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The brain response to personally familiar faces in autism: findings of fusiform activity and beyond

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Summary

Past functional MRI (FMRI) studies of autism have reported reduced activation in response to the faces of strangers primarily in the 'fusiform face area' (FFA). An alternative and potentially stronger test of FFA function in autism is one that attempts to affect levels of FFA activity using factors believed to modulate function in this brain region, such as face familiarity and the perception of face identity. The current study presented personally meaningful faces, such as mother and co-worker, as well as stranger faces in a rapid event-related FMRI design. Seven autistic and nine normal control adults participated and pressed a button in response to all female faces. A deconvolution analysis revealed significant FFA activity in response to familiar and stranger faces in both autism and normal control groups. Individuals with autism also showed greater fusiform activity in response to familiar faces than stranger faces, as well as the prototypical right hemisphere dominance in response to both types of faces. Normal subjects showed additional activation to familiar faces in the posterior cingulate, amygdala and medial frontal lobes, including the anterior cingulate. Subjects with autism showed a similar, but more limited, network in response to familiar faces. This network included the amygdala and implies that this structure, involved in multiple socio-emotional functions, can be responsive in autism in the presence of stimuli that represent high reward value, such as mother's face. Furthermore, the presence of a distinct network to process familiar faces in autism, one that included limbic structures and was not found in response to the faces of strangers, suggests socio-emotional processing in autism. A potentially noteworthy trend, however, was evidence for a reduction in medial frontal lobe function in the autism group. The main finding of FFA activity in autism stands in contrast to most past FMRI studies of face processing in this disorder. This positive result may reflect the use of personally significant faces that enhanced attention and motivation in the autistic participants. Furthermore, given the proposed role of the FFA in establishing person identity, the use of almost a dozen different personally familiar faces for each participant (totalling 32 non-repeating faces) may have additionally maximized FFA involvement. Therefore, dysfunction in the FFA found in other studies of autism may reflect defects in systems that modulate the FFA, rather than the FFA itself.

Keywords: autism; face processing; FMRI, fusiform face area; amygdala

Abbreviations: AFNI = Analysis of Functional Neuroimages; BOLD = blood oxygen level-dependent; FFA = fusiform face area; FMRI = functional MRI; IRF = impulse response function; ROI = region of interest.

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Introduction

The image of a person with autism is of someone with poor eye contact, abnormal emotion modulation and expression, and an aloofness that often makes him appear uninterested in the social world. Despite over 60 years of close scientific scrutiny, the pathobiology of such aberrant social behaviour remains elusive. One plausible and widely tested hypothesis is that face processing, a primary feature of most human social interactions, is impaired in autism. Such a pivotal dysfunction could stymie the development of more sophisticated social skills (Dawson *et al*., 2002). Behavioural studies report that people with autism have difficulties in making social–emotional judgements about faces (Weeks and Hobson, 1987; Tantam *et al*., 1989; Adolphs *et al*., 2001), reduced memory and recognition of faces (Boucher and Lewis,

1992; Klin *et al*., 1999; Blair *et al*., 2002), abnormal eye scan paths when viewing faces (Klin *et al*., 2002) and often fail to show the typical reduction in performance during face inversion tasks (Langdell, 1978; Hobson *et al*., 1988). Yet people with autism are not prosopagnosic, and may perform normally under certain face study conditions. For example, a recent study showed that when children with autism were shown faces in a naturalistic context (i.e. in motion), they were able to perform a face-matching task as well as normal children (Gepner *et al*., 2001). Using a control group matched on verbal mental age, Ozonoff *et al*. (1990) reported no significant group differences between autistic and normal children on an emotion face-matching task, and Celani *et al*. (1999) reported no group differences on a face identity task. Integrating the above findings, one might speculate that the underlying neural circuitry supporting face processing is abnormal, although not entirely dysfunctional, in autism.

The question of whether neural systems that mediate face processing are abnormal in autism has been addressed by functional imaging studies. Across several earlier studies, evidence appeared to be simple, clear and consistent: individuals with autism spectrum disorders have dramatically reduced functional activity in the middle lateral fusiform gyrus, a brain region often referred to as the 'fusiform face area' (FFA), when viewing the faces of strangers. For example, Schultz *et al*. (2000), Pierce *et al*. (2001) and Hubl *et al*. (2003) all found reduced FFA when people with autism processed faces of strangers in comparison to objects or complex patterns. Two studies that tested a variant of face processing that included decoding facial emotions in strangers also reported reduced fusiform activity in autism spectrum patients (Critchley *et al*., 2000; Hall *et al*., 2003). In light of such findings, Schultz *et al*. (2003) speculated that reduced FFA activity in autism may be a neurofunctional marker of the disorder.

In normal subjects, however, the neural response to faces is not an all-or-none phenomenon; factors such as familiarity, emotional valence and enhanced attention have been shown to modulate neurofunctional responding in the FFA. For example, Henson *et al*. (2000, 2003) showed that fusiform activity was greater when normal people looked at familiar faces in comparison with the faces of strangers. Vuilleumier *et al*. (2001) reported that FFA activity was greater in response to faces showing emotion than to faces with neutral expressions. Furthermore, Wojciulik *et al*. (1998) showed that when normal subjects overtly directed their attention to faces, FFA activity was enhanced relative to when attention was directed covertly.

Recently, two new functional MRI (FMRI) studies have raised the possibility that under certain experimental conditions, FFA activation in autism may not differ from normal (Aylward *et al*., 2004; Hadjikhani *et al*., 2004). One of these studies (Aylward *et al*., 2004) used a block design in which the face of a familiar person was shown repeatedly; the control condition was a block in which a picture of a car was shown repeatedly. Autistic subjects did not have significantly different activation from normal in the FFA in response to the familiar face. It is thus possible that, under conditions not investigated by earlier studies of face processing in autism, the FFA may in fact have near-normal or perhaps even normal levels and laterality of activation in patients with this disorder.

Therefore, the present study aimed to utilize more compelling and engaging face stimuli than those used in the earlier imaging studies of autism. Moreover, a stronger test of whether FFA is responsive to faces in autism would be to utilize face stimuli whose properties are known from basic studies to increase FFA activation in normal subjects, namely face familiarity, emotional significance and attention involvement, as well as to present the faces of strangers. Our study maximized this approach by presenting faces from the two extreme ends of the familiarity spectrum, namely, the faces of personally familiar people and those of complete strangers. The faces of family and friends not only bring the added dimension of familiarity to the stimuli, but they also bring personal emotional significance and interest for each subject in the experiment. Haxby *et al*. (2000) have presented a model that claims that the FFA is involved in determining face identity. Thus, our experiment that utilizes many different personally familiar faces potentially maximizes FFA involvement by presenting multiple opportunities to assign identity judgements to a particular face. To reduce the chance of spurious differential responding to one particular personally familiar face as well as habituation to a repeated presented face, almost a dozen different faces from among family and friends were used for each subject. To eliminate general arousal and attentiveness explanations for activation differences between control and contrast stimulus events, we utilized an event-related FMRI design with randomly ordered events, rather than a block design.

