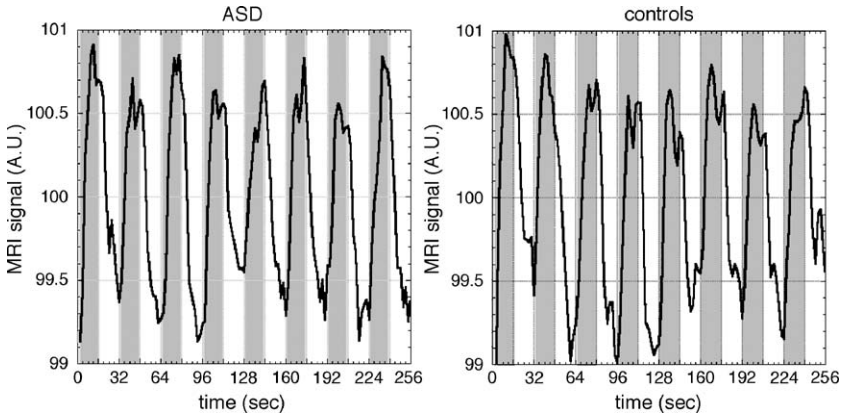

Fig. 6. Time courses in the fusiform gyrus in response to faces. The left panel shows the time course of activation to faces alternating with scrambled faces in the 11 participants with ASD. The right panel shows the time courses of activation to faces alternating with scrambled faces in the 10 normal controls.

the ventral temporal cortex. However, there are regions that maximally respond to specific categories in normal individuals. We looked at the percentage of the response to the non-specific stimulus vs. the specific stimulus in each of these areas (Fig. 8). We found that in the ASD group, the response to objects (vs. scrambled) was 42% (±20%) of the response to faces (vs. scrambled) in the FFA, and in the control group, the response to objects was 54% (±20%) of the response to faces in the FFA. In the FOA, the response to faces was 56% (±27%) of the response to objects in the ASD groups, and the response to faces was 47% (±29%) of the response to objects in the control group. The *t* tests showed no differences between the ASD and control group for either area, $P > 0.05$ (Fig. 8).

Finally, to test further the hypothesis that there is *no difference between our two populations*, we selected anatomically defined regions in the FG, IOG, STS, and ITG. An independent-samples *t* test comparing the activation for faces between the ASD and the control groups in these ROIs showed no difference between both groups (Table 6).

In this study, we systematically investigated the pattern of activation in ventral temporal cortex in response to faces and non-face comparison stimuli in individuals with ASD and an IQ-matched control group. The volume of the fusiform gyrus and the level of fusiform activation to faces was the same in both populations. Moreover, the pattern of activation in response to faces and to objects in the ventral temporal cortex was similar in the two groups, with activation of the FFA for faces, and of a more medial part of the fusiform gyrus for objects. The specificity of the response of the FFA to faces and of the more medial fusiform object area to objects was also similar in both groups. In addition, areas outside of the fusiform gyrus, such as IOG and STS, which have been identified as parts of a distributed system for face perception, showed similar activation for faces in the ASD and control groups. More lateral areas, such as ITG, did not show activation to faces in either group. In contrast to Schultz et al. (2000), we found no evidence that ventral temporal areas normally associated with object perception were abnormally recruited to process faces in individuals with ASD. Further, we found that the pattern of activation to faces was very consistent across individuals in the ASD group. There was no evidence that FFA responsiveness was different between individuals who met research diagnostic criteria for autism and those who met criteria for Asperger disorder or PDD-NOS.

What might explain the discrepancy between our findings and prior findings (Critchley et al., 2000; Pierce et al., 2001; Schultz et al., 2000) of a lack of FFA activation in individuals with ASD? Critchley et al. (2000) demonstrated that, unlike in their normal

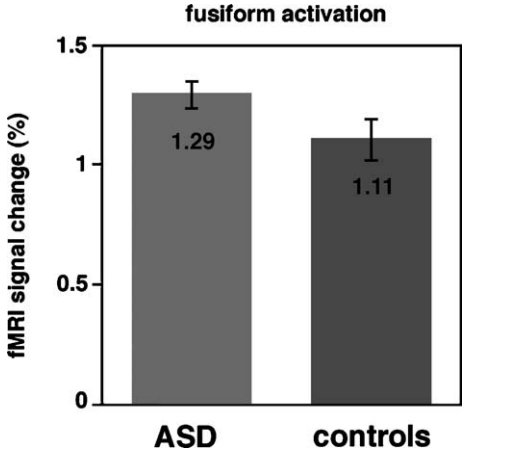

Fig. 7. Average percent signal change in functionally defined ROIs in the FFA of participants with ASD and controls, in the comparison between faces and scrambled faces. The two groups did not differ significantly, $P = 0.2$.

