Differential activation of the amygdala and the ‘social brain’ during fearful face-processing in Asperger Syndrome

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Abstract

Impaired social cognition is a core feature of autism. There is much evidence showing people with autism use a different cognitive style than controls for face-processing. We tested if people with autism would show differential activation of social brain areas during a face-processing task. Thirteen adults with high-functioning autism or Asperger Syndrome (HFA/AS) and 13 matched controls. We used fMRI to investigate ‘social brain’ activity during perception of fearful faces. We employed stimuli known to reliably activate the amygdala and other social brain areas, and ROI analyses to investigate brain areas responding to facial threat as well as those showing a linear response to varying threat intensities. We predicted: (1) the HFA/AS group would show differential activation (as opposed to merely deficits) of the social brain compared to controls and (2) that social brain areas would respond to varied intensity of fear in the control group, but not the HFA/AS group. Both predictions were confirmed. The controls showed greater activation in the left amygdala and left orbito-frontal cortex, while the HFA/AS group showed greater activation in the anterior cingulate gyrus and superior temporal cortex. The control group also showed varying responses in social brain areas to varying intensities of fearful expression, including differential activations in the left and right amygdala. This response in the social brain was absent in the HFA/AS group. HFA/AS are associated with different patterns of activation of social brain areas during fearful emotion processing, and the absence in the HFA/AS brain of a response to varying emotional intensity.

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1. Introduction

Faces are an important source of social information (Bruce & Young, 1986; Darwin, 1872/1965). In particular, facial expressions provide critical signals about the internal emotional states of others (Dolan, 2000). Certain areas of the brain, including areas of the occipital and temporal cortices, the amygdala, the orbito-frontal cortex (OFC) and the anterior cingulate cortex (ACC), are important for processing social information and have been termed the ‘social brain’ (Baron-Cohen, 1995; Brothers, 1990). Recent models of how the brain processes social information emphasize that different brain areas subserve different aspects of social processing (Adolphs, 1999, 2001; Hazby, Hoffman, & Gobbini, 2000). Areas of the occipital and temporal cortices, such as the inferior occipital gyrus (IOG), superior temporal sulcus (STS) and the superior temporal gyrus (STG) are involved in processing facial expressions of emotion and salient parts of the face, such as the eyes and mouth (Allison, Puce, & McCarthy, 1999; Baron-Cohen et al., 1999a; Puce, Allison, Bentin, Gore, & McCarthy, 1998). These areas play important roles in social perception (Adolphs, 2001). The amygdala, the OFC and the ACC receive perceptual information from occipital and temporal cortex areas and are involved in appraising the emotional significance of stimuli and guiding social decisions and social behaviour (Baron-Cohen et al., 1994; Damasio, 1994; Rolls, 1999). Neuroimaging studies have also consistently revealed activations of the medial prefrontal cortex (MPFC) during tasks involving ‘mentalising’ (Frith & Frith, 1999, 2003). In addition, the MPFC’s role in mentalising has been shown in lesion studies, where patients with damage to the MPFC are impaired on tasks involving...
involved in mentalising (Stuss, Gallup, & Alexander, 2001). Neuroimaging studies have reported significantly reduced activity in the MPFC in people with autism during mentalising tasks (Castelli, Frith, Happe, & Frith, 2002; Gallagher et al., 2000; Happe et al., 1996).

The amygdala processes threatening stimuli (LeDoux, 1995, 1996) and may have a more general role in processing social-emotional stimuli and empathy (Adolphs, 2003; Baron-Cohen, 2003; Brothers, 1990). Previous research in animals and humans has shown the amygdala to be involved in appraising biologically relevant stimuli, and influencing cognitive processing in the prefrontal cortex (Aggleton, 2000; Damasio, 1994, 1999; LeDoux, 1995). Recent neuroimaging studies have reported amygdala activation during the processing of threatening facial stimuli (Breiter et al., 1996; Morris et al., 1996, 1998; Morris, Ohman, & Dolan, 1999; Whalen et al., 1998), and provided evidence that the amygdala modulates activity in visual areas related to the processing of social stimuli (Anderson & Phelps, 2001; Lane & Nadel, 2000; Lane et al., 1998; Morris et al., 1998; Vuilleumier & Pourtois, this issue). Consistent with these findings, people with amygdala damage have difficulties in making social judgements and in recognising mental states and emotions in others (Adolphs, Baron-Cohen, & Tranell, 2002; Adolphs, Tranell, & Damasio, 1998; Fine & Blair, 2000; Stone, Baron-Cohen, Calder, Keane, & Young, 2003).