Besides providing a test of the strong version of the fusiform dysfunction hypothesis of autism, the present experiment enables tests of other brain regions that could also be activated by socially significant stimulation (such as familiar faces) based on previous studies of normal individuals. For example, the amygdala has also been shown to be engaged by faces (Whalen *et al*., 1998; Pierce *et al*., 2001). Similar to findings regarding the fusiform, past studies of autism have reported reduced amygdala activity in response to faces (for a review, see Baron-Cohen *et al*., 2000). While traditionally viewed as involved in the perception of stimuli that invoke fear or disgust (Medina *et al*., 2002), the importance of the amygdala in basic stimulus–reward learning, in particular as it relates to social learning, has been recently highlighted (Baxter and Murray, 2002). Therefore, the use of familiar faces, likely high in emotional reward value, might influence amygdala responding. In support of this idea, a recent FMRI study reported an increase in amygdala activity in response to personally familiar faces (Sugiura *et al*., 2001). Beyond the amygdala, socially salient stimuli have been shown to engage a wide range of brain regions, particularly in frontal and cingulate cortices (Adolphs, 2003).

Testing the neural response to personally familiar faces in people with autism also provides a unique opportunity to investigate broader issues of social interest in this disorder. Over the decades, the 'shorthand' description of people with autism seems to imply that they are socially detached, disinterested or aloof. The DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-4th edition) states that children with autism 'may treat adults as interchangeable, or may cling mechanically to a specific person' (American Psychiatric Association, 1994, p. 68). At the extreme, minimal differences in the haemodynamic response between the faces of familiar people and strangers might be expected if autistic individuals were indeed socially detached. On the other hand, the neural responses between familiar and stranger faces would be expected to be different if people with autism attribute personal or social meaning to a particular face.

The present FMRI study aimed to study face processing in autism by taking the first look at the following questions. (i) Can patterns of functional activity in the FFA and amygdala in autism be modulated by the use of multiple, highly familiar and socially significant faces, such as mother and co-worker? (ii) If people with autism show FFA activity in response to familiar faces, is this activity also normally localized (e.g. greater in the right hemisphere FFA)? (iii) Beyond the fusiform and amygdala, do people with autism process familiar and stranger faces differentially? If so, what brain regions are selectively engaged?

Subjects and methods

Subjects

Eight males with autism (age range: 16–42 years) and 10 normal controls (age range: 16–40 years) participated. Autistic subjects were recruited from the Children's Hospital Center for Autism Research, San Diego. All subjects or their legal guardians gave informed written consent. An autism diagnosis was based on meeting criteria on all of the following: DSM-IV (American Psychiatric Association, 1994), Autism Diagnostic Interview (ADI) and ADI-R, (Le Couteur *et al*., 1989; Lord *et al*., 1994) and the Autism Diagnostic Observation Schedule (Lord *et al*., 1989, 2000).

Full-scale intelligence quotients (FS IQs) obtained from the Wechsler Intelligence Scale (WAIS) and WAIS-R, ranged from 55 to 104 (mean 80.3) for the participants with autism. One autistic participant was taking anti-seizure medication and all were found to be negative for fragile-X by DNA or chromosomal analysis. One autistic participant (subject 5, Table 1) was dropped from the final analyses due to excessive motion during the functional scans. See Table 1 for further subject information.

Normal control participants were screened for a history of developmental, psychiatric or neurological disorders and were matched on a one-to-one basis to the final pool of seven autistic subjects for sex, chronological age and handedness. Subject pairs were considered 'matched' if they were the same age ± 2 years. Autism subjects 1, 2 and 8 (see Table 1) had two matches each. Autistic and normal participants were not matched based on IQ because of the co-morbid presence of mental retardation in some of the subjects with autism, thus eliminating this possibility. An alternative approach would be to use mentally retarded matched controls; however, given that the primary purpose of the study was to determine how autism differs from normal individuals, not those with mental retardation, this design option was not chosen.

Table 1 *Subject characteristics for the autism group*

Subject	1	2	3	4	5	6	7	8	Mean (SD)
Age (years)	24	34	42	36	22	18	16	25	27.1 (9.2)
Handedness	Ambi	R	R	L	R	R	R	R	
ADI-R									
Social	30	25	22	21	28	26	25	23	25 (3)
Verbal	16	21	19	22	21	19	16	12	18.2 (3.4)
Non-verbal communication	14	14	13	12	14	13	8	8	12 (2.6)
Restricted interests and repetitive behaviour	11	7	6	10	7	5	7	10	7.9 (2.2)
ADOS									
Communication	5	5	5	5	7	7	6	6	5.7 (0.89)
Social	13	12	7	11	13	9	12	10	10.9 (2.1)
Stereotyped behaviour	2	1	1	2	3	2	2	2	1.8 (.64)
IQ									
Performance	81	80	115	114	81	97	60	74	87.8 (19.4)
Verbal	80	70	86	98	71	94	69	<45	76.6 (16.9)
Full-scale	79	73	100	104	74	95	63	55	80.3 (17.7)

ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; ambi = ambidextrous; L = left; R = right.

One normal participant (the second match for autism subject 2) was dropped from analyses due to the presence of a cortical abnormality found on his MRI scan. Therefore, the final pool contained seven autistic and nine normal control subjects. The study was approved by the University of California San Diego Human Research Protection Program.

Stimuli

Two stimulus sets, 'familiar' and 'stranger', consisting of 32 black and white photographs, were used for each participant. The 'familiar' set consisted of faces of people well known by the participant (for at least 1 year), and included both family members and friends. A family member was defined as any individual related to the subject either genetically (e.g. mother or sibling) or by marriage (e.g. brother-in-law). All subjects had photographs of both their mother and father in their familiar picture set. A friend was defined as any non-family member with whom the subject was in regular contact and included purely social friends as well as co-workers and classmates. Approximately half of the familiar photographs were of 'family' and half were of 'friends' for each subject, with the exception of one normal

subject who was unable to obtain photographs of friends for his picture set. The overall goal was to obtain a set of photographs that contained the faces of people that were personally significant to each subject.

There were no group differences in the number of family [$t(14) = 0.69$, NS] or friend [$t(14) = 0.69$, NS] photographs between groups. Fifty percent of the photographs were of females and all photographs were non-repeating in an effort to avoid a 'repetition suppression effect' whereby the repeated processing of a stimulus produces a decreased response in brain regions associated with that processing (Henson *et al*., 2000). The experimenters, research associates, or the participants themselves took all the photographs of familiar faces using a high-resolution digital camera. Subjects being photographed were instructed to maintain a neutral facial expression.

The 'stranger' photograph set was comprised of faces of people unknown to the participant obtained from volunteers in the community. The experimenters took the pictures of the strangers, who were instructed to maintain a neutral facial expression. All photographs were edited to eliminate the background and insure that the overall size of the face and luminance was consistent across photographs. See Fig. 1 and Table 2 for more information.