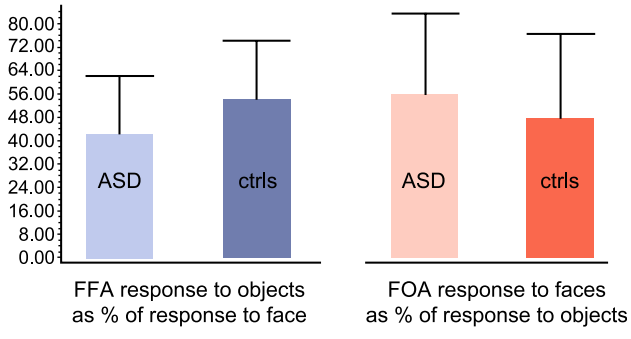

Fig. 8. Specificity of responses. The graph on the left displays the FFA response to objects as a proportion of the FFA response to faces. The graph on the right displays the FOA response to faces as a proportion of the FOA response to objects. There were no significant differences between groups in specificity of response.

Table 6
Mean difference between the ASD and the control group activation for faces in selected ROIs

	Mean difference	$t(19)$	P
FG	0.02	0.51	0.61, n.s.
IOG	0.01	0.28	0.78, n.s.
STS	0.02	0.59	0.55, n.s.
ITG	0.00	0.06	0.95, n.s.

controls, facial expressions of emotion did not activate the amygdala or the FFA in individuals with ASD. However, in the Critchley et al. study, faces were compared to faces, and the factor that changed between conditions was the emotion of the face. Thus, FFA hypoactivation in the ASD group was as likely to have resulted from deficits in affective responsiveness or in emotion perception as from an impairment in the processing of face identity.

In contrast, as in our study, both Schultz et al. (2000) and Pierce et al. (2001) examined brain activation to emotionally neutral faces in individuals with ASD. However, our studies differed in several ways. First, there were several technical differences between our studies. We used a stronger field magnet (3 T) than the previous studies, with a higher signal-to-noise ratio (Takahashi et al., 2003). In the study by Schultz et al. (2000), only one 9-mm slice was used, in a near axial orientation, with maximal risk for susceptibility artifacts. In the study by Pierce et al. (2001), 7-mm sagittal slices were used, with a gap between them. In our study, by using a near coronal orientation (perpendicular to the calcarine sulcus), thinner slices and no gap, we maximized the likelihood to detect fMRI signal in the visual cortex and in the FFA.

A second and more important difference was in the stimuli and the tasks that were used. In Schultz et al. (2000), participants were asked to judge whether the faces, objects, and scrambled images they viewed were the same or different. In Pierce et al. (2001), faces (but not objects) were alternated with sensory control stimuli (similar to our scrambled faces) and the task was to detect targets (e.g., females, circles) that appeared on 25% of trials. In each of these studies, participants were arguably able to perform the task for faces without attending to the central features of the face by using other features such as the shape, peripheral features, or other details of the images. Recent eye-tracking studies have shown that individuals with ASD attend to faces in an abnormal manner, with an especially pronounced decrement in attention to the eye region (Klin et al., 2002; Pelphrey et al., 2002), which is the region of the face that is normally most informative for the purpose of face recognition (Goldstein and Mackenberg, 1966; Joseph and Tanaka, 2003; McKelvie, 1976). It is thus possible that prior findings of FFA hypoactivation in individuals with autism reflect a failure of study participants to attend appropriately to face stimuli. This possibility would be consistent with the recent findings of Davidson and Dalton (2003) who reported that FFA activation to faces in a group of children with autism was positively correlated with the amount of time spent attending to eye region of the faces as revealed by continuous monitoring of children's point of visual regard while they were in the scanner. In our study, by introducing a fixation cross at the center of the stimuli, and by emphasizing in our instructions that fixation on this cross should be maintained throughout the scanning experiment, we ensured that participants were attending to the inner features of the face. Using the same strategy in another study, we were able to obtain very good retinotopic maps for a subgroup of the participants with ASD from this study, which are impossible to obtain in the absence of continuous fixation (Hadjikhani et al., 2003). In addition, by using passive viewing and not requiring active task completion, we may have avoided distracting participants towards peripheral features of the face stimuli, to which they may be more inclined to attend in their efforts to match or discriminate faces.