High-functioning autism and Asperger Syndrome (HFA/AS) are neurodevelopmental conditions characterized by social difficulties and impaired social cognition (APA, 1994). Various lines of evidence implicate abnormalities of the social brain in HFA/AS, particularly the amygdala (Bachevalier, 2000; Baron-Cohen et al., 2000; Howard et al., 2000; Schultz, Romanski, & Tsatsanis, 2000). Recent fMRI studies have reported deficits in amygdala activity in participants with HFA/AS during facial expression processing tasks, with the autism group instead showing enhanced activity in the STG (Baren-Cohen et al., 1999a; Critchley et al., 2000). Two region-of-interest fMRI studies involving face-processing paradigms have also reported that people with autism showed significantly less activation in the fusiform gyrus (FG), an area of the ventral visual stream associated with the processing of faces (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000a). A SPECT study looking at the processing of mental state words reported abnormal activity of the OFC in individuals with autism (Baron-Cohen et al., 1994), an area of the social brain that is highly connected with the amygdala. Neuroimaging studies have also implicated both structural and functional abnormalities of the ACC in autism (Haznedar et al., 1997).

In addition to the functional neuroimaging findings, a number of structural brain imaging studies have now reported abnormalities of the amygdala in people with HFA/AS (Aylward et al., 1999; Howard et al., 2000; Pierce et al., 2001; Salmond, de Haan, Friston, Gadian, & Vargha-Khadem, 2003). However, findings to date have been inconsistent in autism, with some findings reporting smaller amygdala size, others reporting larger amygdala size and others reporting only a proportion of the participants showing abnormalities or no group differences (Pierce & Courchesne, 2000; Salmond et al., 2003; Schultz et al., 2000a; Schultz, Romanski et al., 2000). These inconsistent findings make it unclear how to interpret the evidence, although its possible that abnormalities in both directions can occur, and it may depend on whether the participants involved have autism or AS, so that these findings may not be contradictory (Pierce & Courchesne, 2000). One of the studies reporting abnormalities of the amygdala, also found evidence for structural abnormalities in the OFC and the STG in a large proportion of the participants with autism (Salmond et al., 2003). Additional evidence for dysfunction of the social brain in autism comes from neuropsychological testing, which also suggests amygdala and OFC dysfunction in people with autism (Adolphs, Sears, & Piven, 2000; Dawson, Melzoff, Osterling, & Rinaldi, 1998).

However, some fMRI studies have reported greater activation in the STG in autism compared to controls (Baren-Cohen et al., 1999a; Critchley et al., 2000), indicating further brain imaging studies are needed in autism.

A recent PET study looked at activations in three brain areas in people with and without autism (Castelli et al., 2002). These three brain areas included the MPFC, the temporal pole/amygdala and the superior temporal cortex, which together are hypothesised to form a network underlying ‘mentalising’ or deploying a ‘theory of mind’ (ToM) (Frith & Frith, 1999). ToM involves understanding the behaviour of others in terms of mental states, an ability known to be impaired in autism (Baron-Cohen, 1992; Baron-Cohen, Leslie, & Frith, 1985; Frith, 2001). The task used in the Castelli et al. study involved watching videos of interacting shapes, moving with apparent animate motion but without having any human form. These videos trigger inferences about mental states (e.g., the geometrical movements of the shapes are described as goal-directed, volitional and ‘intentional’) in behavioural studies with participants, while people with autism produce significantly fewer spontaneous mental state attributions in this task (Bowler & Thommen, 2000; Klin, 2000). Castelli et al. (2002) used PET to investigate whether the mentalising network is involved in this task, and whether these areas show reduced activity in autism. Their study confirmed the control group did activate the three areas comprising the mentalising network, and that the group with autism showed significantly reduced activation in all three areas.

Another interesting neuroimaging study looked at neural activity in people with and without autism during face and subordinate-level object perception in two brain areas related to processing objects, the FG area involved in face-processing and the inferior temporal gyrus (ITG) object-processing area (Schultz et al., 2000a). They found that during face-processing the autism group showed less activation in the right FG, and more activation in the right ITG. This pattern of brain activity during face-processing in autism suggests they are using the feature-based strategies that are more typical of non-face object perception.