Design and procedure

Photograph ratings

In order to determine if the quality of the facial expressions was comparable between the familiar and stranger faces, as well as across participants, one-third of the total pool of photographs were randomly selected and rated for quality of facial expression by 14 naïve subjects. Photographs were displayed individually on a computer screen for 2 s, followed by 10 s showing a blank screen. During this time, subjects rated each photo on a 7-point Likert-type scale ranging from negative to positive (ranging from −3 to +3 with a 0 rating denoting a neutral expression).

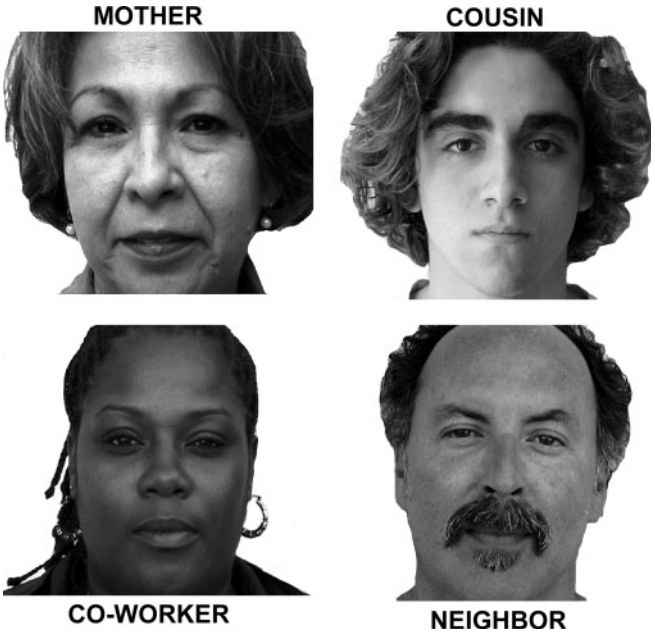

Fig. 1 Sample stimuli showing examples of familiar and stranger photographs. Subjects were instructed to press a button in response to every female face, which occurred during 50% of the trials.

Pre-scanning training

Three of the autistic subjects had no prior experience with participation in FMRI studies and received two approximately 1 h training sessions. During the first training session which took place in the home, subjects practised lying still on the floor while they listened to pre-recorded sounds of both MP-RAGE (magnetization prepared-rapid gradient echo; structural) and EPI (echo-planar imaging; functional) pulse sequences. During the second session, which took place at the UCSD MRI scanner, subjects were exposed to experimental conditions identical to what they would be experiencing during the actual study, with the exception of the photographs which were of strangers, and used only during practice.

Experimental procedure

Participants lay supine within the MR scanner with their head secured in foam padding during each experimental run. A Pentium III-based desktop computer using the Presentation software package (Neurobehavioral Systems, Inc., Albany, CA; http://www.neurobehavioralsystems.com) controlled stimulus presentation and behavioural response acquisition. A video projector displayed stimuli from within the MR control room onto a back-projection screen located at the foot of the MR scanner gurney. Participants viewed the stimuli using a 90° mirror attached to the head coil above their eyes.

Photographs of faces of familiar people and strangers were interspersed amongst trials that presented a black fixation cross of the same length and width as the photographs, against a white background in a rapid event-related FMRI design. The experimental run consisted of 133 trials, with each trial 2500 ms in duration (total scanning time = 5 min 32.5 s). In 64 of the trials, 32 photographs of familiar faces and 32 photographs of strangers were presented for 2000 ms followed by 500 ms of a white screen. Another 32 trials presented pictures from a second set of stranger faces that had eyes gazing to either the right or the left. This second set of stranger faces was not included in the analyses of this study. The remaining 37 trials presented the black fixation cross for 2500 ms (null trials). Participants were instructed to remain fixated on the centre of the screen and press a button to pictures of females using their dominant hand. Participants indicated their responses using a custom-designed optic-fibre single-button device.

The presentation of familiar faces, stranger faces and null trials was randomized within the experimental run with the exception that null trials were always presented in the first two and last three trials of the run. The first two trails of each run were discarded in the FMRI analyses to control for haemodynamic delay effects.

MRI data acquisition

The UCSD Medical Center 1.5 T Siemens Symphony MR scanner (Erlangen, Germany) equipped with the standard clinical head coil was used to collect the functional and anatomical images. Functional whole-brain T2*-weighted images were acquired using a single-shot gradient-recalled echo-planar imaging sequence [TR (repetition time) = 2500 ms; TE (echo time) = 36 ms; flip angle = 90°; FOV (field of view) = 192 mm] with a matrix

Table 2 *Description of the 'familiar' picture set for the autism and normal groups*

	No. of different people in set	No. of mother photos	No. of father photos	No. of family photos	No. of friend photos	No. of female photos	Total no. of photos in set
Autism	10 (2)	4.9 (0.7)	3.9 (1.3)	16.9 (5.9)	15.1 (5.8)	16 (0)	32 (0)
Normal	11 (2)	3.7 (1.1)	3.2 (1.4)	18.3 (8.1)	13.7 (8.1)	16 (0)	32 (0)

SDs are given in parentheses.

size of 64 × 64 (in-plane resolution = 3 × 3 mm). We acquired 133 volumes, each containing 28 contiguous 5 mm slices collected in the sagittal plane with interleaved slice acquisition, in each experimental run. Following the experimental scan, a high-resolution 3D MP-RAGE (TR = 11.08 ms; TE = 4.3 ms; flip angle = 45°; FOV = 256 mm; matrix 256 × 256; 180 slices; sagittal plane; resolution = 1 mm^3) structural scan was acquired for anatomical localization.

FMRI data analysis

All of the image registration and functional analyses were conducted using the Analysis of Functional Neuroimages software package (AFNI; version 2.51e; http://afni.nimh.nih.gov/afni (Cox and Hyde, 1997). Motion correction and three-dimensional registration of each participant's functional images were done using an automated alignment program (3dvolreg), which co-registered each volume in the time series to a fiducial volume (fourth acquired volume) using an iterative process (Cox and Jesmanowicz, 1999). The functional image time series were then smoothed with a Gaussian filter (full-width, half-maximum = 8 mm) and resampled into Talairach coordinates using the AFNI hand landmarking procedure (resampled volumes = 3 mm^3).

