Brain (2000), **123,** 2203–2212

The functional neuroanatomy of social behaviour
Changes in cerebral blood flow when people with autistic disorder process facial expressions

Hugo D. Critchley,[1] Eileen M. Daly,[1] Edward T. Bullmore,[2,4] Steven C. R. Williams,[2] Therese Van Amelsvoort,[1] Dene M. Robertson,[1] Andrea Rowe,[1] Mary Phillips,[1] Grainne McAlonan,[1] Patricia Howlin[3] and Declan G. M. Murphy[1]

Departments of [1]Psychological Medicine and [2]Neuroimaging, Institute of Psychiatry, Kings College, [3]Department of Psychology, St George's Hospital Medical School, London and [4]Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

Correspondence to: Declan G. M. Murphy, Department of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK
E-mail: sphadgm@iop.kcl.ac.uk

Summary
Although high-functioning individuals with autistic disorder (i.e. autism and Asperger syndrome) are of normal intelligence, they have life-long abnormalities in social communication and emotional behaviour. However, the biological basis of social difficulties in autism is poorly understood. Facial expressions help shape behaviour, and we investigated if high-functioning people with autistic disorder show neurobiological differences from controls when processing emotional facial expressions. We used functional MRI to investigate brain activity in nine adults with autistic disorder (mean age ± standard deviation 37 ± 7 years; IQ 102 ± 15) and nine controls (27 ± 7 years; IQ 116 ± 10) when explicitly (consciously) and implicitly (unconsciously) processing emotional facial expressions. Subjects with autistic disorder differed significantly from controls in the activity of cerebellar, mesolimbic and temporal lobe cortical regions of the brain when processing facial expressions. Notably, they did not activate a cortical 'face area' when explicitly appraising expressions, or the left amygdala region and left cerebellum when implicitly processing emotional facial expressions. High-functioning people with autistic disorder have biological differences from controls when consciously and unconsciously processing facial emotions, and these differences are most likely to be neurodevelopmental in origin. This may account for some of the abnormalities in social behaviour associated with autism.

Keywords: Asperger syndrome; attention; autism; facial expression; fMRI

Abbreviations: BOLD = blood oxygenation level-dependent; fMRI = functional MRI; FPQ = fundamental power quotient; ICD = International Classification of Disease; WAIS-R = Wechsler Adult Intelligence Scale—Revised

Introduction
Autism is characterized by pervasive developmental abnormalities in social and emotional behaviour, associated with stereotyped and obsessional behaviours (World Health Organization, 1993; Wing, 1997; Gillberg, 1998). Qualitative impairments in reciprocal social interaction include inadequate appreciation of social–emotional cues (as shown by a lack of responses to others' emotions), poor use of social signals, and a lack of socio-emotional reciprocity.

Individuals with classic Kanner-type autism (Wing, 1997; Gillberg, 1998) also have delayed language development, and many have learning disability (mental impairment). However, ~20% are classified as high-functioning because they are of normal or superior general intellectual skills, despite having a history of early language delay. Individuals with Asperger syndrome have no history of language delay and have normal or superior intellectual abilities, but also show the characteristic impairments of reciprocal social interaction. Although, by definition [International Classification of Disease—Revision 10 (World Health Organization, 1993)] there is always a disparity between social understanding and cognitive skills in autism, this disparity is particularly marked in high-functioning individuals with autism/Asperger syndrome. However, the biological associates of abnormal social behaviour in autism are poorly understood.

The neuropathological basis of autism has not been

determined, and much of the work has focused on classic Kanner-type autism. However, a number of anatomical substrates have been suggested. Damasio and Maurer proposed that autism is due to dysfunction of mesolimbic (dopaminergic) brain areas (ventromedial prefrontal cortex, medial temporal lobe, striatum and limbic thalamus) because damage to these brain regions can cause features of autism (impaired social and emotional functioning, stereotyped behaviours, mannerisms and obsessionality) (Damasio and Maurer, 1978). This hypothesis is supported by studies which have reported that (i) in animals, social deficits and stereotypical behaviour are associated with damage to the medial temporal lobe in infancy (Bachevalier, 1994); (ii) in humans, autistic-type patterns of behaviour are associated with abnormalities in the temporal lobe caused by other neurodevelopmental disorders (e.g. tuberous sclerosis) (Bolton and Griffiths, 1997); and (iii) individuals with autism are impaired on 'frontal' executive tasks (Ozonoff *et al*., 1991; Hughes *et al*., 1994). Non-limbic areas such as the parietal lobe have also been suggested as important in aetiology because the inattention of children with autism to salient social cues resembles inattention and neglect following parietal lobe damage (Bryson *et al*., 1990). Some children with autism are also impaired on neurological tests sensitive to parietal dysfunction (Haas *et al*., 1996). Other investigators have proposed that developmental abnormalities of the cerebellum (Courchesne *et al*., 1988) or dysfunction of cerebellar–cortical serotonergic pathways are patho-aetiological factors for autism (Chugani *et al*., 1997). Consistent with this, acquired cerebellar lesions have been associated with deficits in social and emotional behaviour, executive dysfunction and obsessionality (Schmahmann and Sherman, 1998). Thus the finding that lesions to discrete brain areas may result in clinical symptoms that are also present in people with autism suggests a neurobiological basis and implicates dysfunction of the mesolimbic areas, parietal cortex and cerebellum. However, lesion studies only provide partial insight into the biological basis of autistic disorder.