This is consistent with evidence showing people with autism use a different cognitive style while performing face-processing tasks, which generally involves more reliance on feature-based processing and which is often not as successful socially (Baron-Cohen, 2002; Frith, 2003; Klin et al., 2003). Studies have found that people with autism show less of an ‘inversion effect’ in
face-discrimination tasks compared to controls, and this better performance with inverted face stimuli is thought to reflect a greater reliance on the feature-based processing style (Boucher & Lewis, 1992; Davies, Bishop, Manstead, & Tantam, 1994; Hobson, Ouston, & Lee, 1988a, 1988b; Langdell, 1978). People with HFA/AS also tend to look at different facial features compared to controls. For example, eye-tracking studies have shown that people with autism look more at the mouth region of the face, while controls look more at the eyes (Klin et al., 2002, 2003; Pelphrey et al., 2002), and children with autism are better able to match their peers from isolated pictures of their mouths than controls (Langdell, 1978). Spezio and colleagues (this issue) have shown that when people with autism view faces, they fixate less on the eyes and mouth, they tend to look away from the eyes, and show abnormal direction of their saccades compared to controls.

One way to understand the cognitive style in autism is in terms of their strong drive to 'systemize' (Baron-Cohen, 2003). Systemizing involves focusing on the specifics and details in systems, and consciously working out the rules governing systems. People with autism may try to use a systemizing approach to understand what others are thinking and feeling, instead of the more natural 'empathizing' route (Baron-Cohen, 1999, 2002; Baron-Cohen, Wheelwright, Stone, & Rutherford, 1999). If people with autism are using a different cognitive style during emotional expression perception, then this predicts a different pattern of activations in the various areas of the social brain, rather than merely neural deficits. An fMRI study using the embedded figures task, a test which relies on feature-based processing and on which people with autism perform better than controls (Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983), revealed the autism group showed greater activations in the ventral visual object-feature processing areas of the brain (Ring et al., 1999). Some neuroimaging studies have shown different neural activations in people with autism compared to controls (Jolliffe & Baron-Cohen, 1997; Shah & Frith, 1983), however these studies have not focused on the distributed social brain network.

In the experiment reported here, we used a blocked design to measure the neural response of the amygdala and eight other areas of the social brain in adults with and without autism, while viewing faces with varying intensities of fearful expression. The amygdala, IOG, STG, STS, FG, OFC, MPFC and ACC formed the regions of interest in our statistical analysis. For the linear contrast analyses, investigating areas with varied responses to increasing or decreasing threat we more thoroughly interrogated amygdala activity by applying two ROI corresponding to the major input or decreasing threat we more thoroughly interrogated amygdala activity by applying two ROI corresponding to the major input regions of interest in our statistical analysis. For the linear contrast analyses, investigating areas with varied responses to increasing or decreasing threat we more thoroughly interrogated amygdala activity by applying two ROI corresponding to the major input or decreasing threat we more thoroughly interrogated amygdala activity by applying two ROI corresponding to the major input and output areas of the amygdala which have different functions (Aggleton, 2000; LeDoux, 1996), to investigate whether they might show differential activations during differing levels of threat. By looking at these eight areas of the social brain, we aimed to get further evidence of the pattern of neural differences associated with social processing in people with and without autism.

A deficit model would predict under-activity in areas of the social brain in autism, compared to controls (Castelli et al., 2002; Schultz et al., 2003). A difference model would predict that some areas of the social brain would be more active in controls, and some areas more active in those with autism, consistent with the cognitive style used to perform the task. Based on previous findings, we expect the group with autism to show more activation in perceptual areas of the social brain, and the control group to show greater activations in the higher-level social cognitive areas. Therefore, we predict the autism group to show more activity in the IOG, STS and the STG, the visual areas of the social brain involved in more perceptual aspects of social processing. For the control group, we expected to find more activation in areas involved in higher-level social cognition, including the amygdala, ACC, OFC, MPFC and the FG. We also predict the social brain in the control group to show a modulated response to varied intensities of fearful expression, and that such modulation might be absent in the brain activity in autism.