The analysis of brain activity from individual participants was performed using a deconvolution approach (3dDeconvolve program). The deconvolution analysis is a two-step procedure. In the first step, the impulse response function (IRF), an estimate of the haemodynamic response function, was estimated at each voxel location using as input the FMRI time series data and the input stimulus functions (i.e. vector descriptions of the timing of the presentation of stimuli). We used nine input stimulus functions, one for faces of familiar people, one for stranger faces, one for stranger faces with eyes gazing to the right or left (not included in this report), and six parameters of intra-scan motion obtained from the volume registration procedure including motion in the *x*-, *y*- and *z*-axes (mm units) and for roll, pitch and yaw (degree units). The IRF was estimated from the system response for each stimulus type to a Dirac delta impulse function using a sum of scaled and time-delayed versions of the stimulus time series. The IRF estimation algorithm assumed that the underlying system was linear and time invariant. In the second step, the IRF was convolved with the input stimulus time series and a multiple regression analysis of the FMRI time series data was conducted. The global mean and linear trend of the FMRI data were analysed separately, and were thus effectively removed from the main analysis. In the deconvolution analysis, the IRF was estimated from the first to the fourth functional image acquisition (i.e. the estimated haemodynamic response at 2.5, 5, 7.5 and 10 s) following the presentation of each of the three face types (familiar, stranger and gaze), totalling 12 parameters. Also included in the deconvolution analysis were the six motion parameters obtained from the output of the motion correction procedure described above. Thus, a grand total of 18 parameters were estimated for the 133 volumes (one parameter per 7.4 measurements).

The multiple regression analysis calculated voxel-wise 'goodness of fit' statistics for each stimulus type across these time points (and at each time point individually). This analysis yielded voxel-wise linear contrast weights, a measure of the BOLD (blood oxygen level-dependent) signal, for familiar and stranger faces relative to the fixation baseline. The group analysis was accomplished by submitting the linear contrast scores obtained for each participant from the deconvolution analysis to a two-way analysis of variance (ANOVA) using subject (random effect) and face condition (familiar or stranger faces; fixed effect) as factors. Separate analyses were conducted for the participants with autism and normal control participants. Correction for multiple comparisons was established using a voxel-cluster threshold technique (Forman *et al*., 1995) for an overall corrected level of significance (alpha) of 0.05 (individual voxel $P < 0.001$, two-tailed; minimum cluster threshold required = 702 mm^3). Prior to the application of the cluster threshold correction, clusters of activated voxels were first eroded by removing a voxel classified as active if <33% of voxels within an 8 mm radius were active ($P < 0.001$). Voxels were reinstated as active if a single voxel within 8 mm was still classified as active following the erosion procedure. This two-step procedure reduces the number of clusters connected by thin lines of activated voxels while mitigating the elimination of genuinely activated voxels. General linear tests were conducted to compare the BOLD activation from the first to the third acquisitions following stimulus presentation for familiar faces versus baseline, stranger faces versus baseline and familiar versus stranger faces.

Region of interest analyses

The fusiform gyrus and amygdala were two brain regions of interest (ROIs) that were identified *a priori* for specific analyses. To define these ROIs, we first produced mask images that delineated the right and left hemisphere extent of the ROIs in the Talairach and Tournoux (1988) coordinate system based on the AFNI (Cox and Hyde, 1997) implementation of the Talairach daemon database (Lancaster *et al*., 2000). The resulting mask images were manually adjusted for our research sample relative to the average MP-RAGE structural image based on all our participants using the AFNI drawing plugin program. The final right and left fusiform gyrus maps included 461 and 427 voxels of 3 mm^3, respectively (12 477 and 11 529 μl, respectively), and the right and left amygdala volumes each contained 123 voxels of 3 mm^3 (3 321 μl each). The ROI analyses included only those voxels that fell within the ROI mask.

Fusiform ROI analysis

For each participant, the extent of right and left hemisphere fusiform gyrus BOLD activity was calculated for familiar and stranger faces relative to the fixation condition by identifying all voxels within the

ROI mask whose activity exceeded $t(111) \geq 3.375$, $P < 0.001$. Group, condition and hemisphere differences were analysed using a three-way repeated measures ANOVA, with face condition and hemisphere as within-subjects factors and group as a between-subjects factor.

Amygdala ROI analysis

The amygdala is a small structure relative to the cluster threshold correction used to control for whole-brain type I errors (i.e. 702 mm^3). To examine BOLD activity within the amygdala for each participant group, we applied a false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) of the amygdala ROI to the group statistical maps for familiar and stranger faces relative to the fixation condition, as well as during the familiar versus stranger face comparison (Genovese *et al*., 2002; Keselman *et al*., 2002). Activation within the amygdala ROI was corrected for multiple comparisons to an overall alpha level of $P < 0.05$ using the FDR correction procedure.

Between-groups whole-brain comparison

A between-groups *t* test was performed based on the general linear tests for the three main conditions of interest; familiar faces, stranger faces and familiar versus stranger using a ttest program in AFNI.

Post-scan test

In order to verify that subjects could identify each photograph as a familiar person, post-scan tests were conducted where subjects verbally named each familiar photograph shown on a printed page. One autistic subject had significant expressive language difficulties and was instead asked to point to the correct printed photograph (e.g. 'point to the picture of your mother').

Results

Photograph ratings, behavioural performance and post-scan test

Photograph ratings

Although the affect ratings for the familiar (mean 0.37 ± 0.23) and stranger (-0.15 ± 0.34) photographs were both close to zero, a rating that denotes a neutral facial expression as was intended by design, the difference between the two categories of photographs was statistically significant [$t(13) = 6.9$, $P < 0.05$].

Behavioural performance

Behavioural data were unavailable for one normal subject. No group differences were found in reaction times to identify faces as female [autism = 803 ms, normal = 748 ms, $t(13) = 1.384$, $P > 0.05$] or in overall percent accuracy [98% for both groups $t(13) = 0.874$, $P > 0.05$].

Post-scan test

While all subjects correctly identified the photographs during the post-scan test, one autistic subject responded to each one by saying 'that picture looks like my <mother, sister etc.> but it is not my <mother, sister etc.>, a response that might be expected by someone with Capgras syndrome, a disorder where affected individuals believe that people they know have been replaced by imposters (Hirstein and Ramachandran, 1997).

ROI analyses

Fusiform gyrus

The numbers of active voxels for familiar and stranger faces in the left and right hemisphere fusiform ROI for both groups are shown in Fig. 2A. The analysis of the extent of BOLD activation in the fusiform gyrus ROI revealed no group main effect or interaction involving group, indicating that autistic and normal participants showed similar activation patterns within the fusiform ROI. There was a significant hemisphere $\times$ face condition interaction [$F(1,14) = 11.20$, $P < 0.01$], indicating that both groups showed greater activation for familiar faces in the right hemisphere fusiform ROI relative to the left hemisphere fusiform activity. Stranger faces showed the same right hemisphere dominance pattern in both groups. Overall, there was greater activation in the right hemisphere fusiform ROI than in the left [$F(1,14) = 23.91$, $P < 0.001$] and activation for familiar faces was greater than for stranger faces [$F(1,14) = 20.88$, $P < 0.001$]. None of the other two-way or three-way interactions were significant.

Amygdala

As shown in Fig. 3, there was significant bilateral activity in the amygdala in the familiar face versus fixation condition for both the autism and normal groups. There was no significant activity within the amygdala in either group in the stranger versus fixation comparison, or the stranger versus familiar face comparison.

