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Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI

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Summary

Processing the human face is at the focal point of most social interactions, yet this simple perceptual task is difficult for individuals with autism, a population that spends limited amounts of time engaged in face-to-face eye contact or social interactions in general. Thus, the study of face processing in autism is not only important because it may be integral to understanding the social deficits of this disorder, but also, because it provides a unique opportunity to study experiential factors related to the functional specialization of normal face processing. In short, autism may be one of the only disorders where affected individuals spend reduced amounts of time engaged in face processing from birth. Using functional MRI, haemodynamic responses during a face perception task were compared between adults with autism and normal control subjects. Four regions of interest (ROIs), the fusiform gyrus (FG), inferior temporal gyrus, middle temporal gyrus and amygdala were manually traced on non-spatially normalized images and the percentage ROI active was calculated for each subject. Analyses in Talairach space were also performed. Overall results revealed either abnormally weak or no activation in FG in autistic patients, as well as significantly reduced activation in the inferior occipital gyrus, superior temporal sulcus and amygdala. Anatomical abnormalities, in contrast, were present only in the amygdala in autistic patients, whose mean volume was significantly reduced as compared with normals. Reaction time and accuracy measures were not different between groups. Thus, while autistic subjects could perform the face perception task, none of the regions supporting face processing in normals were found to be significantly active in the autistic subjects. Instead, in every autistic patient, faces maximally activated aberrant and individual-specific neural sites (e.g. frontal cortex, primary visual cortex, etc.), which was in contrast to the 100% consistency of maximal activation within the traditional fusiform face area (FFA) for every normal subject. It appears that, as compared with normal individuals, autistic individuals 'see' faces utilizing different neural systems, with each patient doing so via a unique neural circuitry. Such a pattern of individual-specific, scattered activation seen in autistic patients in contrast to the highly consistent FG activation seen in normals, suggests that experiential factors do indeed play a role in the normal development of the FFA.

Keywords: autism; fMRI; amygdala; face perception; fusiform gyrus

Abbreviations: EPI = echo-planar image; FFA = fusiform face area; fMRI = functional MRI; ROI = region of interest; FG = fusiform gyrus; ITG = inferior temporal gyrus; MTG = middle temporal gyrus

Introduction

The face is at the epicentre of human social interactions, and from the beginning of life the normal infant attends vigorously to this stimulus (Bryant, 1991). Disruption of this normal predisposition for face perception is characteristic of a relatively common developmental disorder, autism. Affected individuals are well noted for difficulties with perception of facial affect (Hobson, 1986; Hobson *et al*., 1988; Bormann-Kischkel *et al*., 1995), direction of eye gaze (Baron-Cohen *et al*., 1997; Leekam *et al*., 1997), as well as diminished rates of eye contact (Phillips *et al*., 1992; Hobson and Lee, 1998) and social interactions with others (Lord and Magill-Evans, 1995; Pierce and Schreibman, 1995). Thus, autistic individuals can be thought of as relatively 'face inexperienced'. Limited experience with the human face is not only a common characteristic in autistic infants and children, it may also be one of the first developmentally

critical mis-steps in a cascade of events leading to the profound impairment in social communication that is central to this disorder.

Twin studies show autism to be among the most heritable of neuropsychiatric disorders (Bailey *et al*., 1995), and neuroanatomical studies point to a biological time of onset possibly as early as the first trimester and certainly within the first 2 years of postnatal life (Courchesne *et al*., 1999). Presumably, the diminished capacity of the autistic infant and child to orient towards and interact with the human face is the result of observable structural and/or functional brain defects. It is not surprising, then, that of the few autism/functional MRI (fMRI) papers currently published, over half have investigated some aspect of face processing (Baron-Cohen *et al*., 1999; Critchley *et al*., 2000; Schultz *et al*., 2000). Such studies, however, utilized a combination of both autism and Asperger's subjects in the same sample and the degree to which such groups represent aetiologically similar or distinct populations is still unknown. Nonetheless, these reports provide evidence that temporal lobe structures are functionally abnormal in individuals with pervasive developmental disorders. For example, both Baron-Cohen *et al.* and Critchley *et al*. found reduced amgydala activation in response to a social intelligence and an emotion processing task, respectively (Baron-Cohen *et al*., 1999; Critchley *et al*., 2000), whereas Schultz and colleagues found reduced activity in the fusiform gyrus (FG) and increased activity in the nearby inferior temporal gyrus (ITG) during a more traditional face processing task (Schultz *et al*., 2000).

Behavioural experiments on face processing in autism also present an interesting profile; autistic patients do have some ability in face identification, such as in distinguishing female from male faces (Teunisse and De Gelder, 1994), but with increasing task difficulty, performance typically drops away from normal (Boucher and Lewis, 1992). Moreover, in behavioural tests, autistic patients do not show the normal processing advantage of normally oriented faces over inverted faces (Hobson *et al*., 1988; Tantam *et al*., 1989), and do not process faces holistically, but instead rely on individual features (e.g. the presence of a hat) (Weeks and Hobson, 1987). Interestingly, both types of performance abnormality are characteristic of adults with acquired fusiform lesions (Farah *et al*., 1995). The similarity in behavioural performance on face processing tasks between individuals with acquired fusiform lesions and individuals with autism, suggests that individuals with autism may possess structural abnormalities in this cortical region. Currently, however, there are no structural reports of the FG in autism and, thus, obtaining such information was one goal of the present study.

The amygdala has also been shown to play an essential role in face processing, but in contrast to the more basic face processes subsumed by the FG such as identification (Haxby *et al*., 2000), the amygdala supports more extended face processing tasks. For example, the amygdala has been shown to be involved in understanding a face as threatening or not (Morris *et al*., 1998), or monitoring the direction of gaze of a face (Kawashima *et al*., 1999), and establishing the reward value of stimuli in general (Baxter *et al*., 2000). During normal development, the amygdala may thus work in concert with the FG, to identify faces as socially significant stimuli. Interestingly, apparently contradictory MRI evidence suggests that this structure is abnormally enlarged (Howard, 2000), abnormally small (Aylward *et al*., 1999*a*) or not different (Haznedar *et al*., 2000) in volume from normal in autism. Autopsy data reveal increased cell packing density (Bauman and Kemper, 1994); however, this does not provide direct evidence for either enlargement or reduction of volume in this structure. Despite the inconclusiveness of structural data on the amygdala in autism, it is a widely held belief that abnormalities of this structure are pivotal to the social dysfunction seen in autism (Bachevalier, 1994; Baron-Cohen *et al*., 2000; Howard, 2000). An additional goal of the present study, therefore, was to obtain structural volume measures of the amygdala and to compare such measures with those of the FG.