2. Methods

2.1. Participants

All participants gave informed consent to participate in the study. Thirteen male volunteers with high functioning autism or AS (12 = AS, 1 = HFA; mean age ± standard deviation, 31.2 ± 9.1, full-scale IQ 118 ± 17.1) and 13 healthy male volunteers (mean age ± standard deviation, 25.6 ± 5.1, full-scale IQ 117.9 ± 9.6) were recruited for participation. Two additional male controls were recruited, but one was excluded because English was not his first language, and the other control volunteer was excluded because of a technical problem with the collection of his behavioral data. Data from these two control participants was not included in the analysis or results. IQ was assessed for every participant using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). The participants with HFA and AS all had a diagnosis based on established international criteria (APA, 1994), from qualified professional clinicians. In addition, all of the participants with HFA/AS completed the Autism Spectrum Quotient (AQ), a self-administered questionnaire for measuring the degree of autistic traits (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). The scores for our participants with HFA/AS (N = 13, mean AQ score = 35.6, S.D. = 6.5, 76.9% scoring 32+) matched very closely the scores found in Baron-Cohen et al. (2001) (N = 58, mean AQ score = 35.8, S.D. = 6.5, 80% scoring 32+). All participants were over 18 years of age, right-handed, free of medication affecting mental activity and had no history of seizures or concussions.

2.2. Stimuli

The pictures of faces used for the experiment were taken from a standard set (Landis et al., 1998), and the scrambled pictures were created from the faces to serve as a matched baseline condition. The pictures were created black and white for the experiment. There were three levels of intensity for the fearful expressions of emotion; faces with neutral expressions, faces with a low intensity of fear expression, and faces with a high intensity of fear expression. To produce the low and high intensity fear face expression sets, a group of fearful face pictures were rated by 10 judges on the degree of fear expression they displayed, using a scale from 0 to 7 (0 representing no fear and 7 representing extremely high fear). Faces scoring 0 from any judge were excluded. The eight high fear face stimuli were chosen from the faces that received an average rating value between 1 and 3.9 (mean rating 2.5, S.D. 0.9). For the no fear stimuli, we showed a group of neutral expression pictures to the 10 judges and asked them to choose the emotional label that best described the expression in the picture. The labels included the six basic emotions (sad, angry, fear, disgust, surprise and happy) as well as neutral. The eight stimuli representing no fear were chosen from the photographs labelled as neutral by every judge. To create the scrambled face stimuli we randomly took eight examples from the stimuli chosen for the experimental conditions, and overlaid a grid on each. We first counted the amount of
Fig. 1. Examples of experimental stimuli for each condition: (a) scrambled faces, (b) neutral expressions, (c) low fear expressions and (d) high fear expressions.

2.3. Procedure

Before being scanned, all participants were trained on the task and familiarised with the pictures. Each participant underwent one scanning session lasting 8 min 18 s. During the session participants viewed a series of pictures presented using DMDX (Forster & Forster, 2003) on a screen within the participants’ field of view. Each picture was presented on the screen for 3 s, followed by a blank screen for 750 ms, followed by the next picture. Four different picture types were presented: faces with a high intensity of fearful expression, faces with a low intensity of fearful expression, faces with a neutral expression and scrambled faces. The four types of pictures were presented in separate blocks, with eight trials in each block. The blocks lasted 30 s and were repeated four times in a blocked-randomised order. Thus, each participant viewed 128 pictures in total.

Throughout the experiment, participants were required to press a response button with their right index finger as quickly as they could whenever a picture was presented on the screen. The task did not require them to explicitly judge or recognize the emotional expression of the faces. In addition to the neuroimaging task, participants also viewed a series of facial pictures depicting five basic negative emotions (fear, anger, disgust, surprise and sadness) during a post-scanning session in a quiet room. Twelve pictures of each of the five emotions were shown in a randomised order, making 60 pictures in total. Participants had a sheet of paper in front of them with the names of the five emotions, and for each facial emotional picture participants were instructed to decide which emotion word best described the emotion in the picture. No time limit was given to make a response, and we first ensured that all participants knew the meaning of each emotion word.

A repeated measures ANOVA was run on the emotion labelling performance outside the scanner, with emotion (fear versus anger versus disgust versus sad versus surprise) as the within-subject factor and group (controls versus autism) as the between-subjects factor. A repeated measures ANOVA was also performed for the reaction times (RTs) and accuracy measures during scanning, with condition (high fear versus low fear versus no fear versus scrambled) as the within-subject factor and group (controls versus autism) as the between-subjects factor.
2.4 fMRI data acquisition

Scans were carried out at the Wellcome Brain Imaging Centre, Addenbrooke’s Hospital, Cambridge UK, on a 3 T Bruker Medspec Advance system (Bruker Medical, Ettlingen, Germany) equipped with a head volume coil. A gradient-echo EPI sequence was used for image collection (TE, 30ms; TR, 3s). One-mm-thick slices were acquired for each participant. The first 8 EPI images were discarded to avoid T1 equilibration effects, leaving 160 images per participant. Twenty-one transaxial slices were acquired for each image (each slice 4 mm thick with 1 mm gap between slices; matrix size, 128 × 128; FOV, 25 cm × 25 cm). All participants were protective earplugs and ear-defenders.