Whole-brain analyses

Event-related response to familiar faces

In both autism and normal groups, BOLD Signal changes in response to familiar faces were observed in multiple regions of the brain beyond the FFA (see Figs 2B, 3 and 4). However, there were significant group differences as well as similarities in activation patterns. First, as illustrated in Fig. 4, a major difference in functional activity between groups was found in the medial frontal lobes. A large, bilateral cluster of activity that included the anterior cingulate was found only in the normal group, and not in the autism group. In addition, posterior cingulate activity to familiar faces was found bilaterally only in the normal control group. Secondly, similar areas of activation in the autism and normal groups were also seen and included the FFA, inferior and middle occipital gyri bilaterally, and lingual gyrus bilaterally. While both groups also showed parahippocampal gyrus activity, this was found in the right hemisphere in the autism group and in the left hemisphere in the normal group. Additional sites of activation can be found in Table 3.

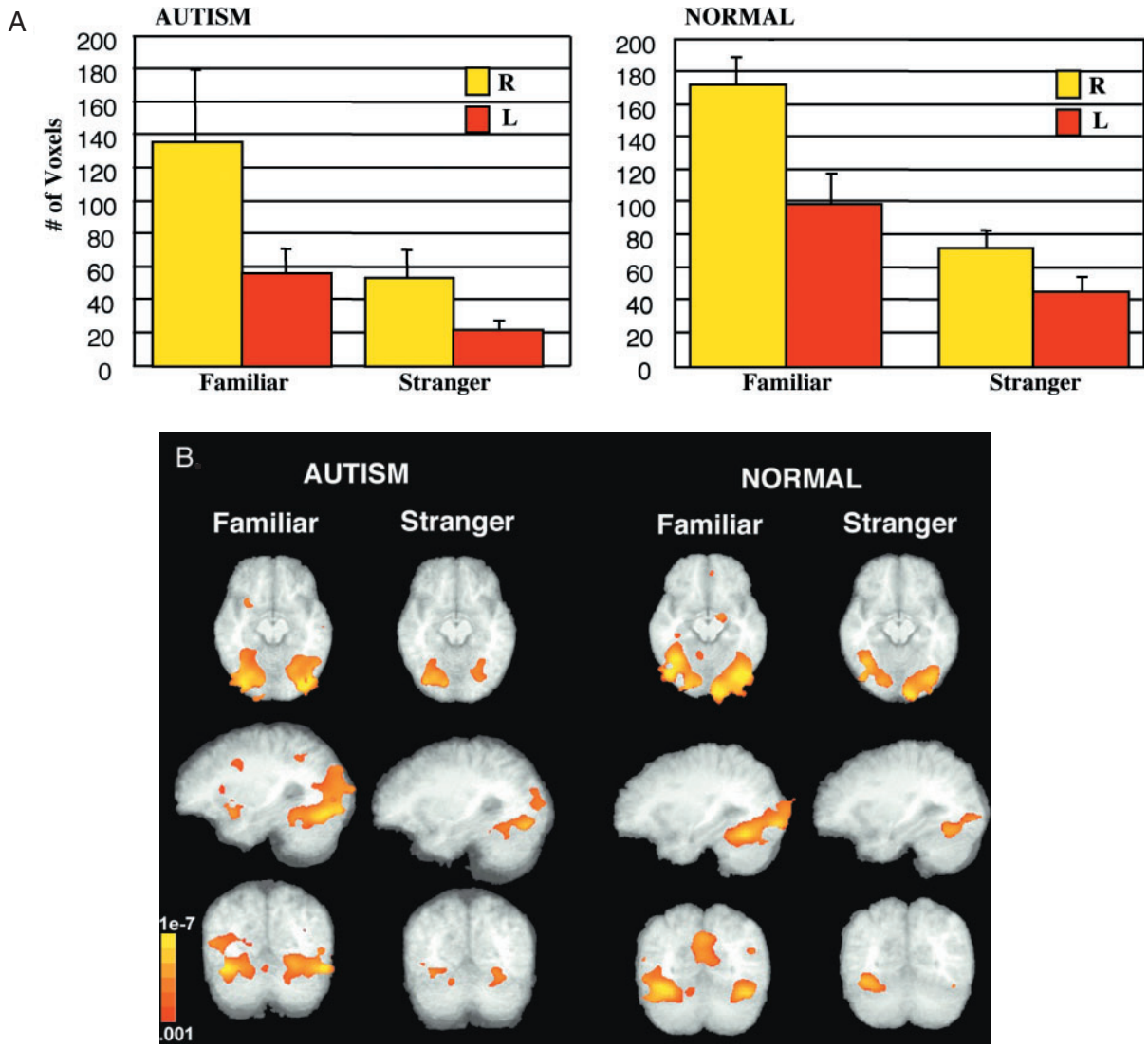

Fig. 2 (**A**) Bar graphs (with SE) illustrating the mean number of voxels significantly active in the autism (left graph) and normal (right graph) groups in the fusiform gyrus. Data are shown for the right and left fusiform during both the familiar and stranger faces conditions. Both the autism and normal groups showed the expected right greater than left asymmetry. (**B**) Functional maps obtained from both the familiar and stranger faces conditions overlaid on the averaged anatomical images for each group. Both groups showed widespread activity in temporal–occipital regions, including the FFA. The colours used in the functional maps represent *P* values associated with a *t* statistic.

Event-related response to stranger faces

While viewing the faces of strangers, sites of significant functional activity were found primarily in ventral temporal-occipital cortex for both groups. For example, both groups showed bilateral FFA, lingual and middle occipital gyrus activity. Only the normal group showed significant bilateral activity in the inferior occipital gyrus in this condition. See Table 3.

Familiar versus stranger faces

As shown in Fig. 5, comparison of familiar faces versus strangers yielded significant functional activity in the medial frontal lobes including rostral anterior cingulate and middle frontal gyrus in the normal, but not the autism group. Both groups showed activation in the posterior cingulate which extended into the precuneus.

Between-groups whole-brain analysis

Using the correction threshold, no between-group differences were found for any of the three conditions of interest.

Post hoc analysis

Given the observed differences in patterns of functional activity between the two groups as illustrated in the within-groups functional maps (e.g. see medial frontal lobe activity observable in the normal, but not the autism group, Fig. 5), a failure

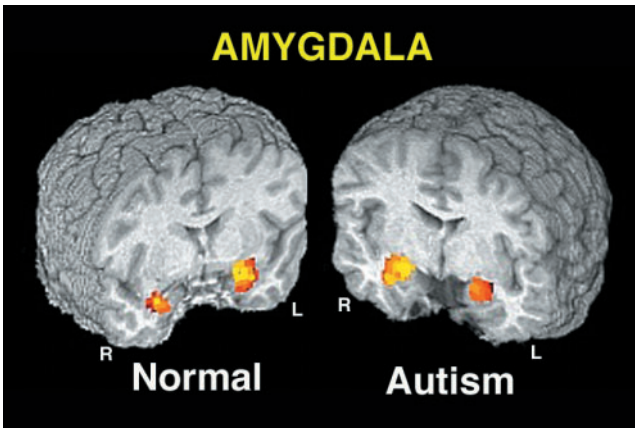

Fig. 3 Significant functional activity during the presentation of familiar faces versus fixation in the amygdala is shown overlaid on a 3D volume rendered brain. For purposes of illustration, functional activity was overlaid on a single brain from each group. The colours used in the functional maps represent *P* values associated with a *t* statistic.