There is direct evidence for neurobiological abnormalities in autism. Although there have been very few post-mortem studies of people with autism, these have shown megencephaly (Bailey *et al*., 1998) and abnormal distribution of neurones in both limbic and non-limbic areas (Bauman and Kemper, 1985; Bailey *et al*., 1998). *In vivo* brain imaging studies of brain anatomy in autism have also reported megencephaly (Piven *et al*., 1995), as well as abnormal gyrification of cortical regions (including the parietal lobe) (Piven *et al*., 1990; Courchesne *et al*., 1993), hypoplasia of the cerebellar vermal lobules (Courchesne *et al*., 1988; Hashimoto *et al*., 1995) and decreased volume of the corpus callosum (Piven *et al*., 1997), the anterior cingulate (Hazneder *et al*., 1997; Abell *et al*., 1999) and the left inferior frontal gyrus and occipitotemporal junction (Abell *et al*., 1999). Contrary to animal models (Bachevalier, 1994), in human autism the hippocampal complex is reported to be of normal size (Piven *et al*., 1998), and one study reported an increase in volume of the (left) amygdala, bilateral anterior cerebellar lobes and vermis, and the lateral temporal lobe visual cortex (Abell *et al*., 1999). Thus, imaging studies of autism suggest regionally distributed differences in brain anatomy.

PET studies, although not always consistent in their findings, have reported delayed metabolic maturation of the prefrontal cortex in autistic children (Zilbovicius *et al*., 1995), and in adults reduced: (i) functional associations between frontal and parietal regions at rest (Horwitz *et al*., 1988); (ii) prefrontal and anterior cingulate metabolism during attentional and verbal learning tasks (Seigel *et al*., 1995; Haznedar *et al*., 1997); and (iii) medial prefrontal blood flow during 'theory of mind' tasks (Happe *et al*., 1996). A functional MRI (fMRI) study reported reduced amygdala activation in high-functioning adults with autism when they were explicitly appraising mood from pictures of eyes (Baron-Cohen *et al*., 1999). Thus, *in vivo* anatomical studies suggest that individuals with autism have diffuse abnormalities in brain development, and functional imaging studies have highlighted dysfunction of neuronal pathways involving the frontal lobe and perhaps the amygdala.

Facial expressions of emotion are important and culturally universal social signals (Ekman, 1998) and can be processed both explicitly (consciously) and implicitly (unconsciously). The rules and skills guiding normal social interactions are complex, but include the appreciation and understanding of other people's thoughts and intentions ('theory of mind') and the explicit and implicit processing of emotional expression. Normal children acquire theory of mind skills in the first 3–4 years of life, and process non-verbal social cues implicitly unless circumstances are exceptional. Many of the social impairments in people with autism are consistent with a deficit in theory of mind and/or differences in the processing of other people's emotions (Baron-Cohen *et al*., 1994). For example, children or less able adults with autism are frequently impaired on theory of mind tests and when interpreting people's feelings from emotional facial expressions. In contrast, many high-functioning adults can score normally on tests of theory of mind (Bowler, 1992) and the explicit identification of facial emotion, and may learn to guide their everyday social interactions by consciously (explicitly) applying intellectual strategies (e.g. understanding that someone will behave positively because their mouth is turned up at the corners, i.e. they are smiling). Nonetheless, they still exhibit significant social impairment. Thus, people with autism may not simply have a deficit in theory of mind, or in the ability to process explicitly emotion per se; rather, they may have abnormalities in the normal functional interaction between the use of explicit and implicit strategies that people without autism use to guide social behaviour.

We have reported previously that, in healthy controls, temporal lobe regions are activated during the explicit processing of facial expression, whereas limbic/paralimbic areas are activated during implicit processing (Critchley *et al*., 2000). Therefore, we used fMRI to determine if there are

Table 1 *Description of fMRI subjects with autistic disorder*

Subject	Age (years)	Clinical diagnosis	Behavioural features of autism			WAIS			Full-time employment*	Further education*
			Impaired social skills	Obsessions/stereotyped behaviour	Language delay	FSIQ	VIQ	PIQ		
1	30	AS	Yes	Yes	No	90	88	91	Yes	No
2	44	Autism	Yes	Yes	Yes	87	87	87	No	No
3	47	Autism	Yes	Yes	Uncertain	91	93	89	No	No
4	39	AS	Yes	Yes	No	107	99	117	Yes	Yes
5	28	AS	Yes	Yes	No	128	118	132	Yes	Yes
6	39	AS	Yes	Yes	No	109	99	119	No	Yes
7	41	AS	Yes	Yes	No	122	126	109	Yes	Yes
8	41	AS	Yes	Yes	No	89	110	68	No	No
9	26	AS	Yes	Yes	Uncertain	95	96	94	No	Yes

*At the time of scanning. For subject 9, diagnosis was reached on the basis of clinical history and interview without parental informant. AS = Asperger syndrome; FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ.

significant differences between high-functioning adults with autistic disorder (we use the term 'autistic disorder' in this paper to describe individuals who meet ICD-10 criteria for autism or Asperger syndrome and who are of normal intelligence, i.e. IQ $>$ 70) and healthy controls when explicitly and implicitly processing facial expressions. Because some high-functioning adults with autistic disorder report that they use explicit mechanisms to guide social behaviour but still display abnormal social behaviour, it was hypothesized that there are significant differences between people with autistic disorder and controls in the comparison of explicit versus implicit processing of facial expressions (as reflected by a significant diagnosis $\times$ experiment interaction). In addition, it was hypothesized that individuals with autistic disorder would show less activity than controls in brain areas associated with the implicit processing of facial expressions.

Methods

Subjects

We studied nine high-functioning adult male volunteers [mean age $\pm$ standard deviation, 37 $\pm$ 7 years; FSIQ (full-scale IQ) 102 $\pm$ 15] clinically diagnosed, using ICD-10, as having Asperger syndrome (seven subjects) or autism (two subjects) (Table 1). Diagnosis was confirmed where possible with the Autism Diagnostic Interview (Lord *et al*., 1994), a structured interview of parental informants to aid the diagnosis of autism. We also studied nine right-handed adult male controls (27 $\pm$ 7 years; FSIQ 116 $\pm$ 10). Intelligence was measured using the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (Wechsler, 1981), and subjects with autistic disorder were tested outside the scanner on their ability to recognize faces, using the Warrington recognition memory task for faces (Warrington, 1984). There were no significant differences between groups in age or intelligence. All subjects were screened to exclude co-morbid psychiatric illness (e.g. schizophrenia, depression) and neurological and extracerebral disorders that might affect brain function (e.g. epilepsy or hypertension), and they gave informed consent, in accordance with the Declaration of Helsinki, for a protocol passed by the local research ethics committee (Bethlem and Maudsley Hospitals). The subjects were familiarized with the stimuli and task procedure before scanning.