It might be argued that our finding of FFA activation to faces in individuals with ASD lends support to the argument that this cortical area is innately specified to process face identity (Kanwisher et al., 1997) and contradicts the notion that this area is dedicated more generally to perceptual computations requiring visual expertise, which is acquired through experience (Gauthier et al., 1999). However, a potential problem with this argument is that it may incorrectly assume that individuals with autism are not "experts" at face recognition. As we have pointed out, individuals with ASD do not exhibit a primary deficit in face recognition, such as is found in prosopagnosia, and they appear capable of the perceptual computations necessary to discriminate among the faces of the countless individuals they encounter in their everyday lives. Thus, the abundant evidence from experimental paradigms that children and adults with ASD are deficient in incidental learning and recognition of faces would seem to point to abnormalities in other components of the complex neural system for face processing, mediating, for example, attention to, interest in, and appropriate affective responses to faces.

Face perception is mediated by a distributed neural system (for reviews, see Haxby et al., 2000, 2002). The initial stage of face perception is face detection, involving a fast perceptual processing of highly salient stimuli by a network of areas comprising the superior colliculus, the amygdala, the thalamic lateral geniculate nucleus, the pulvinar and the striate cortex (Adolphs, 2002b; de Gelder et al., 1999; Vuilleumier et al., 2003). The visual system then divides into distinct but interactive routes. These routes consist of a system specialized for the analysis of invariant aspects of faces necessary for the perception of identity (FFA, IOG) and systems mediating functions such as the perception of gaze (STS) as well the perception of facial expressions and affective evaluation and response to faces (amygdala, STS, orbital prefrontal cortex, premotor cortex) (Adolphs, 2002b; De Gelder et al., 2003; Haxby et al., 2002). These latter systems comprise a vital social perceptual network necessary for interpreting and responding to the multifaceted nonverbal information faces communicate. They are crucial to social and communicative competence and, for that reason, are most likely to be implicated in the neuropathology of autism. Moreover, we know from a previous study that facial expressions do have an influence on facial identification (De Gelder et al., 2003) and deficits in the emotional aspects of face perception could in turn affect the quality of face identification in ASD.

Although the fusiform gyrus is intricately connected with other components of the social perceptual network described above, our findings suggest that it is not critically involved in the face-processing impairment and social-communicative deficits that characterize autism. Recent research has, however, implicated several other components of the extended face perception system in autistic face-processing deficits. As noted above, Davidson and Dalton (2003) have linked FFA hypoactivation to inattention to the eye region, which they interpret as active avoidance of gaze contact resulting from autonomic hyperreactivity to salient social stimuli. This affective dysregulation is seen as driven by a disturbance in social-affective brain circuitry, including the amygdala and prefrontal cortices as well

as the anterior cingulate and insular cortex and the ventral striatum (Davidson and Irwin, 1999). The notion of affective dysregulation in autism, which builds in part on the structural complexity of the amygdala and its inhibitory and excitatory functions, seems particularly promising and worthy of serious future inquiry because it can account for hypo-arousal and seeming social indifference as well as social anxiety in individuals with ASD (Hirstein et al., 2001).

We do not yet know which specific components or interconnections are affected in autism. However, a simple story regarding fusiform gyrus dysfunction appears unlikely. The components of the face-processing system most involved in interpreting information communicated through facial movements such as shifts of gaze and emotional expression, and assigning affective significance to faces and the social signals they convey, are likely to be the most critical nodes in autistic face-processing impairments, as they also are most closely linked to the defining social-affective and communicative impairments that are pathognomonic of autism.

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