In addition to the great importance of face processing research for the study of autism, this topic is also of intense interest in the field of basic neuroscience. Using fMRI technology, a host of studies have uncovered a remarkable phenomenon: the fusiform gyrus is consistently active during face viewing in virtually all studies of normal humans (see Haxby *et al*., 1994; Puce *et al*., 1995; Clark *et al*., 1996; Kanwisher *et al*., 1999; Cabeza and Nyberg, 2000). The consistency of fMRI and neuropsychological results is such that it is now near dogma that face processing uniformly engages a specific region of the FG; indeed, this special brain region is sometimes referred to as the fusiform face area (FFA) and many believe that the specificity of this region is driven mainly by genetic factors (Farah *et al*., 1998; Kanwisher, 2000). New evidence, however, raises the possibility that the specialization of the fusiform region for face processing might instead be based largely on experiential factors. In a recent study, Gauthier and colleagues not only showed that the FFA was active during face viewing, but also, during bird or car viewing for subjects who were either car or bird experts (Gauthier *et al*., 2000). In short, these authors suggest that the functional specialization of the FFA may have evolved for the processing of extremely familiar objects, of which faces are the most likely candidate for the majority of normal individuals.

Such remarkable invariance in response to faces in the adult brain suggests that in normal development there are powerful factors, genetic and/or experiential, that inevitably lead to this specific neural organization. The underlying developmental factors are largely unknown because the usual modes of obtaining such information (e.g. animal models) are unavailable with regard to the neurobiological development of human face processing. Despite these significant hurdles, it may yet be possible to identify factors that influence FFA functional development utilizing autistic subjects, a population with limited experience with faces throughout life. If FFA reflects a largely innately determined, specialized

processing module (Kanwisher, 2000), then despite developmental face inexperience, the mature autistic FFA might be predicted to be engaged, but perhaps to a weaker degree, by the human face. On the other hand, if FFA reflects the emergence of a special processing capacity driven by extensive experience with faces (Tarr and Gauthier, 2000), then the mature autistic FFA might be predicted not to be engaged by human faces. A final goal of the present study, therefore, was to investigate these two alternatives.

The study of autism brings with it some unique methodological challenges and, currently, there is no agreed upon standard for analysing functional data from psychiatric populations with multiple, developmental anatomical brain defects. Defects in regional morphometrics, such as hypoplasia in cerebellum (Courchesne *et al*., 1988; Bailey *et al*., 1998) and area dentata of the hippocampus (Saitoh *et al*., 2001), reduced parietal volume (Courchesne *et al*., 1993), thinning of the corpus callosum (Piven *et al*., 1997), abnormal overall brain volume (Piven *et al*., 1995) and deviant brain growth (Courchesne *et al*., 2001) noted in both children and adults with autism, suggest that special consideration be taken when interpreting functional results. Two approaches that have been described in the literature are the spatial normalization and the 'native space' approach; each associated with its own set of strengths and weaknesses. The spatial normalization approach, such as Talairach, is one of the most widely used analysis methods in the field of functional neuroimaging. Individual brains are warped into a 'standard space' by use of specific anatomical markers (e.g. superior edge of anterior commissure) identified for each subject. The strength of such an approach is detection of consistent sites of activation within a subject group, as well as easy detection of major global differences between two study groups (e.g. autism and normal). Such an approach is vital for understanding the ways in which functional patterns are consistent across individuals, and establishes more firmly hypotheses about regional functional specification in normal individuals (e.g. functional activity in the FG associated with face perception). However, this approach may be limited in providing information about individual differences and unique patterns of functional activity associated with populations with developmental brain defects. Consider the following hypothetical illustration: several autistic participants in a research study exhibit activation precisely in the FFA region of FG in response to faces; however, due to hypoplasia or hyperplasia of surrounding neural tissue differing in degree of severity for each individual with the disorder, the 'FFA' would not fall within the same Talairach coordinates after images were warped into standard space. Averaging such data would thus lead to the spurious finding of null results for FFA activity in autism.

During the alternative, or 'native space' approach, regions of interest (ROIs) are chosen *a priori* and manually traced for each individual subject on their unwarped MRI images. Functional values are obtained by measuring the proportion of functional activity that falls within individually-defined anatomical boundaries of each ROI. Because such an approach utilizes each subject's anatomical data to interpret their functional data, it respects individual differences in both structural morphometrics and volume. Furthermore, such a method promotes detailed inspection of the exact location and extent of functional activity for each subject. Such an approach might thus prove invaluable for discovering pathobiological trends in autism including those relating to compensatory neurofunctional reorganization, as well as defects in structure associated with defects in function within individual subjects. Although this approach affords high certainty regarding the localization of effects, a significant weakness is that regions and patterns of functional activation not chosen *a priori* as study ROI(s) may be missed. One possibility, therefore, is to analyse data using both spatial normalization and native space approaches (Pierce and Courchesne, 2000; Müller *et al*., 2001). While labour intensive, the marriage of these methods affords multiple advantages including: information about anatomical volumes for identified ROIs, certainty about localization of functional activity, identification of group trends and differences and detection of unexpected functional patterns. Since such a thorough combined approach provides the range of information needed to begin the study of neurofunctional organization in autism, it was thus adopted by the present study.

The purposes of the present study were to: (i) investigate basic face processing in a group of subjects with a clear diagnosis of autism using fMRI; (ii) establish links between neurofunctional activity with underlying anatomical abnormalities in patients with autism; (iii) test hypotheses regarding genetic or epigenetic processes in the development of specialized face processing regions. It was predicted that autistic individuals would show both a structural and functional defect in regions related to face processing, to include both the FG and amgydala. Furthermore, given the significant heterogeneity of biological defect in this disorder, it was predicted that individual subject data would reveal unique and non-overlapping patterns of activity between autistic patients, in contrast to the predicted consistent pattern in response to faces seen in normal subjects.

Methods

Subjects

Seven male adults with autism (age range 21–41 years) and eight normal controls (age range 20–42 years) participated. Subjects were diagnosed as autistic if they met criteria for autism based on all of the following diagnostic instruments: DSM-IV (American Psychiatric Association, 1994), Childhood Autism Rating Scale (Schopler *et al*., 1986), ADI (Autism Diagnostic Inventory; Le Couteur *et al*., 1989) and the ADOS (Autism Diagnostic Observation Schedule; Lord, 1999). Full-scale IQs (intelligence quotients), as evaluated

Table 1 *Subject information (autism group)*

	Subject						Mean (SD)
	1	2	3	4	5	6	
Gender	M	M	M	M	M	M	
Age (years)	23	33	41	35	21	24	29.5 (8.0)
Handedness*	Right	Right	Right	Left	Right	Left	
CARS†	35.5	32.5	30	36	39	31	34 (3.4)
ADI–R‡							
Social	30	25	-	21	28	22	25.2 (3.8)
Verbal	16	21	-	22	21	13	18.6 (3.9)
Non-verbal communication	14	14	-	12	14	8	12.4 (2.6)
Restricted interest and rep. behav.	11	7	-	10	7	6	8.2 (2.2)
IQ							
Non-verbal	81	80	92	106	81	87	87.8 (10.0)
Verbal	80	70	89	100	71	84	82.3 (11.3)
Full scale	79	73	89	102	74	85	83.7 (10.9)
Behaviour: face task							
% Overall accuracy	83.3	95	88.3	98.3	98.3	96.7	93.3 (6.12)
False alarms	8	1	0	1	1	2	
Misses	2	2	7	0	0	0	
Behaviour: control task							
% Overall accuracy	100	100	88.3	100	100	96.7	97.5 (4.7)
False alarms	0	0	0	0	0	2	
Misses	0	0	7	0	0	0	