Experimental tasks

In two separate experiments, facial stimuli from a standard series (Ekman and Friesen, 1975) were presented to subjects pseudorandomly in alternating (on/off) 30 s conditions. Each face was presented for 3 s with an interstimulus interval of 0.75 s. In the 'on' condition, subjects viewed mixed high-emotion facial expressions (four happy, four angry), whereas in the 'off' (control) condition the subjects viewed neutral facial expressions. In Experiment 1 (explicit task) subjects were asked to attend to and judge the facial expression of each stimulus, and signalled their judgement by pressing one of two buttons of a hand-held response pad with the right thumb. The direction of the response was indicated by a legend beneath the stimuli (HAPPY/ANGRY – NEUTRAL). In Experiment 2 (implicit task), subjects attended to and judged the gender of each face (which was counterbalanced across both phases of the task), responding according to the legend: MALE – FEMALE. Thus, both experiments examined the processing of happy and angry faces relative to neutral faces, and required the subjects to attend to each face stimulus. Only in Experiment 1 (explicit task) did the subjects consciously attend to the emotional expression depicted on each face (Fig. 1). The order of the experiments was counterbalanced pseudorandomly across subjects to control for session effects that might otherwise introduce bias from time-dependent differences in the cognitive set or physiology of the subjects or from technical artefacts such as scanner drift, which may affect the signal-to-noise ratio.

Data acquisition and analysis

Subjects were scanned while performing these tasks using a 1.5 Tesla GE Signa System (General Electric, Milwaukee,

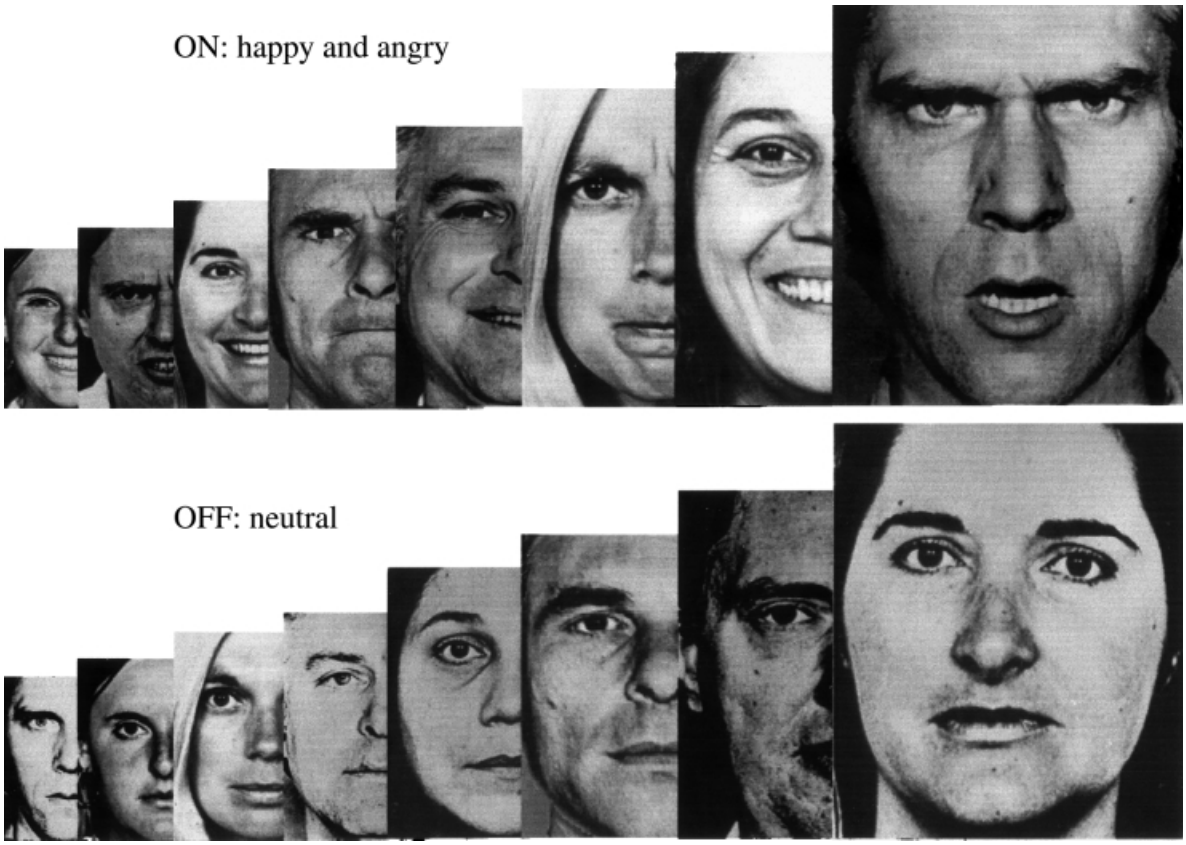

Fig. 1 Stimuli used in the experimental tasks. In two experiments with a repeated on/off block design, subjects were shown pictures from a standard series. In both experiments, subjects were presented with a mixture of four happy and four angry faces in the on condition and eight neutral faces in the off condition. The stimuli were pseudorandomized and counterbalanced for gender in each phase. Stimuli were presented for 3 s with an interstimulus interval of 0.75 s. There were five repetitions of the on/off phases, over 5 min. In Experiment 1 (explicit task), subjects attended to and judged the facial expressions. In Experiment 2 (implicit task), subjects attended to and judged the facial gender.