2.5 Data analysis

Image processing and statistical analysis were performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Brain images were realigned to the first image. Linear normalisation into the standard stereotaxic space of Talairach and Tourenoux was performed using a representative brain from the Montreal Neurological Institute series as a template. Residual anatomical discrepancies were reduced through spatial smoothing with a Gaussian kernel filter of 6 mm. Statistical analyses were performed on a group basis according to the implementation of the general linear model (GLM). Since errors in normalisation may occur because of the loss of BOLD signal near air-tissue interfaces at high magnetic field strengths, areas of susceptibility were masked prior to normalisation. Areas of susceptibility artefact were manually “masked” prior to co-registration of each image with the Montreal Neurological Institute (MRI) EPI template image. Masking was done by hand using MRIcro (MRI-cro, Chris Rorden, chris.rorden@nottingham.ac.uk), and any areas affected by susceptibility were filtered. This mask was saved as a region-of-interest (ROI) and then used during normalisation (the masked areas were then not taken into account during normalisation).

Conditions were modelled as box-car functions convolved with a canonical hemodynamic response function. Data was high-pass filtered to remove low frequency drifts in signal. A first level, within-participants analysis using the GLM was performed on the functional data from each subject individually. Each of the resulting contrast images was taken through to a second-level, between-participants group analysis (i.e. random-effects model). A global threshold was set at p < .001 uncorrected for multiple comparisons. Since we had a priori hypotheses for areas of the social brain, described in more detail below, we applied a correction for multiple comparisons across a small volume of interest (p-values of activations in each ROI, which survived the global threshold. We report activations in social brain areas surviving this correction at p < .05.

Independent samples t-tests revealed the two groups did not differ significantly from each other on mean for chronological age, t(24) = 1.93, ns, and full scale IQ, t(24) = 1.71, ns. The results for the emotion labelling task outside the scanner revealed a main effect of group, F(1,24) = 12.44, p < .01, with the autism group performing worse than the control group. There was also a main effect of emotion, F(4,96) = 22.79, p < .001, with fear being recognised worse than anger, sadness and surprise, and disgust being recognised worse than sadness. Planned post hoc t-tests revealed a significant group difference for fearful expression, t(24) = 3.89, p < .001, with the autism group (mean score ± standard deviation, 4.66 ± 1.90) performing significantly worse than the control group (mean score ± standard deviation, 9.62 ± 2.22). There were also significant group differences on labelling anger, t(24) = 2.95, p < .01 and disgust, t(24) = 2.30, p < .05. The emotional labelling results are presented and discussed in more length elsewhere (Ashwin et al., submitted for publication). Binomial probabilities analyses for a 5-choice response outcome shows that 6 out of 12 is significantly above chance (p < .05), so both the control and the autism group were scoring above chance for all the emotions in the task. The statistics on both RT and accuracy in the scanner did not reveal any significant effects involving condition or group (p > .05 for all).

3. Results

3.1. Behavioural data

3.1.1. Within group analysis: control group

The main effect of faces in the control group, involving a contrast of all the face conditions (high fear, low fear and neutral) minus the baseline scrambled face condition, revealed activations in the right IOG, the MPFC and bilaterally in the amygdala (see Table 1; Fig. 2). The coordinates for the amygdala (8-mm radius, L, x, y, z = ±11, ±16; R, x, y, z = ±10, ±16) were derived from a neuroimaging experiment involving fearful faces (Breiter et al., 1996; Morris, Buxtel, & Dolan, 2001; Morris et al., 1996, 1998, 1999; Whalen et al., 1998). The coordinates for the SFO were the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000). The MPFC ROI (16-mm radius, x, y, z = ±4) was a voxel by voxel by voxel (x, y, z) within the SFO, as described by Critchley et al. (2000). The amygdala ROI (8-mm radius, L, ±x, y, z = ±21, ±13; R, ±x, y, z = ±15, ±14) was the centre of activations reported from previous neuroimaging face-processing studies using participants with autism (Critchley et al., 1999; Critchley et al., 2000).
In the experiment reported here, we tested if adults with autism show a differential pattern of neural activity in various social brain areas, compared with typical control adults during the perception of fearful facial expressions. Results confirmed differential activations of social brain areas in both of the groups. In addition, areas of the social brain in the control group showed a differential response to varied intensities of fearful expression, a phenomenon not seen in the autism group. These results confirm that autism involves an atypical pattern of activation within the social brain during the processing of facial expressions of emotion. These differences include less activation in the left amygdala and left OFC in autism, and a lack of modulated activity in other areas of the social brain that process social and emotional stimuli.