ADI not available for subject 3. M = male. *Based on neurological examination; †Childhood Autism Rating Scale (cut-off score for autism = 30); ‡Autism Diagnostic Interview—Revised [cut-off scores for autism: social = 10, verbal = 8, non-verbal = 8, repetitive behaviour (rep. behav.) = 3].

by the Wechsler Intelligence Scale, ranged from 73–102 (mean 84) for the subjects with autism. None of the subjects were taking medication and all were found to be negative for fragile-X by DNA or chromosomal analysis. Autistic subjects were familiar with general fMRI procedures as the result of past participation in experiments. Due to excessive motion, one autistic subject was dropped from analyses. Table 1 provides descriptive information for the autism group.

Normal control subjects were screened for history of developmental, psychiatric or neurological disorders, and were matched on a one-to-one basis to autistic subjects for sex, chronological age and handedness. Mean ages in the autism and control samples were nearly identical (29.5 versus 28.3). The complete experimental protocol was approved by the Institutional Review Board of the University of California, San Diego and all subjects signed consent forms prior to entry in the experiment.

Imaging

Images were acquired on a GE Signa 1.5 T system using a custom-made head gradient coil. Axial localizers were used to select the range of sagittal slices for echo-planar image (EPI) acquisition. Whole brain sagittal images were acquired with a single-shot gradient-recalled echo-planar pulse sequence [TR (repetition time) = 2500 ms; TE (echo time) = 40 ms; flip angle = 90°; FOV (field of view) = 24 cm; number of slices = 19; slice thickness = 7 mm; slice gap = 1 mm; matrix = 64 × 64; time points = 98]. Subsequent to functional imaging, 19 echo-planar phase map images were acquired at each of the 19 slice locations, and used later to correct for EPI distortions caused by magnetic field inhomogeneities. Anatomical sagittal images (3D MP-RAGE pulse sequence: TR = 30 ms; TE = 5 ms; flip angle = 45°; matrix = 256 × 256 × 128; FOV = 24 cm; slice thickness = 1.2 mm) were acquired immediately after EPIs and were later co-registered with EPIs for functional analyses.

Image preprocessing and motion correction

An unwarping algorithm (Reber, 1998) using phase maps acquired during each session was applied to correct for distortion of EPIs due to magnetic field inhomogeneities. The first two time points of each time series (corresponding to the first 5 s of data acquisition), are typically characterized by magnetic field inhomogeneities, and were discarded from further analyses.

In order to correct for motion distortion, an automated alignment program was used (Cox, 1996). The basic technique aligns each volume in a time series to a fiducial volume (in this case, time point 49, the mid-point of the imaging run), using an iterative process (Cox and Jesmanowicz, 1999). No significant differences were found between groups.

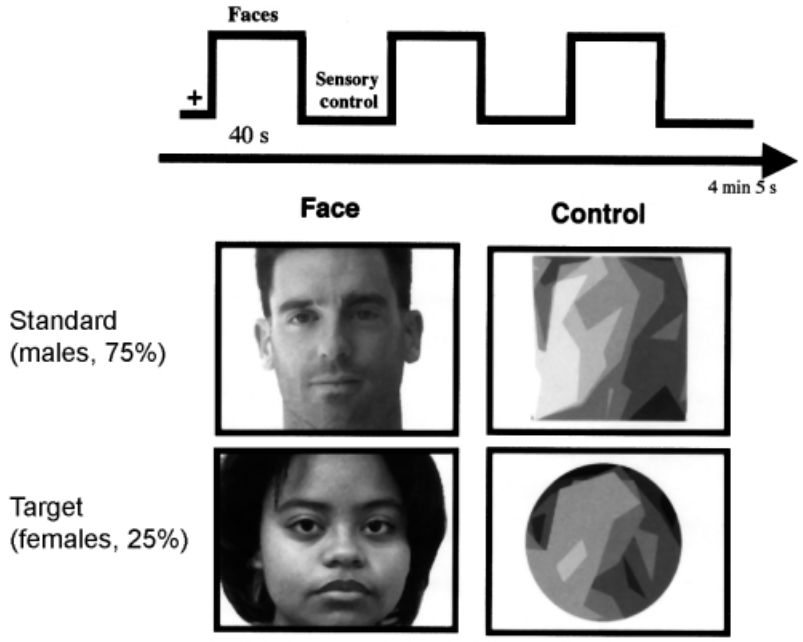


Fig. 1 Boxcar wave function illustrating the alternating face perception and shape perception (control) tasks and sample stimuli. During the 4 min, 5 s scan, subjects viewed a series of 120 non-repeating pictures (60 faces and 60 shapes) across six blocks (20 pictures per block) and pressed a button in response to target stimuli (female faces or circles).

Experimental conditions

Changes in blood oxygen level-dependent contrast were measured as subjects performed a face perception task (i.e. button press in response to female faces) alternating with a shape perception task (button press in response to circles). During the 4 min, 5 s scan, face perception and shape perception conditions alternated in a standard block design (six blocks, 40 s each; the words 'female' or 'circle' were presented as task reminders during the first second of each block). One hundred and twenty non-repeating stimuli were presented for 1.5 s, with a 450 ms inter-stimulus interval. Face stimuli were 60 non-repeating, full-face, neutral expression, grey scale photographs of males (standards) and females (targets). In order to equate the grey scale and mean luminance between the two conditions, each of the face images was morphed into either a square (standard) or circle (target). See Fig. 1 for task design and an example of stimuli. Standards and targets were presented at a 3 : 1 ratio for both tasks. All subjects practised a short version of the tasks prior to entering the scanning session using stimuli not used during testing.

ROIs

Prior to analyses, three cortical ROIs: FG, ITG and middle temporal gyrus (MTG), and one subcortical ROI (amygdala) were manually traced on unwarped, high-resolution anatomical images for each subject. Figure 2 illustrates both the location and extent of the ROIs. The fusiform gyrus was selected as the primary cortical ROI due to reported consistent involvement of this structure during face processing tasks (Allison *et al*., 1994; Farah, 1996; Haxby *et al*., 1996; Puce *et al*., 1996; Kanwisher *et al*., 1999). In the event that compensatory mechanisms may have involved the re-mapping of face processing to nearby cortical tissue in autistic subjects, ITG and MTG were chosen as secondary cortical ROIs to serve as contrast sites to the FG. Furthermore, both structures have been shown to be responsive to both faces and objects, but more consistently to objects than faces (Sergent *et al*., 1992; Allison *et al*., 1994). If subjects with autism process faces as objects, as has been suggested by Schultz and colleagues (Schultz *et al*., 2000), then increased cortical activity in these regions might be observed.