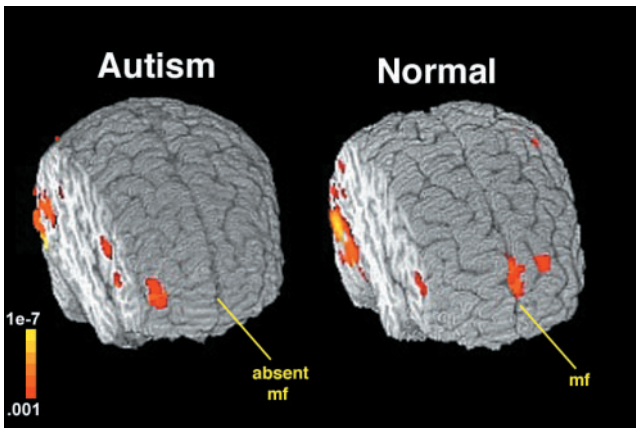

Fig. 4 Significant functional activity during the presentation of familiar faces versus fixation in the medial frontal lobes (see yellow line) overlaid on a 3D volume rendered image. For purposes of illustration, functional activity was overlaid on a single representative brain from the autism (left) and normal (right) group. The absence of medial frontal activity in the autism group can also be seen in Fig. 5. The colours used in the functional maps represent *P* values associated with a *t* statistic.

to find statistically significant between-group differences during a direct comparison was unexpected. A more liberal analysis ($P < 0.01$, uncorrected), aimed at detecting trends to guide future studies, revealed group differences consistent with the within-group whole-brain functional maps described above for the following conditions.

Familiar faces

Greater functional activity was observed in the right hemisphere in the anterior cingulate, medial frontal lobe, putamen, supramarginal gyrus, caudate and left thalamus in the normal group relative to the autism group.

Stranger faces

Greater functional activity was observed in the right inferior parietal lobe, right caudate and right medial frontal lobe in the normal group relative to the autism group.

Familiar versus stranger faces

Greater functional activity was found in the right postcentral gyrus in the autism group relative to the normal group. Greater functional activity was found in the right precuneus and left thalamus in the normal group relative to the autism group.

Discussion

A major result of the present study is that when people with autism are exposed to compelling faces, such as the face of their mother or co-worker, the FFA responds much like the FFA in normal subjects. This effect is compatible with multiple studies of normal individuals (Henson *et al*., 2000, 2003; Vuilleumier *et al*., 2001; Winston *et al*., 2003) and one study of autism (Aylward *et al*., 2004) that demonstrated enhanced FFA activation in response to familiar or emotionally valent faces. Surprisingly, the individuals with autism in the present study also showed significant FFA activity in response to the faces of strangers. This finding is in sharp contrast to most previous imaging studies on face processing in autism, including our own (Critchley *et al*., 2000; Schultz *et al*., 2000; Pierce *et al*., 2001; Hall *et al*., 2003; Hubl *et al*., 2003). Also resembling the functional activity found in normal subjects, individuals with autism showed greater activation to personally familiar faces than to the faces of strangers. Furthermore, they showed the prototypical right hemisphere dominance in the fusiform in response to both familiar and stranger faces. Taken together, the present findings make it unlikely that a defect in the FFA is a 'marker' of autism. Instead, a parsimonious conclusion is that in autism, the FFA is capable of responding to face stimuli, but whether or not it does so may have more to do with influences from other neural systems including those responsible for social drive and motivation or cognitive and attentional engagement. The evidence to date, therefore, raises the hypothesis that when hypoactivation of FFA is observed in autistic subjects, it may be indicative of abnormalities in systems that modulate the FFA.

Understanding what factors were unique in the present study, as one of the first to report significant FFA activity in response to faces in autism, may hold considerable explanatory value for the interpretation of both past and future studies of this disorder. The major difference between previous studies on this topic and the present one was the inclusion of multiple, non-repeating, personally familiar faces. It is well known that autistic individuals display a restricted range of interests and minimal exploration of their environment (Pierce and Courchesne, 2001). However, restricted attention and interest in autistic children is not immutable given that many studies have shown that language, social behaviour, cognitive test scores and skin conductance responses can

Table 3 *Talairach coordinates and associated t values of significant (individual voxel P < 0.001) clusters of activation for both normal and autism groups based on whole brain analyses*