3.2.6. Linear analysis: decreasing intensity of fear

A contrast of neutral faces minus the high fear faces, to show areas sensitive to decreasing level of fearful expression, revealed activation for the control group in the right amygdala and in the MPFC (see Table 2; Fig. 4). There were no significant activations for this contrast in the autism group.

4. Discussion

In the experiment reported here, we tested if adults with autism show a differential pattern of neural activity in various social brain areas, compared with typical control adults during the perception of fearful facial expressions. Results confirmed differential activations of social brain areas in both of the groups. In addition, areas of the social brain in the control group showed a differential response to varied intensities of fearful expression, a phenomenon not seen in the autism group. These results confirm that autism involves an atypical pattern of activation within the social brain during the processing of facial expressions of emotion. These differences include less activation in the left amygdala and left OFC in autism, and a lack of modulated activity in other areas of the social brain that process social and emotional stimuli.

During the perception of fearful faces, the group of control participants showed significantly more activation in the left amygdala and the left OFC compared to the group with autism. This is consistent with the idea that these brain areas are involved in attaching emotional significance to stimuli in the control population (Adolphs, 1999; Adolphs, Tranel, & Damasio, 1998; Damasio, 1994; LeDoux, 1996), and that they are not functioning normally in autism (Bachevalier, 2000; Baron-Cohen, 1995; Baron-Cohen et al., 1998, 2003; Howard et al., 2000; Schulte, Romanski et al., 2000; Stone, Baron-Cohen, & Knight, 1998). The current results are consistent with neuropsychological data, as patients with damage to the amygdala and the OFC are impaired on tasks requiring social perception and social cognition, and show abnormal social behaviour (Adolphs, 1999; Adolphs et al., 1998, 2003; Howard et al., 2000; Baron-Cohen et al., 2000; Damasio, 1994; Rolls, 2000).

Similarly, people with autism also show deficits in social behaviour and perform poorly on tasks measuring theory of mind and empathizing (Baron-Cohen, 1995; Baron-Cohen, Wheelwright, & Jolliffe, 1997; Baron-Cohen, Wheelwright et al., 1999; Baron-Cohen et al., 1999a). Previous tasks measuring aspects of face and emotion processing in people with autism reveal deficits similar to patients with amygdala and OFC damage (Adolphs et al., 2000, 2002; Howard et al., 2000; Stone et al., 1998, 2003). The decreased activations in the amygdala and OFC in the autism group compared to the controls may reflect deficits in the ability to label social stimuli as emotionally significant, or in the ability to properly utilise and integrate affective information, both of which are important in successful social behaviour. These differences may be associated with abnormalities in the way people with autism view faces (Spezio et al., this
Our findings of reduced amygdala and OFC activation in the HFA/AS group differs from a recent finding that people with autism show increased amygdala and OFC activation compared to controls during a face-processing task (Dalton et al., 2005). However, the Dalton study involved tasks of explicit emotion and familiarity judgements, and the participants were much younger and lower-functioning and so could have been more anxious in the scanning environment. Another recent brain imaging study reported decreased amygdala activity in people with autism compared to controls during the explicit processing of facial emotions (Critchley et al., 2000). In addition, people with paranoid schizophrenia are reported to show abnormal amygdala activity during implicit processing of fearful faces, suggesting abnormal amygdala function in other psychiatric conditions (Russell et al., this issue). Clearly more neuroimaging studies looking at the explicit and implicit processing of emotional expressions in autism are needed.