Wis., USA) fitted with ANMR hardware and software (ANMR, Woburn, Mass., USA) at the Institute of Psychiatry, London. A quadrature birdcage headcoil was used for RF (radio frequency) transmission and reception. One hundred T_2*-weighted images depicting blood oxygenation level-dependent (BOLD) contrast were acquired [TE (echo time) 40 ms, TR (repetition time) 3000 ms] over 14 non-contiguous slices parallel to the intercommissural line (in-plane resolution 3.1 mm, slice thickness 5 mm, slice skip 0.5 mm), and a high-resolution inversion recovery echoplanar image of the whole brain was acquired during the same session for the purpose of spatial registration [TE 73 ms, TR 16 000 ms, 43 slices, in-plane resolution 1.5 mm, slice thickness 3 mm). The subjects were secured during scanning to prevent head movement, and standard methods were used to correct for residual movement (Friston *et al*., 1996). Generic brain activation mapping software (Brammer *et al*., 1997) was used to calculate the power of the BOLD signal changes at the frequency of alternation between the on and off conditions. This was expressed for each voxel as the fundamental power quotient (FPQ; power of frequency-related signal change divided by its standard error) and was represented in a parametric map, registered to standard coordinates (Talairach and Tournoux, 1988). The significance of BOLD signal changes was computed from the median value of FPQ at each voxel of the observed parametric maps after comparison with a null distribution of median FPQs from randomized parametric maps. *Post hoc* analysis of the time-course of regional increases in BOLD signal was applied in the analyses to determine the relationship between regional signal changes in the on and off conditions. We used a factorial design to examine significant regional BOLD activity in the brain due to the main effect of diagnosis (autistic disorder versus control) and the diagnosis $\times$ experiment interaction. ANOVA (analysis of variance) of voxel-wide BOLD signal changes was constrained to brain areas that showed significant activation ($P < 0.001$) in at least one of the four conditions. The total search volume for ANOVA was 355 voxels, and the expected number of false-positive activations at $P < 0.01$ was 4 voxels. We report voxel clusters of $\geqslant 3$ showing significant ($P < 0.01$) diagnosis $\times$ task interaction. Where there was a significant interaction, we plotted the mean power (FPQ) of the BOLD signal change (from a $3 \times 3 \times 3$ voxel volume) for each individual performing each experiment, in order to determine whether the significant interaction at that location

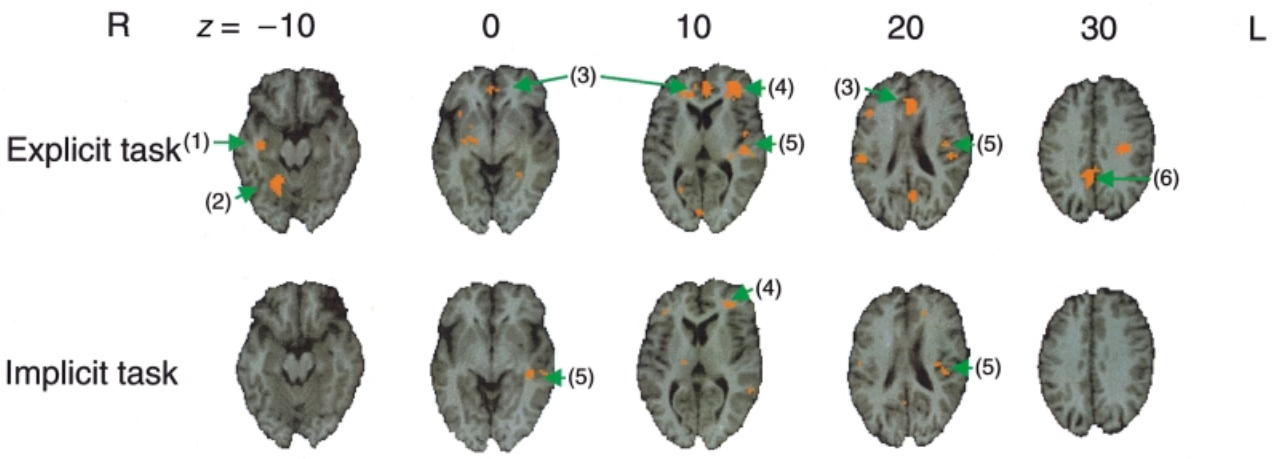

Fig. 2 Patterns of significant ($P < 0.001$) activations of nine subjects with autistic disorder during explicit and implicit processing of emotional facial expressions. Group data in-phase with the processing of happy and angry faces (versus neutral expressions) are plotted in red on axial slices of a normalized template brain derived from the structural scan of one subject. Vertical distances of axial sections are given above in millimetres, corresponding to Talairach *z*-coordinates. Experiment 1 tested the explicit processing of facial expressions: subjects judged the emotional content of visually presented facial stimuli by signalling with a button-press response if the face depicted a happy, angry or neutral expression. Experiment 2 tested the implicit processing of facial expression: subjects judged the gender of facial stimuli by signalling with a button-press response if the face was male or female. Brain regions indicated are (1) right amygdalohippocampal junction; (2) right fusiform gyrus; (3) anterior cingulate cortex; (4) left dorsolateral prefrontal cortex; (5) left superior/middle temporal gyrus; and (6) posterior cingulate/precuneus.

was due to differences unique to one task (e.g. underactivity during implicit processing in individuals with autistic disorder).

Results

Behavioural performance

Subjects with autistic disorder and controls were debriefed after scanning, and both groups reported no difficulties in viewing or judging the face stimuli. However, although the subjects with autistic disorder performed well above chance, performance data showed that they made more errors than controls during the explicit processing of facial expressions (Experiment 1, controls 97% correct, subjects with autistic disorder 82% correct). The number of errors made by subjects with autistic disorder during this task correlated (Pearson) significantly with deficits in performance of the Warrington face recognition memory task ($r = 0.915$, $P < 0.05$). Thus, subjects with autistic disorder may have had different subjective experiences of task difficulty compared with controls, which were not elicited at debriefing. These may have contributed to the differences in brain activity described below.