Condition	Autism			Normal		
	Right *x*, *y*, *z* {*t* value}	Left *x*, *y*, *z* {*t* value}	Region	Right *x*, *y*, *z* {*t* value}	Left *x*, *y*, *z* {*t* value}	Region
Familiar faces						
			Occipital–temporal			**Occipital temporal**
	37, −58, −13 {4.6}	−34, −52, −13 {9.4}	Fusiform G.	34, −56, −10 {6.2}	−39, −68, −13 {13.5}	Fusiform G.
	31, −84, −8 {5.2}	−34, −85, −13 {5.2}	Inferior occipital G.	36, −83, −5 {5.2}	−12, −91, −10 {9.3}	Inferior occipital G.
	33, −83, −8 {5.3}	−38, −82, 3 {11}	Middle occipital G.	45, −73, −6 {8.3}	−37, −75, −10 {13.9}	Middle occipital G.
	11, −87, −3 {6.5}	−7, −81, 5 {6.5}	Lingual G.	1, −94, −1 {5.6}	−13, −94, −11 {6.3}	Cuneus/lingual G.
		−52, −16, −13 {4.9}	Middle temporal G.			
			Limbic			**Limbic**
	12, −44, 5 {6.1}		Parahippocampal G.		−13, −7, −9 {5.2}	Parahippocampal G.
					−25, 4, −21 {4.3}	Uncus
				2, 45, −2 {6.0}	−5, 45, −2 {7.9}	Anterior cingulate G.
				3, −52, 23 {7.2}	−1, −49, 26 {7.9}	Posterior cingulate G.
					−1, 7, 29 {4.3}	Cingulate G.
			Frontal			**Frontal**
		−37, −19, 56 {4.5}	Precentral G.		−37, −19, 59 {4.6}	Precentral G.
	37, 55, 17 {5.2}		Superior frontal G.		−19, 56, 21 {4.4}	Superior frontal G.
	52, 25, 14 {4.5}		Inferior frontal G.	46, 35, 12 {5.3}		Inferior frontal G.
	31, 7, 32 {5.7}		Inferior frontal G.	1, 52, 14 {4.2}	−2, 49, 22 {4.4}	Medial frontal G.
	46, −22, 47 {4.6}		Postcentral G.	43, 34, 14 {6.4}		Middle frontal G.
			Other			**Other**
	37, −52, 35 {4.8}		Supramarginal G.		−40, −70, 32 {5.2}	Angular G.
	19, 10, −6 {5.8}		Lentiform nucleus		−40, 1, 5 {4.7}	Insula
	7, −1, 8 {4.7}		Thalamus	1, −62, 36 {5.6}	−1, −62, 32 {5.7}	Precuneus
Familiar > stranger						
	2, −42, 33 {4.4}	−2, −43, 35 {4.6}	Posterior cingulate G.	1, −49, 17 {5.7}	−2, −49, 17 {5.5}	Posterior cingulate G.
	1, −55, 35 {4.8}	−1, −55, 35 {4.9}	Precuneus		−37, −70, 38 {4.6}	Precuneus
				1, 55, 17 {4.1}	−1, 47, 20 {5.2}	Medial frontal G.
					−40, 16, 38 {4.0}	Middle frontal G.
					−19, 31, 41 {4.2}	Middle frontal G.
				1, 47, 2 {5.1}	−2, 47, 2 {5.3}	Anterior cingulate G.
Stranger faces						
	30, −54, −12 {6.4}	−30, −54, −10 {6.6}	Fusform G.	37, −55, −9 {6.7}	−34, −62, −10 {4.4}	Fusiform G.
	36, −77, −9 {6.5}	−36, −83, 3 {12.3}	Middle occipital G.	40, −71, −10 {6.4}	−34, −77, −10 {11.7}	Middle occipital G.
	10, −88, −1 {5.0}	−14, −80, 2 {7.9}	Lingual G.	19, −76, −10 {6.9}	−29, −71, −10 {8.2}	Lingual G.
		−40, −70, −21 {5.0}	Declive		−43, −67, −15 {6.3}	Fusiform G.
	43, −19, 47 {9.1}		Postcentral G.	42, −75, −3 {5.3}	−33, −74, −3 {4.7}	Inferior occipital G.

Multiple structures contained within a single cluster are listed separately. Functional activity in the amygdala is reported separately in Fig. 3. For ease of comparison between groups, where possible, clusters with similar anatomical locations are listed in the same row.

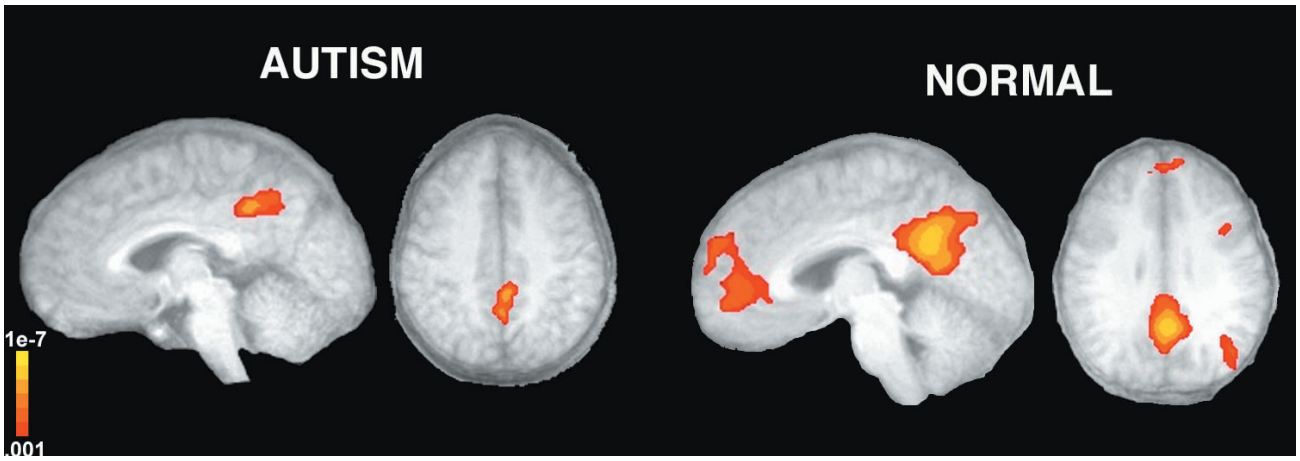

Fig. 5 Significant functional activity in the familiar faces versus stranger faces comparison for both the autism (left) and normal (right) group. Note that the only brain region significantly active in the autism group was in the posterior cingulate and precuneus region. The colours used in the functional maps represent *P* values associated with a *t* statistic.

be enhanced if appropriate motivational 'high-interest' stimuli are used (van Engeland *et al*., 1991; Koegel *et al*., 1997; Pierce and Schreibman, 1997). The familiar faces used in the present study may have enhanced motivation and interest in the autistic subjects to a far greater degree than the faces of strangers used in past studies. This raises an important question: are hypoactivation findings in FMRI studies of autism due to a true functional failure in a particular brain region, or to low interest and motivation?

An additional factor that may have contributed to FFA activity in autism was the use of a randomized rapid event-related design. All previous FMRI studies utilized a 'block design' in which the faces of strangers were presented repeatedly, usually 20 or 30 in a row. Whereas normal subjects might be expected to show sustained interest to a series of novel faces, this would not be expected of people with autism, who are well known for showing a disinterest in strangers. Thus, presenting stranger faces exclusively, as done in previous studies, may have served to increase the relative difference in neural responding between normal and autistic subjects. The use of a rapid event-related design may have generated a certain level of anticipation for autistic subjects who awaited the appearance of the next familiar face at the moment of each stimulus trial. Haxby *et al*. (2000) have proposed that the FFA is strongly involved in the assignment of person identity. Given that the current experiment utilized almost a dozen different personally familiar faces for each subject (for a total of 32 non-repeating photographs), this design potentially maximized FFA involvement as it relates to assigning person identity. Therefore, regardless of whether the face that was eventually displayed was familiar or a stranger, autistic subjects may have begun each trial with heightened interest, attention and readiness to assign a person identity to a particular face. This speculation would also help explain why FFA activity in the present study was found in response to both stranger and familiar faces. While many elements of face processing are presumed to be automatic, previous studies have shown that FFA activity is not entirely so, in that increased FFA activity is modulated by increased attention (Wojciulik *et al*., 1998).

