

# Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes

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## Summary

Ten able adults with autism or Asperger syndrome and 10 normal volunteers were PET scanned while watching animated sequences. The animations depicted two triangles moving about on a screen in three different conditions: moving randomly, moving in a goal-directed fashion (chasing, fighting), and moving interactively with implied intentions (coaxing, tricking). The last condition frequently elicited descriptions in terms of mental states that viewers attributed to the triangles (mentalizing). The autism group gave fewer and less accurate descriptions of these latter animations, but equally accurate descriptions of the other animations compared with controls. While viewing animations that elicited mentalizing, in contrast to randomly moving shapes, the normal group showed increased activation in a previously identified mentalizing network (medial prefrontal cortex, superior temporal sulcus at the temporo-parietal junction and temporal poles).

The autism group showed less activation than the normal group in all these regions. However, one additional region, extrastriate cortex, which was highly active when watching animations that elicited mentalizing, showed the same amount of increased activation in both groups. In the autism group this extrastriate region showed reduced functional connectivity with the superior temporal sulcus at the temporo-parietal junction, an area associated with the processing of biological motion as well as with mentalizing. This finding suggests a physiological cause for the mentalizing dysfunction in autism: a bottleneck in the interaction between higher order and lower order perceptual processes.

**Keywords:** anterior cingulate; autism; extrastriate cortex; superior temporal sulcus; temporal poles; Theory of Mind

**Abbreviations:** BA = Brodmann area; FFA = fusiform face area; FuG = fusiform gyrus; GD animations = animations eliciting descriptions of goal directed behaviour; IOcG = inferior occipital gyrus; Rd animations = animations of randomly moving shapes, eliciting simple behavioural descriptions; SPM = statistical parametric mapping; SFG = superior frontal gyrus; STS = superior temporal sulcus; TG = temporal gyrus; TmP/Am = temporal pole adjacent to amygdala; ToM = Theory of Mind; ToM animations = animations eliciting mental state attributions

## Introduction

The pervasive tendency to explain one's own and others' actions in terms of beliefs, desires and goals has been termed 'Theory of Mind' (ToM) or 'mentalizing'. According to one influential theory, autism is the result of impaired mentalizing, as manifest in a lack of social insight and impaired communication. This theory was first tested by Baron-Cohen *et al.* (1985). Reviews of recent experimental studies indicate that the original findings have been replicated, and that this area of research has become a very active branch of cognitive

neuroscience (Baron-Cohen *et al.*, 2000). By comparing tasks that differ only in the mentalizing component, experiments have ruled out that mentalizing difficulty is due to greater task complexity or lower general ability (e.g. Perner *et al.*, 1989; Leslie and Thaiss, 1992; Sodian and Frith, 1992). Evidence suggests that even able individuals with high-functioning autism read minds differently. Although their performance on standard laboratory tests of false belief attribution can be perfect, they experience long developmental delays when

acquiring the skill and are prone to errors on more advanced tests of ToM (Happé, 1994; Klin, 2000; Baron-Cohen *et al.*, 2001; Roeyers *et al.*, 2001).

There is overwhelming evidence that symptoms of autism result from abnormal brain development, probably as the result of genetic factors (for reviews see Bailey *et al.*, 1996; Happé and Frith, 1996). However, information on structural brain abnormalities in autism to date has been sparse as well as inconsistent. This is probably due to a number of factors, including the difficulty of carrying out post-mortem studies, the technical challenges presented by the need to quantify structural images, and the extreme heterogeneity of the autism spectrum. In the first histopathological studies, Bauman and Kemper (1994) described cellular abnormalities, in particular reduced neuronal cell size and increased cell packing density in the hippocampal complex, subiculum, entorhinal cortex, amygdala, mamillary body, medial septal nucleus and anterior cingulate gyrus. Outside the limbic system, reduced numbers of Purkinje cells were found in the posterior and inferior regions of the cerebellum. In a more recent neuropathological study, abnormalities in the limbic system were not investigated, but pathology was found in various cortical regions including the cerebellum and the brain stem (Bailey *et al.*, 1998). This study also documented enlarged brain size in autism.

Most of the cases studied to date had not only autism, but also mental retardation and epilepsy so that the specificity of the findings remains uncertain. Preliminary neuroanatomic data are available from one case of Asperger syndrome. Small neuronal cell size and increased cell packing density were found throughout the amygdala and the entorhinal cortex, while other parts of the limbic system appeared to be normal (Bauman, 1996). Structural imaging studies with high-functioning individuals with autism are now also beginning to contribute to the gradually emerging picture of the extent and type of neuroanatomic abnormalities. Again, inconsistencies make it difficult to draw firm conclusions. Abnormalities in a volumetric study suggest that frontal lobe cortex volume is increased in a subset of children with autism and that this increase correlates with the degree of cerebellar abnormality (Carper and Courchesne, 2000). Abell *et al.* (1999), using voxel-based morphometry, found relative decreases of grey matter in paracingulate sulcus and inferior frontal gyrus, and increases in periamygdaloid regions and middle temporal and inferior temporal gyrus. Howard *et al.* (2000), using a different type of analysis, also showed increases in periamygdaloid regions, while Aylward *et al.* (1999) found reduced volumes of amygdala and hippocampus. These latter structural studies are complemented by findings from a case with congenital left amygdala abnormality and Asperger syndrome. This individual, although of normal intelligence, showed profound failure on mentalizing tasks (Fine *et al.*, 2001).