Brain activity associated with task performance

When subjects with autistic disorder performed the experiments, explicit processing of emotional facial expressions was associated with significantly ($P < 0.001$) increased activation of the right amygdalhippocampal junction (Talairach coordinates of cluster centroid, *x*, *y*, *z*: 35, –3, –13), right fusiform gyrus (29, –50, –10), anterior cingulate/medial prefrontal cortex (6, 34, 14), left dorsolateral prefrontal cortex (–25, 36, 9), left superior temporal gyrus (–48, –28, 12) and posterior cingulate/precuneus (4, –53, 28). Implicit processing of facial expressions in subjects with autistic disorder was associated with significant activation in the left superior and middle temporal gyrus (–52, –28, 4), cerebellar vermis (–3, –72, –18) and left anterior insula (–23, 17, 4), extending to the left dorsolateral prefrontal cortex (Fig. 2).

To explore the differences between controls and subjects with autistic disorder when processing facial expressions explicitly and implicitly, we used a 2 × 2 factorial design to determine the main effect of experiment (explicit versus implicit processing), the main effect of diagnosis, and the diagnosis × experiment interaction. In the main effect of experiment, activity in the left fusiform gyrus was greater during the explicit processing of the expressions than during the implicit processing. Activity in the left insula and left anterior hippocampus was greater during the implicit task than during the explicit task (Table 2).

Group differences during explicit and implicit processing of facial expressions

In the main effect of diagnosis, individuals with autistic disorder had significantly greater activity than controls in the left superior temporal gyrus (auditory cortex) and left peristriate visual cortex, whereas controls had significantly more activity in the right fusiform cortex (Table 2).

It was hypothesized that adults with autistic disorder, compared with controls, would show greater abnormalities during the implicit processing of expressions than when they

Table 2 *Significant regional differences in BOLD activation when high-functioning subjects with autistic disorder and controls processed facial expressions explicitly and implicitly*

Brain region	Brodmann area	Side	Coordinates			Corrected *P* value	No. voxels
			x	*y*	*z*		
(**A**) Main effect of task: explicit > implicit							
Fusiform gyrus	37	L	–20	–64	–13	0.004	3
Main effect of task: implicit > explicit							
Insula	–	L	–43	–6	9	0.0000	8
Hippocampus	–	L	–35	–25	–7	0.0000	4
(**B**) Main effect of group: subjects with autistic disorder > controls							
Superior temporal gyrus	22	L	–58	–28	4	0.0002	
Lingual/fusiform gyrus	18/19	L	–20	–61	4	0.0006	4
Main effect of group: controls > subjects with autistic disorder							
Fusiform gyrus	19	R	23	–58	–13	0.007	4
(**C**) Diagnosis × task interaction (subjects with autistic disorder versus controls) × (explicit versus implicit task)							
Cerebellar vermis	–	–	3	–61	–18	0.008	11
Pallidum	–	L	–20	–11	9	0.001	5
Middle temporal gyrus	21	L	–49	–42	4	0.006	3
Putamen	–	L	–23	17	4	0.004	3
Lateral cerebellum	–	L	–26	–69	–18	0.0000	5
Insula	–	L	–43	–6	9	0.0000	4
Amygdalohippocampal junction	–	L	–30	–11	–8	0.0000	4

(**A**) Areas showing significant main effect of task. (**B**) Areas showing significant main effect of diagnosis. (**C**) Areas showing significant diagnosis × task interaction. L = left; R = right.

attended explicitly to facial emotion. This was tested by examining the diagnosis × experiment interaction, to identify brain areas that differed significantly between groups in relative activity during explicit versus implicit processing of expressions. The cerebellar vermis, left lateral cerebellum, striatum (left globus pallidus and putamen), paralimbic and limbic areas (left insula and the amygdalohippocampal junction) and left middle temporal gyrus showed a significant diagnosis × experiment interaction (Table 2).

To interpret these findings further, we determined the task-related activity in each of these brain areas for each subject. In keeping with the hypothesis that subjects with autistic disorder would show less activity than controls during the implicit processing of expressions, the left cerebellum and left amygdalohippocampal region were activated in controls but not in subjects with autistic disorder (Fig. 3). However, during the explicit processing of expressions, the left middle temporal gyrus was activated in controls but not in subjects with autistic disorder. Task-dependent differences in the other brain areas where a significant diagnosis × condition interaction was expressed (i.e. the cerebellar vermis, left pallidum and left insula) were not readily interpretable (e.g. activity in the cerebellar vermis was increased in the explicit task in controls but increased in the implicit task in the subjects with autistic disorder). It is possible that that these regions may reflect the differential recruitment of separate neural systems by the two groups when explicitly and implicitly processing facial expression, but this remains speculative.

Discussion

Facial expressions are an outward display of emotional state, and are important cues in social communication (Ekman, 1998). Significant differences between subjects with autistic disorder and controls were found during the processing of facial expressions in the activity of early visual and auditory cortices (main effect of diagnosis), despite the fact that the groups were matched on the basis of age, IQ, education and occupational level. There were also significant differences in the relative patterns of activity during the explicit and implicit processing of facial expressions in the cerebellum, mesolimbic areas (insula, amygdalohippocampal junction and putamen) and lateral temporal lobe. Thus, high-functioning individuals with autistic disorder appear to have significant biological differences from controls in the function of brain areas that have previously been implicated in the aetiology of autism (e.g. Damasio and Maurer, 1978), particularly when shifting from explicit to implicit processing of facial expressions. However, caution is required in the interpretation of these results for a number of reasons. First, we could not address the developmental time course of these impairments in the autism group. Secondly, although subjects with autism were able to perform well above chance in the experimental