The group with autism showed significantly more activity than the control group in the superior temporal cortex and the ACC for the main effect contrast involving all the facial stimuli (high fear, low fear and neutral). Activations in the superior temporal cortex have been shown during tasks of social perception, such as those involving attention to specific social features, including eyes and mouths (Adolphs, 2001; Allison et al., 1999; Haxby et al., 2000; Puce et al., 1998). Neuronal studies in monkeys have shown cells in the temporal cortex respond preferentially to perceptual aspects of social stimuli, like specific aspects, such as positions of the eyes and mouths (Hasselmo, Rolls, & Bayliss, 1989; Perrett, Hietanen, Oram, & Benson, 1992; Perrett & Mistlin, 1990; Perrett et al., 1985). These findings have led to the idea that temporal cortex areas involved in visual processing (e.g. STS, STG and IOG) are involved in more perceptual aspects of processing social-emotional stimuli, which is then sent on to other areas of the social brain like the amygdala and OFC.
involved in higher-level social cognitive processing (Adolphs, 2001). Previous fMRI experiments involving participants with and without autism have reported significantly greater activations in autism in the STG (Baron-Cohen et al., 1999a; Critchley et al., 2000), which is consistent with our results. Findings from research with humans and animals suggests the ACC plays a role in behaviours involved in the monitoring and evaluating of one's own performance or internal state (Ochsner & Lieberman, 2001). Neuroimaging studies report activity in the ACC associated with conscious awareness and attention to emotional processes (Lane & Nadel, 2000; Lane et al., 1998).

The increased activation in the ACC in the autism group was an unexpected finding, but is consistent with behavioural and clinical accounts of how people with autism process social and emotional information. People with autism report having to consciously think about the details and rules during social situations (Grandin, 1995), and they also find social and emotional tasks harder, as shown by impaired performance in tasks of social and emotional processing (Adolphs et al., 2000; Baron-Cohen et al., 2000; Howard et al., 2000). Therefore, people with autism may require more conscious effort when deciphering social situations and emotional expressions in others. People with autism...
also pay more attention to specific social features when processing faces (Hobson et al., 1988a, 1988b; Langdell, 1978), and previous brain imaging studies have shown greater activations in HFA/AS compared to controls in early visual and perceptual areas in the temporal cortex (Baron-Cohen, Wheelwright et al., 1999; Baron-Cohen et al., 1999a; Critchley et al., 2000; Ring et al., 1999). The activations seen in the superior temporal cortex and the ACC by the HFA/AS group in the present study are consistent with a more effortful, conscious and perceptual style of face-processing with attention to social features, which may reflect a systemizing strategy (Baron-Cohen, 2003).

The results of this study provide further support that the amygdala plays a key role in the perception of threatening social stimuli in the control population (Morris et al., 1996, 1998, 1999), and that autism involves a deficit in normal amygdala function (Bachevalier, 2000; Baron-Cohen et al., 2000; Howard et al., 2000). As predicted, the main effect contrast for the control group revealed a significant neural response in the amygdala bilaterally when viewing faces with varying intensities of fearful expression, while the group with autism did not show any significant amygdala activations in the same contrast. The group comparison confirmed that the control group activated the left amygdala more than participants with HFA/AS.

This is consistent with previous neuroimaging studies of autism reporting decreased amygdala activity to facial stimuli (Baron-Cohen et al., 1999a; Critchley et al., 2000; Pierce et al., 2001). The lack of amygdala activity by the autism group during fearful face perception may account for the lack of response of the social brain to varied intensities of fearful expression, as the amygdala modulates neural activity in other brain areas to facilitate processing of biologically relevant stimuli. Thus, our findings lend further support for the amygdala theory of autism (Baron-Cohen et al., 2000), since the group with autism show a reduced neural response in the amygdala, even during a task that consistently and robustly activates the amygdala in control participants.

In addition to the amygdala, the control group also activated the IOG and the MPFC while viewing fearful faces. The IOG is an area of the ventral visual processing stream that is involved in the early perception of facial features, and has shown activations in previous neuroimaging studies involving face perception (Haxby et al., 2000; Ishai et al., 2000; Puce et al., 1998). The MPFC has been consistently activated in neuroimaging studies involving tasks of mentalising about others (Frith, 2003; Frith and Frith, 1999, 2003). Mentalising includes the perception of the emotions of others (Baron-Cohen, 2003; Castelli et al., 2002; Castelli, Happe, Frith, & Frith, 2000), and people seem to rapidly and automatically try to work out what others may be thinking or feeling (Baron-Cohen, 1995). The control group in our study were presented with faces with varying levels of fearful expressions, and may have automatically inferred thoughts and feelings about the people in the pictures. MPFC activation was not seen in the autism group, who have deficits in mentalising about oth-
ers and who have shown reduced MPFC activation in previous neuroimaging experiments of mentalising (Castelli et al., 2002; Gallagher et al., 2000; Happe et al., 1996).