The methodology utilized to define the cortical ROIs (in particular the FG) was dictated by the following consideration: possible group differences in the volume of the FFA subregion within the fusiform gyrus cannot be precisely determined because there are no known gross anatomical landmarks defining the extent of this region on individual *in vivo* MRIs. However, potential differences between autistic and normal subjects can be reasonably assessed by measuring the volume of grey and white matter that encompasses the possible range of the FFA within a comparable length of the fusiform cortex in each subject. Therefore, for each subject, the FG ROI was defined as that

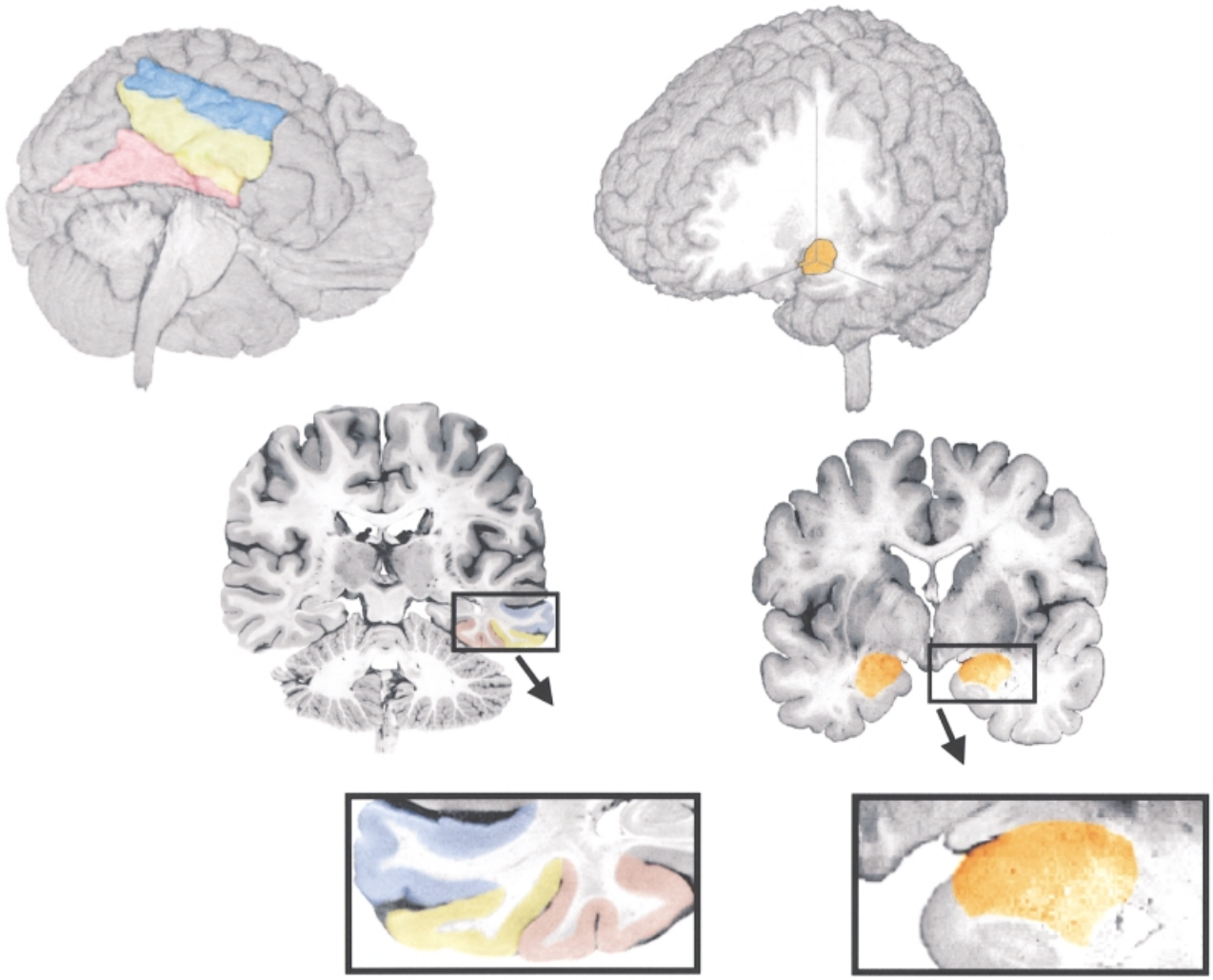


Fig. 2 Depiction of location and extent of cortical (middle temporal gyrus, blue; inferior temporal gyrus, yellow; fusiform gyrus, red) and subcortical (amygdala, orange) ROIs used for analyses in 'native' (i.e. unwarped) space on 3D-volume rendered brains. Below, coronal slices show a close up view of anatomical boundaries used for tracing ROIs. Coronal images courtesy of the University of Washington Digital Anatomist Program.

volume of cortex beginning with the slice located at the temporo-occipital notch and extending anteriorly in the coronal plane 35.1 mm (36 slices × 0.975 mm). The same boundaries were used to define the extent of the ITG and MTG measurements; however, for these secondary ROIs every fourth slice (corresponding to each functional slice) was measured and volumes were obtained by multiplying area measures by four. Therefore, all three structures were traced on the same set of coronal MRIs in the slice range depicted in Fig. 2. For the one subcortical ROI, the amygdala, the entire structure was traced by expert anatomists (procedure described below). Anatomical identification of ROIs was performed by experienced anatomists and was guided by human brain atlases (Duvernoy, 1991; Jackson and Duncan, 1996; Mai *et al*., 1997). For all ROIs fully automated algorithms linked anatomist-determined landmarks and automatically calculated associated volumes. The following is a description of anatomical landmarks used during ROI measurements.

Fusiform gyrus

The FG lies immediately lateral to the parahippocampal gyrus in the temporal lobe and extends for most of the length of the inferior occipitotemporal surface. The medial boundary used during tracing was defined by the collateral sulcus and the lateral boundary by the temporo-occipital sulcus, which runs anterior to posterior from the temporal pole to the occipital gyrus. The superior boundary was defined by a straight line between the cortical ribbon at the apex of each sulcus.

Inferior temporal gyrus

The ITG runs anterior to posterior from the temporal pole to the temporo-occipital incisure, which borders the lateral

occipital gyrus. The medial boundary was defined by the temporo-occipital sulcus, and the lateral boundary by the inferior temporal sulcus. The superior boundary was defined by a straight line between the cortical ribbon at the apex of each sulcus.

MTG

The MTG runs anterior to posterior from the temporal pole to the parietal–temporal border, at which point it becomes angular gyrus. The medial boundary was defined by the superior temporal sulcus and the inferior boundary by the inferior temporal sulcus.