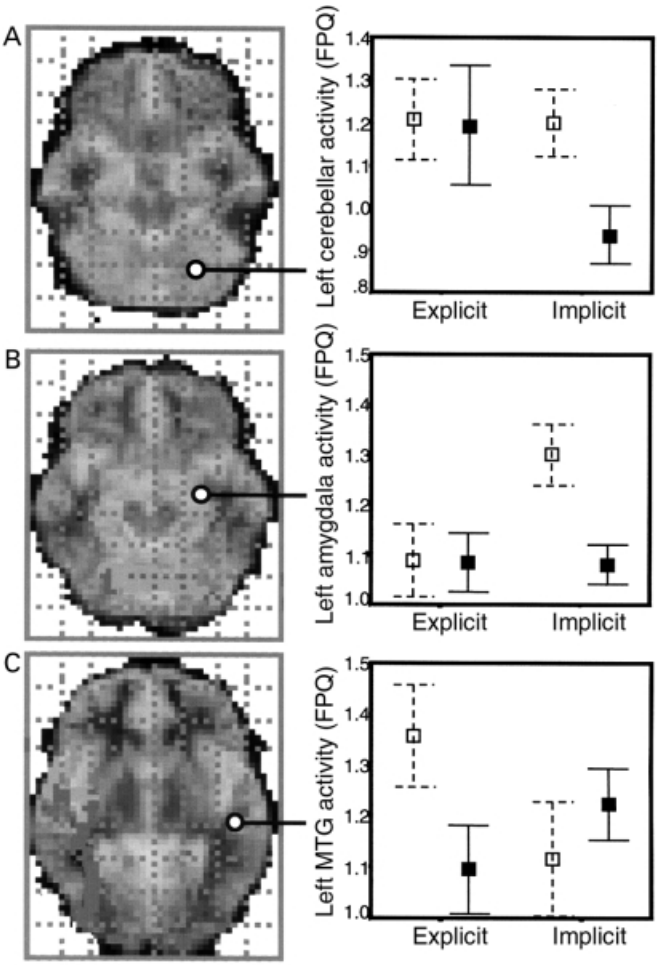

Fig. 3 Task-related activity of brain areas showing significant diagnosis × condition interaction. For each subject the average signal change (mean FPQ) during each experimental task was calculated from 3 × 3 × 3 voxel volumes at Talairach coordinates of the clusters having significant interactions. The mean and standard error of the FPQ in (**A**) the left cerebellum, (**B**) the left amygdalohippocampal junction and (**C**) the left middle temporal gyrus are plotted for controls and subjects with autistic disorder for the explicit and implicit tasks. The data for controls are represented by open squares and those for autistic subjects by filled squares. The locations of these brain areas are indicated on corresponding axial sections of a structural MRI template image derived from 12 subjects.

tasks, their performance was below that of controls. Thus, our results could have been confounded by differences in task performance, and perhaps by differences in subjective task difficulty that were not elicited at debriefing. Thirdly, our use of the term 'implicit' to denote emotional processing when subjects were attending to facial gender does not exclude the covert, but conscious, processing of facial expression during this task. Facial stimuli were not masked and were presented long enough for the subjects to process both the emotional and the gender attributes of the faces. Also, half the subjects performed the implicit task after the explicit emotion recognition task as a result of our counterbalancing the order of the tasks. Thus, the extent to which subjects carried over the instructions from the previous task may have influenced the between-group differences in patterns of activation. Further studies are required to address these issues.

The differences in brain function we observed in this study provide some support for the hypothesis that autism is associated with cerebellar abnormalities, and other research has reported significant differences in the anatomy of the cerebellum (Courchesne *et al*., 1988; Hashimoto *et al*., 1995). However, macroscopic cerebellar abnormalities may occur in the absence of autistic symptoms, and are not apparent in everyone with autism (Kleiman *et al*., 1992; Ciesielski and Knight, 1994). Moreover, oculomotor tests for cerebellar dysfunction are normal in adolescents and adults with autism (Minshew *et al*., 1999). Nonetheless, our study suggests that people with autistic disorder differ from controls in the activity of two cerebellar regions during the implicit, but not the explicit, processing of facial expressions. In adults without autism, cerebellar damage may give rise to clinical symptoms that resemble features of autism (impaired executive skills, flattening of affect and abnormal social behaviour). It has been suggested that these cognitive/affective symptoms arise from dysfunction of the pathways connecting the cerebellum to the prefrontal, limbic and striatal regions of the brain (Schmahmann and Sherman, 1998). Also, abnormal 5-hydroxytryptamine (serotonin) neurochemistry within one such cerebellar-thalamocortical pathway has been reported in children with autism (Chugani *et al*., 1997). Thus, some of the functional abnormalities observed in the present study may reflect abnormal cerebellar structure, and perhaps abnormal serotonergic function.

Our finding that people with autistic disorder have abnormal activity within the medial temporal lobe, striatum and insula when processing facial emotion are broadly consistent with Damasio and Maurer's mesolimbic model of autism (Damasio and Maurer, 1978), and previous studies have implicated these brain areas in the processing of facial expressions (e.g. Sprengelmeyer *et al*., 1996; Phillips *et al*., 1997; Morris *et al*., 1999). Because high-functioning people with autism have social deficits despite the preservation of explicit intellectual skills, we explored which brain areas mirrored this dissociation (i.e. we determined where activity during the explicit task did not significantly differ between the controls and autism group but was significantly different during the implicit task). The amygdalohippocampal junction and left cerebellum showed this pattern of activity. Previous studies of healthy controls reported that the amygdala region is active during the implicit processing of expressions (Morris *et al*., 1999; Critchley *et al*., 2000); also, the amygdala is implicated in normal social and emotional behaviour and in the learning and representation of the motivational meaning of stimuli (Gaffan, 1992; LeDoux, 1998). Thus, dysfunction of the amygdalohippocampal complex may partially explain some of the social deficits in people with autism. This suggestion is supported by reports that lesions affecting the medial temporal lobe in infancy are associated with social

abnormalities and autism-like behaviours (e.g. stereotypies) (Bachevalier, 1994; Bolton and Griffiths, 1997). Also, studies of people with autism have reported: (i) abnormalities in the distribution of pyramidal cells in the medial temporal lobe (Bauman and Kemper, 1985); (ii) (left) amygdala enlargement (Abell *et al*., 1999); and (iii) functional abnormalities in amygdala activity during a theory of mind task (Baron-Cohen *et al*., 1999). Thus, the amygdala region may form an important part of the pathogenic substrate of autism. However, our findings also suggest that people with autistic disorder have functional abnormalities in other brain regions when processing facial expressions, including the right fusiform gyrus, early sensory cortices, insula and cerebellum.