Our study also revealed that the presence of familiar faces elicited significant functional activity in the amygdala in both the normal and autism groups. As a structure interconnected with a variety of brain systems, and one in which both structural and functional abnormalities have been found in autism (Pierce *et al*., 2001; Sparks *et al*., 2002; Schumann *et al*., 2004), interpretations of amygdala function in this disorder will undoubtedly be controversial for some time. At the extreme, the presence of significant amygdala activity in the autism group in response to familiar faces could be used as evidence against the 'amygdala theory of autism'. A different interpretation would be that the amygdala is involved in many functions, some of which may be more or less spared in this disorder. The amygdala is a structure with at least 12 distinct nuclei (Amaral *et al*., 1992); the functions of each, however, currently are not completely understood. The amygdala's role in fear and fear conditioning is well established (Calder *et al*., 2001), though there is growing evidence that this structure also has a role in processing positive emotions, particularly specific kinds of stimulus–reward learning (Baxter and Murray, 2002). Furthermore, the nuclei involved in processing positive emotions and stimulus–reward learning may be distinct from those involved in the fear response (Baxter and Murray, 2002). The faces of socially significant people used in this experiment, such as mother, are powerful exemplars of visual stimuli that hold significant reward values. For autistic subjects who mainly live at home and are in close contact with family members, the reward value of such faces may be particularly high. Stimulus–reward learning, one of the most basic forms of learning, may therefore have some functional capacity in autism. The success of a wide range of behavioural interventions for children with this disorder necessarily relies on this capacity (Eikeseth *et al*., 2002; Green *et al*., 2002).

Animal model studies of autism have shown that both adult and infant monkeys with ibotenic acid lesions restricted to the amygdala, a method that spares passing fibres, do not exhibit a behavioural profile suggestive of autism (Emery *et al*., 2001; Prather *et al*., 2001). For example, infant monkeys with amygdala lesions displayed behaviours suggesting a strong social interest in others, not social disinterest, as the autism profile would predict (Prather *et al*., 2001). On the other hand, there is evidence that humans with amygdala lesions do have difficulties with interpreting facial expressions as well as theory of mind tasks, two areas of considerable challenge for individuals with autism (Siegal and Varley, 2002; Stone *et al*., 2003). The exact role of the amygdala in the development of the autism phenotype is currently unclear.

In the autism group, the only region significantly active when familiar faces were directly compared with the faces of strangers was the posterior cingulate, a region thought to play a role in normal human social emotional experience. It is part of a network recruited when normal subjects imagine a positive autobiographical scene (Damasio *et al*., 2000), see the faces or hear the voices of emotionally significant people in their lives (Shah *et al*., 2001), or hear the names of family members or friends (Maddock *et al*., 2001). In a review of the past decade of research on the posterior cingulate, Maddock (1999) concluded that this region plays a prominent role in the evaluation of emotionally salient stimuli or in the retrieval of significant autobiographical memories (Maddock *et al*., 2001). In a recent study that disentangled the interaction between memory and emotional arousal effects, Maddock *et al*. (2003) concluded that activation in the posterior cingulate is not valence specific, but is associated with emotionally arousing stimuli in general. Thus, we believe that functional activity in this cortical limbic region reflects a component of emotional memory, possibly emotional arousal, for autistic subjects. In combination with amygdala and parahippocampal activity seen in the autistic individuals in the present study, such limbic activity begins to provide evidence that under some conditions people with autism may, just like normal subjects, engage in emotion processing in response to the faces of personally familiar people.

Within the autism group, a potentially noteworthy omission in the normal network involved in responding to familiar faces was in the medial frontal lobes, including anterior cingulate cortex. A direct comparison between the autism and normal groups, however, revealed a difference in this region only at $P < 0.01$, uncorrected. While this group difference is therefore only a statistical trend, the importance of medial frontal lobe function in normal socio-emotional responding, combined with reports of medial frontal dysfunction in autism, warrants further consideration. This frontal region is important in cognitive and affective functions and receives and integrates information from widespread cerebral and subcortical systems (Bush *et al*., 2000). Anterior cingulate cortex, for instance, is active in normals during retrieval of episodic memories, imagining an emotionally significant autobiographical event in one's life, integrating information with emotional overtones, anticipating and monitoring complex and potentially conflicting information, and experiencing intense emotions or drive states (Bush *et al*., 2000; Allman *et al*., 2002). Significantly reduced functional activation has been reported previously for medial frontal regions in autism (Happé *et al*., 1996; Haznedar *et al*., 2000; Castelli *et al*., 2002). Early developmental overgrowth followed by arrest of growth in medial frontal cortex has been reported in a recent MRI study of 2- to 11-year-old autistic children (Carper and Courchesne, 2004). Abnormalities in autism involving the anterior cingulate include reduced NAA (Friedman *et al*., 2003); reduced choline (Levitt *et al*., 2003); abnormal white matter diffusion patterns (Barnea-Goraly *et al*., 2004); reduced volume in adult patients (Haznedar *et al*., 1997); and increased neuron packing (Bauman and Kemper, 1994). Not surprisingly, therefore, the view has often been expressed that medial frontal cortex abnormality may play an important role in autism (Damasio and Maurer, 1978; Frith and Frith, 1999; Haznedar *et al*., 1997; Mundy, 2003; Courchesne *et al*., 2004).

In contrast to our previous FMRI work (Allen *et al*., 1997; Pierce *et al*., 2001), the present study used a spatial normalization, rather than a 'native space' approach for analyses. As we have commented previously, this approach has its limitations (Pierce and Courchesne, 2000). Neural abnormalities in autism have been reported throughout the cerebrum and cerebellum (Cody *et al*., 2002). For some individuals with autism, structural measures may be several standard deviations from the normal mean (Courchesne *et al*., 2003). It cannot be ruled out that the abnormal structure of the brain in autism could contribute to unwanted variability in the precise location of various brain structures after the normalization procedure. Such a procedure could therefore lead to erroneous conclusions when an absence of functional activity is observed. It is less likely, however, that the spatial normalization procedure in and of itself could introduce noise in such a way as to lead to a finding of significant functional activity, as was observed in the fusiform and the amygdala in our sample of autistic subjects.

It is possible to interpret the present data from a modular point of view with specific claims about the FFA, amygdala or medial frontal lobes in autism, but this would be overly reductionistic. This is not our intention, as there is abundant evidence of functional and anatomical abnormality in many additional regions including the cerebellum, parietal lobes, brainstem and hippocampus (Piven, 1997; Bailey *et al*., 1998; Pierce and Courchesne, 2002). While certain brain regions may play particularly important and potentially specific roles in the autism phenotype, such as the medial frontal lobes or cerebellum, we have conjectured previously that pre- and perinatal pathological growth perturbations trigger cascades of maldevelopment in numerous neural systems, resulting in aberrant connectivity and incomplete or inefficient neural networks (Courchesne *et al*., 1994, 2001, 2003). During normal development, an extended developmental period of experience guides the establishment of neural networks that are maximally adaptive for processing a wide variety of

information, but in autism we hypothesize that the rapid pace of early brain growth initially creates connections without such extended 'experience-tuned' adaptive consequence (Courchesne *et al*., 2001, 2003). Once the rate of brain growth slows, later experience might still guide selection of adaptive connections and elimination of maladaptive ones, but by that later age, the normal array and functioning of neural assemblies may not be fully achievable. The strength of using neuroimaging with autistic patients is that we can begin to see how the brain in this disorder operates as a whole.

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