Amygdala

Volumes were measured using 3D reconstructed datasets allowing anatomist-determined landmarking and tracing in axial, coronal and sagittal views; tracings followed established anatomical conventions (Jack *et al*., 1992; Shenton *et al*., 1992; Watson *et al*., 1992; Cendes *et al*., 1993; Bilir *et al*., 1998; Aylward *et al*., 1999*b*; Convit *et al*., 1999) and included the following definitions and procedures. Laterally and antero-inferiorly, tracings of the amygdala were bounded by the white matter of the temporal lobe, including the anterior commissure. Postero-inferiorly, tracings were bounded by the temporal horn of the lateral ventricle. Superiorly and medially, tracings followed the margin of the temporal lobe to the lateral termination of the entorhinal sulcus, and to complete the medial boundary so as not to include the entorhinal area or gyrus ambiens, a straight line was drawn from the semi-annular sulcus along the superior–lateral border of the alveus to the most medial extent of the temporal horn of the lateral ventricle. Using the sagittal plane and beginning with the most medial slice where the temporal lobe was present, a line was drawn along the superior margin of the temporal lobe. This was continued, moving laterally, until the margin of the temporal lobe no longer extended posterior to the optic tract. At that point, the margin of the temporal lobe was traced to its posterior extent. Next, a straight line was drawn from this posterior extent tangential to the inferior aspect of the anterior commissure and another straight line was drawn from the inferior border of the anterior commissure to the inferior border of the optic tract. These lines together defined the superior and anterior boundaries of the amygdala on the more lateral slices.

Statistical analyses

Anatomical analyses of ROIs in 'native space' using unwarped images

The volumes (in cm^3) for each ROI were calculated based on the anatomical measurements described above. *t*-Tests were then performed that contrasted the volumes for each ROI between patients and control subjects (one-tailed for FG and amygdala, two-tailed for ITG and MTG).

Functional analyses of ROIs in 'native space' using unwarped images

Correlational analyses based on a study by Bandettini and colleagues (Bandettini *et al*., 1993) were performed using the Analysis of Functional Neuroimages package (Cox, 1996). Changes in MR signal intensity within voxels were correlated with a haemodynamic model response function, consisting of a boxcar wave with sloped sides approximating the anticipated rise time of the MR signal. Significantly activated voxels were those which exceeded a threshold equivalent to one-tailed $P < 0.05$, Bonferroni corrected for multiple comparisons based on the total number of voxels within the ROIs. For each ROI, activation volume was divided by the anatomical volume to yield a percentage volume active measure. *t*-Tests were subsequently performed between patients with autism and the normal group for percentage volume active values.

Functional analyses of group-averaged Talairach-normalized images

In order to identify activations that may have occurred outsides ROIs, data were transformed into Talairach space, using a landmark-based nonlinear normalization algorithm (Cox, 1996). EPIs were smoothed with a 1-voxel Gaussian filter, and groupwise *t*-tests were performed. Statistical maps for within-group comparisons were created using a *t* statistic based on the mean absolute difference in voxel intensities between experimental and control conditions. Significance was established using a voxel-cluster threshold technique (Forman *et al*., 1995) for an overall alpha level of 0.05 (voxelwise $P < 0.0001$; cluster size $\geqslant 512$ mm^3).

Results

Behavioural performance

Subjects with autism were not significantly different from normal controls in terms of accuracy and response times on either the face (autism 93.3% ± 6.12, mean ± SD, 708 ms ± 111, versus normal 99.7% ± 0.68, 683 ms ± 161) or shape (autism 97.5% ± 4.7, mean ± SD, 639 ms ± 89, versus normal 100%, 616 ms ± 142) perception tasks. Behavioural performance data for individual autistic subjects can be found in Table 1.

Anatomical analyses of ROIs

The analysis of structural volumes revealed that amygdala volumes were significantly smaller bilaterally in the autism group compared with the normal group. As can be seen in Table 2, the amygdala was reduced on average by ~15% in

Table 2 *Regions of interest (ROIs): structural and functional volumes and percentage of ROI active*

ROI	Hemisphere	Structural volume (cm^3)		*P*-value	Functional volume (cm^3)		% ROI activated		*P*-value
		Autism	Normal		Autism	Normal	Autism	Normal	
Fusiform gyrus	Right	4.95 ± 1.03	5.45 ± 0.93	n.s.	0.19 ± 0.13	0.85 ± 0.38	3.77 + 0.02	15.74 + 0.07	0.0005
	Range	(3.6–6.1)	(4.3–6.5)		(0.03–0.39)	(0.44–1.6)	(0–0.07)	(0.08–0.26)	
	Left	4.76 ± 1.27	5.07 ± 0.67	n.s.	0.11 ± 0.15	0.39 ± 0.24	2.50 + 0.03	7.33 + 0.04	0.01
	Range	(3.1–6.8)	(4.0–5.6)		(0–0.28)	(0.09–0.85)	(0–0.07)	(0.02–0.15)	
Inferior temporal gyrus	Right	5.72 ± 0.66	6.31 ± 1.56	n.s.	0.13 ± 0.11	0.32 ± 0.24	2.29 + 0.02	5.20 + 0.04	n.s.
	Range	(4.9–6.7)	(4.2–9.6)		(0.07–0.34)	(0–0.67)	(0–0.06)	(0–0.11)	
	Left	5.89 ± 0.87	6.55 ± 1.45	n.s.	0.09 ± 0.09	0.24 ± 0.27	1.74 + 0.02	3.77 + 0.04	n.s.
	Range	(4.5–6.7)	(4.1–8.9)		(0–0.25)	(0–0.81)	(0–0.04)	(0–0.12)	
Middle temporal gyrus	Right	7.40 ± 1.58	7.51 ± 0.58	n.s.	0.10 ± 0.10	0.12 ± 0.16	1.38 + 0.01	1.50 + 0.02	n.s.
	Range	(5.3–9.2)	(6.4–8.0)		(0–0.29)	(0–0.40)	(0–0.03)	(0–0.04)	
	Left	6.68 ± 1.45	6.41 ± 1.02	n.s.	0.15 ± 0.13	0.18 ± 0.37	2.07 + 0.02	2.17 + 0.05	n.s.
	Range	(5.7–9.5)	(5.4–8.2)		(0–0.30)	(0–1.0)	(0–0.03)	(0–0.12)	
Amygdala	Right	0.87 ± 0.12	1.01 ± 0.11	0.025	0.04 ± 0.06	0.06 ± 0.05	4.04 + 0.68	6.21 + 0.05	n.s.
	Range	(0.73–1.0)	(0.81– 1.1)		(0–0.16)	(0–0.14)	(0–0.17)	(0–0.12)	
	Left	0.92 ± 0.13	1.09 ± 0.13	0.02	0.05 ± 0.07	0.21 ± 0.10	4.97 + 0.07	19.80 + 0.10	0.008
	Range	(0.71–1.0)	(0.92–1.3)		(0–0.17)	(0.12–0.35)	(0–0.16)	(0.06–0.35)	

The data presented are means and standard deviations with range in parentheses. All *P*-values represent Bonferroni corrected values.

the autism group. FG volume in the autism group was also smaller, on average ~8% smaller, than in the normal group but this difference did not reach significance. ITG and MTG volumes were not significantly different between subject groups.