We found a bilateral neural response in the amygdala to fearful face perception in the control group. Some previous neuroimaging studies have reported amygdala activation to fearful faces presented within conscious awareness only in the left amygdala, while other studies using fearful faces presented below conscious awareness have reported activation in the right amygdala (Dolan, 2000; Dolan & Morris, 2000). This has led to the idea there might be a lateralisation in the role of the left and right amygdala, with the left amygdala involved in the processing of stimuli having aversive features presented within conscious awareness and the right amygdala involved in processing aversive stimuli presented outside of conscious awareness (Dolan, 2000; Dolan & Morris, 2000). Consistent with some other studies (Whalen et al., 1998) our data do not support this hypothesis.

Our task involved pictures always presented within conscious awareness, yet our main effect showed a neural response in both the left and right amygdala. The hypothesis of lateralised amygdala function would have predicted activity only in the left amygdala in our experiment.

The linear contrast analyses looking at brain areas responding to increasing and decreasing amounts of fear revealed an interesting effect in the amygdala areas and also gave some insight into why we did not see FG activation in the main effects contrast. In the linear contrast analysis revealing brain areas sensitive to increasing fear, the left peri-amygdala area near the substantia innominata/basal forebrain was significantly activated (Fig. 3). In the linear contrast analysis revealing brain areas sensitive to decreasing fear, the right peri-amygdala was activated near the amygdala-striatal transition area (Fig. 4). This suggests amygdala regions might be responsive to the level or intensity of threat, with output regions increasing in activity with increasing threat, and input areas increasing with decreasing threat. However, these ideas require further investigations in order to elucidate more clearly differential roles of the left and right amygdala.

We were surprised the control group did not show activations in the FG in the main effect contrast (all face conditions minus scrambled faces) in our study, which was expected based on previous neuroimaging studies involving faces. The linear contrast analyses gave some insight into why we did not find FG activation in the main effect contrast. In addition to the left dorsal peri-amygdala area, the linear analyses in the control group also revealed that the bilateral FG and the right STS showed increased activations as the intensity of fearful expression increased. Therefore, visual processing areas of the social brain showed increasing activity as the level of threat increased. This modulated response most likely explains why there were no FG activations in the main effects contrast, since activity in the FG showed a varied response to the different conditions, which corresponded better to the statistical design of the model in the linear analysis, rather than the model involved in the main effects contrast. Therefore, there was FG activation in during perception of faces varying in fearful expressions, it just showed a linear response with varying intensities of fear.

The increasing activations in social-perceptual brain areas, which correspond to the increasing intensity of fear, probably involve feedback connections from brain areas further downstream. A likely candidate for the feedback is the amygdala, since this area has connections to areas of the social brain (Amaral & Price, 1984) and plays a role in modulating activity in early visual areas to facilitate processing of biologically important stimuli (Anderson & Phelps, 2001; Lane et al., 1998; LeDoux, 1996; Morris et al., 1998; Vuilleumier & Pourtois, this issue). The MPFC also showed a response to varied levels of fearful intensity, although it showed reduced activations as the level of threat increased. This area is associated with higher-level cognitive functions including mentalising (Frith & Frith, 1999, 2003). One might speculate that this is because higher-level cognitive functions, like mentalising, might not be needed in a highly threatening situation, where vigilance and the fight-or-flight response might be better suitable for survival. Thus, in response to increasing threat, areas involved in perception might be facilitated and areas involved in higher-order cognition might be inhibited to successfully deal with the threat. The group with autism did not show any brain areas responding to increasing or decreasing fear, suggesting the amygdala in autism may not be modulating activity in other areas of the social brain to facilitate the processing of biologically important stimuli, such as people.

5. Conclusion

During perception of fearful faces, control adults showed activation in areas of the social brain involved in the automatic emotional appraisal of biologically relevant stimuli, while the group with autism showed significantly more activation of areas involved in the conscious and feature-based analysis of social and emotional stimuli. These differences in activation are consistent with differences in facial processing strategies in people with and without autism. Further, the control group showed responses in the amygdala and other areas of the social brain to varied intensities of fearful expression, consistent with the idea that the amygdala modulates activity in other brain areas to facilitate processing of biologically relevant stimuli. The autism group did not show any activation of the amygdala or other brain areas to varied intensities of fearful expression. This provides further evidence for the amygdala theory of autism, and that the amygdala deficit may have effects on activity in other brain areas. We conclude that the pattern of activity in the autistic brain during social processing supports both a deficit and a difference model.

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