In the main effect of group, subjects with autistic disorder had reduced activity of the right fusiform gyrus, an area implicated in the general processing of faces (e.g. Kanwisher *et al*., 1999). Moreover, it was hypothesized that people with autistic disorder would not be impaired in the explicit processing of facial expressions; however, they made significantly more errors than controls and had reduced activity in left middle temporal gyrus during the explicit processing of facial features and emotional expressions. The deficits in performance on the task were significantly correlated with deficits for memory for faces (Warrington face recognition memory task), and so may reflect a more generalized deficit in processing facial features. The middle temporal gyrus is a visual cortical area that is important in the processing of facial features (Puce *et al*., 1998), and is activated during the explicit processing of facial expressions (Critchley *et al*., 2000). The fusiform and middle temporal gyri are both strongly modulated by 'top-down' attentional mechanisms, and it is therefore unclear whether the observed group differences in the activity of these regions reflect a primary deficit in facial processing or result from different attentional mechanisms operating with respect to faces in individuals with autistic disorder. Nevertheless, our findings suggest that the cortical representation of facial features may be abnormal in people with autism, and this may be the basis of the observed errors in the explicit task and in the Warrington face recognition memory task. Moreover, although explicit cognitive strategies may assist people with autistic disorder in some aspects of social behaviour, some individuals may have abnormalities in the representation of facial features within cortical visual areas, which impair these strategies and affect behaviour.

Although we only examined adults, autism is neuro-developmental in origin, and therefore our observations may have arisen from differences present during brain development. The core deficits of autism (lack of social reciprocity and circumscribed behavioural repertoires) are apparent in early childhood, and can be modelled experimentally in non-human primates by damage to medial temporal lobe structures (amygdalohippocampal complex) in infancy (Bachevalier, 1994). The amygdala has an important role in learning and representing the motivational meaning of stimuli (Gaffan, 1992). We speculate that abnormalities in these mechanisms during development may provide a basis for understanding the development of some behavioural features of autism. For example, in infancy, if social stimuli (e.g. faces, voices and touch) cannot be associated with internal states of comfort/discomfort, then they would not acquire special meaning (salience), preferential attention or the development of specialized processing streams (e.g. cortical language or face areas). Thus, a failure in associative learning of salience may arise from local lesions or abnormal neuronal architecture in the medial temporal lobe (e.g. Bauman and Kemper, 1985) or from abnormal connectivity with other regions. In the normal development of the human brain, different regions undergo dynamic maturational processes at different regionally specific times. However, in autism, evidence suggests diffuse abnormalities in brain development (e.g. Piven *et al*., 1990; Bailey *et al*., 1998; Abell *et al*., 1999) which may impair interregional connectivity (Horwitz *et al*., 1988) and result in transient metabolic abnormalities in specific association regions (Zilbovicius *et al*., 1995). We hypothesize that the functional abnormalities we observed, and the social deficits of autism, may arise from impaired learning and representation of the motivational meaning of social stimuli during a critical period of early brain development. Moreover, if such mechanisms contribute fundamentally to autism, it is probable that, in the majority of people with autism, this would result from abnormal connectivity due to widespread anomalies in regional brain maturation rather than simply focal lesions of medial temporal lobe structures (Piven *et al*., 1998; Abell *et al*., 1999). However, more detailed studies of the neural mechanisms contributing to the development of emotional skills in children are needed to enhance understanding of the patho-aetiology of autism and to aid the interpretation of studies of adults with autism.

In summary, high-functioning adults with autistic disorder, compared with controls, have abnormalities in regional brain activity during the explicit and implicit processing of emotional facial expressions, indicating dysfunction of pathways between limbic and paralimbic regions, the cerebellum and the extrastriate visual cortices. These findings may partly explain the social impairments of people with autism, but further studies are required to elucidate how these abnormalities arise and change with age.

Acknowledgement

E.T.B. was supported by the Wellcome Trust.

References

Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, et al. The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. Neuroreport 1999; 10: 1647–51.

Bachevalier J. Medial temporal lobe structures and autism. A review of clinical and experimental findings. [Review]. Neuropsychologia 1994; 32: 627–48.

Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, et al. A clinicopathological study of autism. Brain 1998; 121: 889–905.

Baron-Cohen S, Ring H, Moriarty J, Schmitz B, Costa D, Ell P. Recognition of mental state terms. Clinical findings in children with autism and a functional neuroimaging study of normal adults. Br J Psychiatry1994; 165: 640–9.

Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, et al. Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci 1999; 11: 1891–8.

Bauman M, Kemper TL. Histoanatomic observations of the brain in early infantile autism. Neurology 1985; 35: 866–74.

Bolton PF, Griffiths PD. Association of tuberous sclerosis of temporal lobes with autism and atypical autism. Lancet 1997; 349: 392–5.

Bowler DM. 'Theory of mind' in Asperger's syndrome. J Child Psychol Psychiatry 1992; 33: 877–93.

Brammer MJ, Bullmore ET, Simmons A, Williams SC, Grasby PM, Howard RJ, et al. Generic brain activation mapping in functional magnetic resonance imaging. A nonparametric approach. Magn Reson Imaging 1997; 15: 763–70.