Functional analyses of ROIs in 'native space' using unwarped images

As shown in Table 2, the percentage volumes of activation were smaller in the autism group bilaterally in the FG, as well as in the left amygdala compared with normal controls. No group differences were observed in the right amygdala, ITG and MTG.

Consistent with the majority of studies in the literature, normal subjects in the present study showed significantly greater percentage volume active to faces in the right than in the left FG ($t = 3.63$, $P < 0.008$). On average, the percentage volume active in the right FG in the normal group was four times greater than in the autistic group (Table 2).

Functional analyses of group-averaged Talairach-normalized images

Group-averaged whole brain data were additionally analysed in Talairach normalized space in order to verify these ROI-based results and to further investigate whether there were regions of functional activity that may have occurred outside the study's four primary ROIs. After correction for multiple comparisons using a cluster threshold model, within-group *t*-maps replicated the main results from the native space ROI analyses. Specifically, the FG and amygdala in normal subjects showed robust activation, but in the autism group there were no neural regions of positive activation that reached the significance threshold (Fig. 3). Furthermore, functional activation in ITG and MTG showed no group differences**.**

In the normal group, analyses revealed two additional regions, inferior occipital gyrus and superior temporal sulcus, that responded significantly more to faces than to control stimuli. In contrast, there was no activation in these two additional sites that met the correction threshold in the autism group.

In both subject groups, deactivations, which will be referred to as 'reverse-activations' were seen in some scattered regions (Fig. 3). For the autistic subjects, significant clusters of reverse-activations were noted in left postcentral gyrus, left inferior parietal lobe, right cingulate and right parahippocampal gyrus. For the normal group, significant clusters were found in bilateral cerebellum and bilateral superior and inferior parietal lobes.

Examination of individual-specific sites of maximal activation

Because analyses of spatially normalized as well as native space data revealed no consistent location of significant activation in response to faces in the autism group, data from individual autistic patients were visually inspected. This examination suggested that each autistic patient had a distinct region of functional activation in response to faces throughout cerebral cortex and cerebellum, which stands in contrast to the consistent FG activation noted in normal subjects. Given this observation, after spatial normalization, functional foci of maximal signal intensity or 'hot spots' that met the significance threshold were identified for each individual autistic and normal subject. Intensity was defined as the least squares fit of each voxel time series. For every normal subject, the site of maximum signal intensity or 'hot spot' in response to faces fell within the fusiform face area, as seen in Fig. 4. In contrast, each autistic patient displayed a unique functional hot spot location in response to faces ranging from the frontal lobe, FG (i.e. 'FFA'), occipital lobe, anterior FG, cerebellum and frontal lobe, for Subjects 1–6, respectively (see Fig. 4).

Correlations involving functional activation and anatomical volume

The percentage functional volumes activated in right FG and right amygdala were significantly correlated in the autistic patients ($r = 0.86$, $P < 0.02$), but not in normal subjects ($r = –0.09$). Also, in the autistic patients, there was a trend involving the left amygdala in which reduced percentage volume activated tended to be associated with reduced anatomical volume ($r = 0.65$, $P < 0.15$). In normal subjects, there was a strong positive correlation between greater percentage volume activated and anatomical volume for the left amygdala ($r = 0.80$, $P < 0.02$). No other significant correlations or trends were found between FG and amygdala structure in either group.

Discussion

In striking contrast to virtually every existent fMRI study of face processing in normally developed humans (Cabeza and Nyberg, 2000), we found that in our patients with autism, a disorder involving profoundly reduced experience with faces throughout development, there was either abnormally weak or no activation in the FFA in response to the human face. The FFA was the site of maximal activation for only one autistic patient, and in this single case the volume of activation was less than that in every normal individual. In every other autistic patient, faces maximally activated aberrant and individual-specific neural sites (e.g. frontal cortex, primary visual cortex and cerebellum). Thus, compared with normal individuals, autistic individuals 'see' faces utilizing different neural systems, with each patient apparently doing so via a unique neural circuitry.

The present study is the first to investigate basic face perception using exclusively a sample of patients with autism. The overall finding of decreased bilateral FG as well as

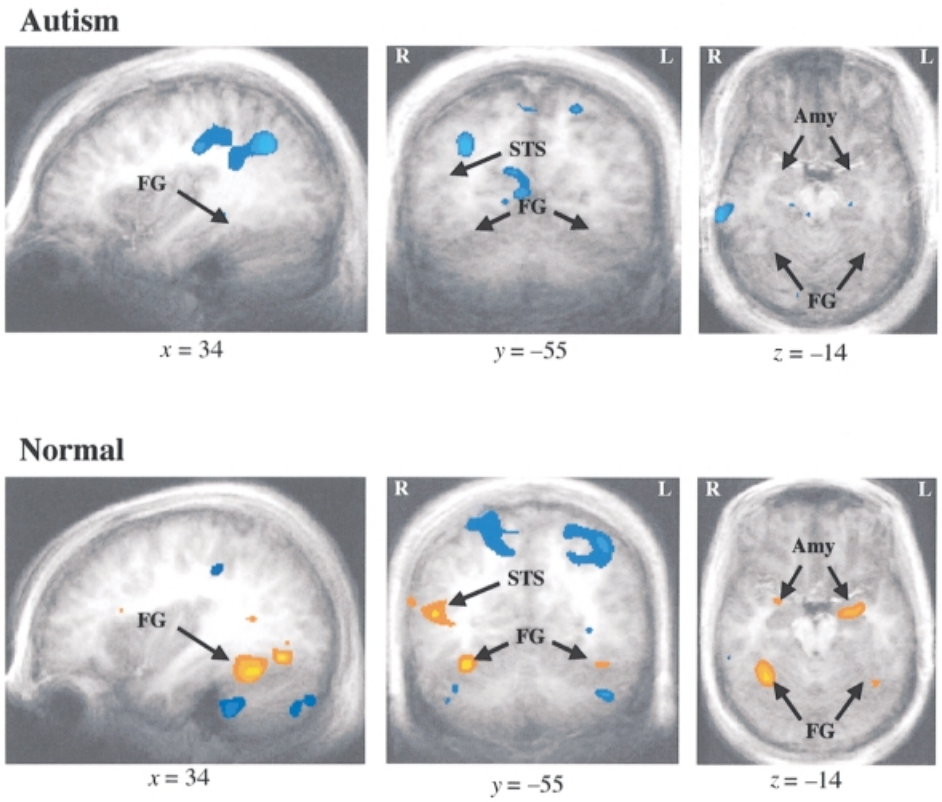
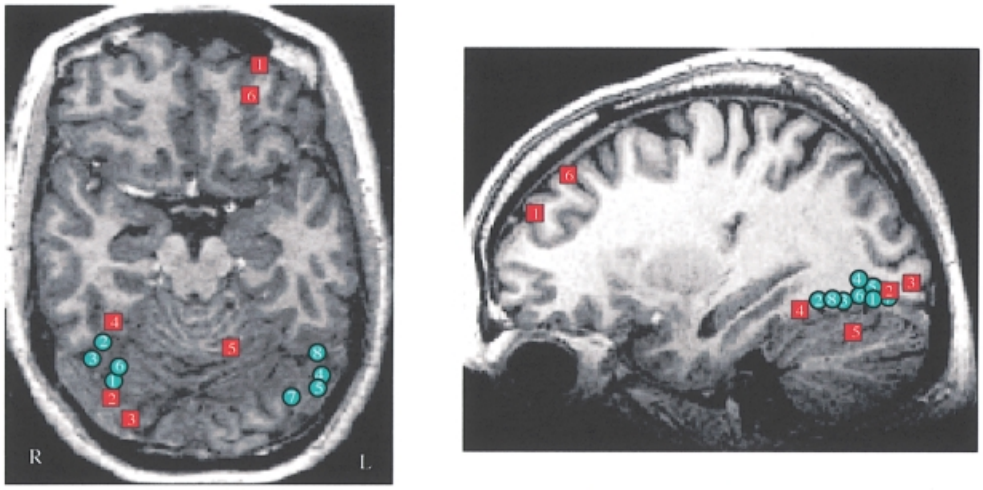


Fig. 3 Within group *t*-maps for both autism and normal groups showing significant regions of activation (statistically significant positive activation noted by yellows and orange, deactivation noted by blues). Note FG, superior temporal sulcus (STS) and amygdala (Amy) activation in normals, in comparison with a lack of positive activation in the autism group. Decreased functional activity in the autism group is likely due to the inconsistent patterns of activation noted across individual autism subjects, which would fail to be seen when results are averaged. Also see Fig. 4 for an illustration of inconsistent functional maps in autism.

amygdala activity in the autism group is consistent with other studies that utilized mixed patient samples of both autism and Asperger's subjects (Critchley *et al*., 2000; Schultz *et al*., 2000). In addition to differences in sample constituency and tasks (e.g. basic face perception versus emotion perception) between the present study and others, one interesting difference relates to the pattern of neurofunctional activity observed in group averages. For example, Schultz and colleagues reported increased activity in unexpected neural regions (i.e. ITG) in the autism/Asperger's subject group during a face perception task (Schultz *et al*., 2000). In contrast, the present study found an absence of positive functional activity in the autism group averaged data. One possibility is that differences in study populations contributed to these different functional patterns of activity. Another possibility relates to the noted reduction in temporal cerebral blood flow in autism (Gillberg *et al*., 1993; Chugani *et al*., 1996; Ryu *et al*., 1999), which would make assaying functional activity in this region difficult. Furthermore, it is currently unknown whether patterns of cerebral vasculature are different from normal in this disorder. The most likely explanation, however, relates to the clear evidence of unique and non-overlapping functional maps in response to faces for the autistic subjects in the present study; some individuals exhibited a maximal response to faces in frontal cortex, while others in temporal cortex, while another in occipital cortex and, finally, in the cerebellum. Given this lack of overlap between subjects, an average of such data would result in an overall image showing no positive functional activity (see below for further discussion). In contrast, such group-averaged data did show several regions of deactivation including postcentral gyrus, inferior parietal lobe, cingulate and parahippocampal gyrus for autistic subjects. Although the precise interpretation of deactivations is not firmly established, one possibility is that they reflect enhanced neural processing during the control condition in comparison with the experimental condition and are thus often referred to as 'reverse-activations'. Therefore, the presence of significant clusters of reverse-activations highlights the fact that there were consistent regions of activation across subjects during the shape processing condition for autistic subjects. Significant clusters of reverse-activations may also suggest that subjects displayed preferential attention to the visually complex shapes in the control condition in comparison with the faces.



Subject	BA	Talairach coordinates *x*	*y*	*z*
1	L. middle frontal (10)	−26	55	20
2	R fusiform (19)	22	−81	−8
3	R post. fusiform/inf. occipital (19/18)	30	−73	−12
4	R ant. fusiform (36/37)	30	−45	−16
5	L cerebellum	−18	−57	−28
6	L middle frontal (9)	−26	43	36

Fig. 4 After spatial normalization, centres of maximum signal intensity for each subject were identified using the program 3dclust in AFNI (Analysis of Functional Neuroimages). Each symbol represents an activation 'hot spot' for a single subject as overlaid on both an axial and sagittal image. For purposes of illustration, peak activations were collapsed across the superior to inferior axis on the axial image and were collapsed across the left to right axis on the sagittal image. Autism = red squares 1–6, normal = green circles 1–8. Note that the region with the highest signal intensity change between experimental and control conditions for *all* normals is located within the fusiform gyrus (green circles), in contrast to hot spots across the cerebrum and cerebellum for autistic participants. Talairach coordinates for each 'hot spot' for autistic subjects are listed below.

The finding of fractionated and inconsistent neurofunctional maps across individual autistic subjects in response to faces has also been found during a simple motor task with autistic patients (Müller *et al*., 2001), and raises perhaps the single most important question of this research: how do such unique functional maps in autism occur? Several likely interacting possibilities are present. First, new data suggest the general phenomenon of misguided brain growth in autism. Courchesne and colleagues reported that in a sample of 60 autistic and 52 normal children ranging in age from 2 to16 years, by the age of 2 years, 85% of autistic children had brain volumes larger than the normal average (Courchesne *et al*., 2001). This accelerated growth, however, did not continue into adolescence, where brain volume measures were not different from normal. Furthermore, a new study by Nelson and colleagues reported that from the earliest days of life, concentrations of certain brain growth factors [BDNF (Brain derived neurotrophic factor), NT-4 (Neurotrophin 4), VIP (vasoactive intestinal peptide) and CGRP (Calcitonin gene related peptide)] NT-4 (Neurotrophin 4), VIP (vasoactive intestinal peptide) and CGRP (calcitonin gene-related peptide)] were elevated in 97% of the autism neonate blood samples studied, but only 9% in children with cerebral palsy and 0% of normal controls (Nelson *et al*., 2000). Although an intriguing possibility, it is currently undetermined whether the aberrant overexpression of these important brain growth proteins early in development plays a role in the enlarged cerebral volumes in children with autism found by Courchesne *et al*. (2001). Taken together, however, such data do suggest that from the first days of life, the autistic brain may not be organized to receive environmental stimulation in an optimal way. Activity-dependent mechanisms that normally assist in the development and refinement of regional functional differentiation would therefore fail to provide optimal guidance for the developing autistic brain. The degree and extent of early neural abnormalities, as well as differences in the type and intensity of environmental stimulation for each affected child, would predict unique compensatory mechanisms, and thus unique processing nodes, for each individual with the disorder.