Bryson SE, Wainwright-Sharp JA, Smith IM. Autism. A developmental spatial neglect syndrome? In: Enns JT, editor. The development of attention. Research and theory. Amsterdam: North-Holland; 1990. p. 405–27.

Chugani DC, Muzik O, Rothermel R, Behen M, Chakraborty P, Mangner T, et al. Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys. Ann Neurol 1997; 42: 666–9.

Ciesielski KT, Knight JE. Cerebellar abnormality in autism. A nonspecific effect of early brain damage? Acta Neurobiol Exp (Warsz) 1994; 54: 151–4.

Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jernigan TL. Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med 1988; 318: 1349–54.

Courchesne E, Press GA, Yeung-Courchesne R. Parietal lobe abnormalities detected with MR in patients with infantile autism. AJR Am J Roentgenol 1993; 160: 387–93.

Critchley HD, Daly EM, Phillips M, Brammer M, Bullmore E, Williams SC, et al. Explicit and implicit neural mechanisms for processing of social information from facial expressions. A functional magnetic resonance imaging study. Hum Brain Mapp 2000; 9: 93–105.

Damasio AR, Maurer RG. A neurological model for childhood autism. Arch Neurol 1978; 35: 777–86.

Ekman P, editor. The expression of the emotions in man and animals. 3rd ed. Chicago: University of Chicago Press. 1998.

Ekman P, Friesen W. Pictures of facial affect. Palo Alto (CA): Consulting Psychologists Press, 1975.

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med 1996; 35: 346–55.

Gaffan D. Amygdala and the memory of reward. In: Aggleton JP, editor. The amygdala. Neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley-Liss; 1992. p. 471–83.

Gillberg C. Asperger syndrome and high-functioning autism. [Review]. Br J Psychiatry 1998; 172: 200–9.

Haas RH, Townsend J, Courchesne E, Lincoln AJ, Schreibman L, Yeung-Courchesne R. Neurologic abnormalities in infantile autism. J Child Neurol 1996; 11: 84–92.

Happe F, Ehlers S, Fletcher P, Frith U, Johansson M, Gillberg C, et al. 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. Neuroreport 1996; 8: 197–201.

Hashimoto T, Tayama M, Murakawa K, Yoshimoto T, Miyazaki M, et al. Development of the brainstem and cerebellum in autistic patients. J Autism Dev Disord 1995; 25: 1–18.

Hazneder MM, Buchsbaum MS, Metzger M, Solimando A, Spiegel-Cohen J, Hollander E. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. Am J Psychiatry 1997; 154: 1047–50.

Horwitz B, Rumsey JM, Grady CL, Rapoport SI. The cerebral metabolic landscape in autism. Arch Neurol 1988; 45: 749–55.

Hughes C, Russell J, Robbins TW. Evidence for executive dysfunction in autism. Neuropsychologia 1994; 32: 477–92.

Kanwisher N, Stanley D, Harris A. The fusiform face area is selective for faces not animals. Neuroreport 1999; 10: 183–7.

Kleiman MD, Neff S, Rosman NP. The brain in infantile autism. Are posterior fossa structures abnormal? Neurology 1992; 42: 753–60.

LeDoux JE. The emotional brain: the mysterious underpinnings of emotional life. New York, Simon & Schuster; 1998.

Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview—Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 1994; 24: 659–85.

Minshew N, Luna B, Sweeney JA. Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism. Neurology 1999; 52: 917–22.

Morris JS, Ohman A, Dolan RJ. A subcortical pathway to the right amygdala mediating 'unseen' fear. Proc Natl Acad Sci USA 1999; 96: 1680–5.

Ozonoff S, Pennington BF, Rogers SJ. Executive function deficits in high-functioning autistic individuals. Relationship to theory of mind. J Child Psychol Psychiatry 1991; 32: 1081–105.

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, et al. A specific neural substrate for perceiving facial expressions of disgust. Nature 1997; 389: 496–8.

Piven J, Berthier ML, Starkstein SE, Nehme E, Pearlson G, Folstein S. Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. Am J Psychiatry 1990; 147: 734–9.

Piven J, Arndt S, Bailey J, Havercamp S, Andreasen NC, Palmer P. An MRI study of brain size in autism. Am J Psychiatry 1995; 152: 1145–9.

Piven J, Bailey J, Ranson BJ, Arndt S. An MRI study of the corpus callosum in autism. Am J Psychiatry 1997 154: 1051–6.

Piven J, Bailey J, Ranson BJ, Arndt S. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J Autism Dev Disord 1998; 28: 105–10.

Puce A, Allison T, Bentin S, Gore JC, McCarthy G. Temporal cortex activation in humans viewing eye and mouth movements. [Review]. J Neurosci 1998; 18: 2188–99.

Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121: 561–79.

Seigel BV Jr, Nuechterlein KH, Abel L, Wu JC, Buchsbaum MS. Glucose metabolic correlates of continuous performance test performance in adults with a history of infantile autism, schizophrenics, and controls. Schizophren Res 1995; 17: 85–94.

Sprengelmeyer R, Young AW, Calder AJ, Karnat A, Lange H, Homberg V. Loss of disgust. Perception of faces and emotions in Huntington's disease. Brain 1996; 119: 1647–65.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Warrington EK. Recognition Memory Test. Windsor (UK): NFER-Nelson; 1984.

Wechsler D. Wechsler Adult Intelligence Scale: WAIS-R manual. New York: Psychological Corporation; 1981.

Wing L. The autistic spectrum. [Review]. Lancet 1997; 350: 1761–6.

World Health Organization. ICD-10. The International Classification of Disease—Revision 10. Classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization; 1993.

Zilbovicius M, Garreau B, Samson Y, Remy P, Barthelemy C, Syrota A, et al. Delayed maturation of the frontal cortex in childhood autism. Am J Psychiatry 1995; 152: 248–52.

Received March 23, 2000. Revised June 10, 2000.
Accepted June 28, 2000