In addition to the presumed effects of basic molecular defects on widespread cerebral abnormalities present at an

early age in autism, concomitant effects on specific neural structures, such as the amygdala, are likely to be pivotal to the social phenotype of autism. Our finding of decreased structural amygdala volume is consistent with those of Aylward and colleagues (Aylward *et al*., 1999*a*), but inconsistent with Haznedar and colleagues and Howard and co-workers, who found either no difference, or an increase in amygdala volume between autism and normal, respectively (Haznedar *et al*., 2000; Howard *et al*., 2000). This discrepancy across studies is again likely attributable to differences in the constituency of the subject population. Both Aylward and colleagues and the present study used a sample of definite autism cases as diagnosed by multiple diagnostic instruments such as the ADI and ADOS, whereas both Haznedar and colleagues and Howard and colleagues utilized a mixed group of both autism and Asperger's subjects. Importantly, when data were distinguished by subject population, Haznedar and colleagues reported that left amygdalar volumes were larger in the Asperger's patients than in those with autism. Such a report not only implies that the neurobiology is different between groups, but also, that mixing such subjects during analyses may make finding true neurobiological themes difficult.

Nonetheless, the abnormal amygdala structure and function noted in the present study is consistent with the idea that the amygdala is abnormal in autism (Bauman and Kemper, 1994; Baron-Cohen *et al*., 2000; Howard, 2000). During normal development, the amygdala plays a key role in establishing the social significance of a face: it functions to assist the infant in interpreting a face as threatening or fearful (Morris *et al*., 1999), monitoring eye gaze (Kawashima *et al*., 1999) and might be related to assigning hedonic values to stimuli in general (Baxter *et al*., 2000). An absence of normal amygdalar functioning would thus prevent many of the normal social perceptual activities of a newborn and young child. Activity-dependent mechanisms that normally assist in the development and refinement of this structure would therefore be stymied. Malfunction of the amygdala from birth in autism might thus be an essential neural insult that initiates a cascade of social maldevelopment in this disorder. Furthermore, amygdala defects probably prevent effective afferent and efferent connections with other neural regions, in particular, the fusiform gyrus. Interestingly, FG volumes were smaller in autism in comparison with normal subjects, but volumes were not significantly different between groups.

Unlike autistic subjects, 100% of normal subjects in the present study showed maximal neural responsiveness to faces in the FG. Two opposing explanations have been put forth to explain the invariance of FFA activation in response to faces in normal subjects. One interpretation is that such a phenomenon reflects an innately determined face module that is specific to, and required for, face processing (i.e. the 'domain specific' view) (Kanwisher, 2000). The other view posits the FFA as an experience-dependent neural region, evolved to process subordinate levels of an extremely familiar class of objects (i.e. the 'domain general' view) (Tarr and Gauthier, 2000). Our results suggest that the FFA is not necessary for face processing and thus does not provide support for the domain specific view. Instead of utilizing the FFA, autistic subjects activated multiple and distinct non-FFA regions, ranging from the frontal lobes to the cerebellum, in response to faces. Such a finding suggests that multiple neural regions may be capable of supporting face processing. Although current thinking about functional organization has evolved well past Lashley's notion of equipotentiality (Lashley, 1950), some theorists (Rakic *et al*., 1991; Schlaggar and O'Leary, 1991) have provided interesting evidence of early developmental pluripotentiality of neocortical tissue. If the FFA is indeed specialized to process faces, then the domain specific view might predict FFA activation in autism, but simply at a lower level in all patients. Our results, however, suggest that minimal FFA activation occurred in autistic subjects and, in one subject, FFA activity was essentially absent (i.e. $<1\%$ ROI active). Such low levels of activation occurred in the context of high accuracy and normal reaction times during the face perception task.

The alternative interpretation, the domain general view, would predict low or absent FFA activity in autism in response to faces, because such subjects have minimal expertise or experience in processing subordinate level features of this class of stimuli. fMRI evidence for the domain general view comes from a recent study by Gauthier and colleagues where normal subjects were trained to become experts with a certain class of objects (i.e. 'greebles') and exhibited FFA activity in response to such stimuli only after training (Gauthier *et al*., 1998). It is interesting to note, however, that experiential effects on FFA activity occurred after only 10 hours of 'greebles' training. Although autistic subjects are profoundly face-inexperienced compared with normal individuals, they have surely accumulated sufficient exposure to show such an effect, and yet they do not recruit FFA to process faces. One explanation is that there is a critical period for the development of the FFA that was missed by autistic subjects. This critical period may not be for experience with faces *per se*, but for distinguishing between exemplars of a class of objects, with faces coincidentally being the most consistently present class of objects for newborns and children during such a time. Once this discrimination skill is learned and represented in the FFA it can be applied at any point in life to any class of objects, whether they are faces, greebles, cars or birds. Particularly during periods of neurofunctional refinement, the FFA probably works in concert with other neural regions, such as frontoparietal networks involved in attention. Defects in attention are well documented in autism (Courchesne *et al*., 1994) and may thus contribute to the lack of mature development of the FFA in this disorder.

The present study utilized both a 'native space' as well as spatially normalized group average approach for analysing results. As predicted, such a method provided a rich foundation from which to interpret results; the native space data provided structural volumes for selected ROIs, precise

functional localization for individual subjects as well as individual-specific functional profiles. The spatially normalized data provided additional information regarding regions outside of selected ROIs that were part of the normal subjects' face processing network (i.e. superior temporal sulcus and inferior occipital gyrus), but were absent in patients with autism. Furthermore, this group-average approach afforded the opportunity to look for consistent themes of face processing in the autism group and suggested the idea that there was in fact an absence of a consistent pattern in these subjects. In further combination with other neuroimaging strategies that will provide information on cerebral blood flow (i.e. perfusion imaging) and fibre connection patterns (i.e. diffusion tensor imaging), the neurofunctional study of social perception in autism is poised to begin to elucidate perhaps the most enigmatic aspect of the disorder: why do people with autism avoid social contact?

Although the sample size in the current study was small and results need to be replicated before definitive conclusions can be reached, the present study presents fMRI evidence which favours the view that experience with the human face during development is likely to play a critical role in specifying the neural sites that are maximally responsive to faces, with extremely aberrant developmental experience contributing to extremely aberrant functional maps. Such a view, however, should be interpreted in the context of evidence that suggests fundamental brain abnormalities, such as elevated levels of brain proteins and enlarged cerebral volumes, from an early age in autism. Such abnormalities probably provide a molecular and structural foundation for the difficulties in deriving maximal benefit from environmental stimulation for children with this disorder. Thus, defects in neurobiology both beget and interact with defects in experience. Furthermore, abnormal neurofunctional responding to faces in autism is probably the result of inefficient or faulty networks that extend beyond the FFA and amygdala and include those relating to top-down processes, such as frontoparietal networks involved in attention.

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