Given the scarcity and the inconsistencies of the available anatomical data on the brain in autism, and given that a core symptom of autism is impaired social cognition, interest has

turned to investigating brain activity associated with social cognition in general and with mentalizing in particular. To date, six functional imaging studies of normal volunteers, using PET or fMRI, have been reported that were explicitly concerned with mentalizing. In these studies, mental states had to be attributed on the basis of historical knowledge (Goel *et al.*, 1995), stories (Fletcher *et al.*, 1995; Gallagher *et al.*, 2000; Vogeley *et al.*, 2001), cartoons (Gallagher *et al.*, 2000), cartoon strips (Brunet *et al.*, 2000) and animated geometric shapes (Castelli *et al.*, 2000). In all these studies activity associated with mentalizing was seen in three brain regions: an anterior region of medial prefrontal cortex/anterior cingulate cortex, an area in anterior temporal lobes close to the amygdala, and the superior temporal sulcus at the temporo-parietal junction. These consistent findings suggest that the rudiments of a mentalizing network in the brain are being identified.

Is this network dysfunctional in the case of autism, as the behavioural results suggest, and what might cause the dysfunction? So far, two functional neuroimaging studies of individuals with high-functioning autism (including Asperger syndrome, the subgroup without language or cognitive delay) have explicitly addressed mentalizing, while others have studied the perception of faces without an explicit requirement for mentalizing. Since faces are an important cue for the attribution of mental states, commonalities between these two types of studies in autism might emerge. In a PET study, Happé *et al.* (1996) compared brain activation in five individuals with autistic disorder with six controls while reading stories with a baseline of unconnected sentences. For stories that required mentalizing, the autistic group activated the same network of regions as the controls, but showed significantly less activity in medial prefrontal cortex. In an fMRI study, Baron-Cohen *et al.* (1999) compared six adults with autism with 12 controls. Subjects were asked to judge inner states from photographs of faces in which only the eyes could be seen, and to decide which of two simultaneously presented words best described the mental/emotional state. The baseline condition involved judging gender from the eyes. During performance of the mentalizing task, activity was seen in many brain areas including the three listed above. People with autism showed significantly less activity in the amygdala.

In one study of face perception, Critchley *et al.* (2000) scanned nine people with autistic disorder and nine controls while they observed faces that had neutral expressions or had expressions of happiness or anger. Subjects judged either the expression or the gender of the faces. In another study, Schultz *et al.* (2000) scanned 14 participants with autism spectrum disorder and 28 controls while discriminating between pairs of non-expressive faces, pairs of familiar objects or pairs of patterns. In both studies activity was seen in a region of fusiform gyrus widely accepted to be specialized for the perception of faces (Kanwisher *et al.*, 1997), and this activity was significantly lower in both autistic groups. The autistic groups showed greater activation

than controls in adjacent regions of temporal cortex, but the precise location of these regions was different in the two studies. Lack of activation of the fusiform face area (FFA) in autism was shown also by Pierce *et al.* (2001).

It is striking that while functional abnormalities were observed in all these studies, commonalities are not apparent. This suggests that the precise nature of the abnormality depends upon the task being performed. Thus, the abnormal activity associated with autism may be a secondary consequence of primary pathology located elsewhere. If so, what is this pathology? The aim of the present study was to examine brain activation in able people with high-functioning autism during on-line processing of social interactions in the absence of either verbal stimuli or visual depictions of humans. Unlike the two previous studies on mentalizing in autism, in the present study inferences concerning mental states were based solely on the perception of movement patterns of geometric shapes. Heider and Simmel (1944) demonstrated that viewing animation sequences where simple triangles and dots moved seemingly of their own accord powerfully conveyed the impression of intentional movements and goal-directed interactions. Heider and Simmel's stimuli, and similar animations, which reveal the pervasive tendency to attribute mental states even to simple shapes in motion, have been shown to individuals with autism in several studies (Abell *et al.*, 2000; Bowler and Thommen, 2000; Klin, 2000). All these studies found that even those individuals with autism who passed standard 'false belief' tests used mental state descriptions less extensively or less appropriately than controls.

In the present study we scanned 10 able adults with high-functioning autism or Asperger syndrome, and 10 normal individuals. The participants watched three types of silent animations depicting two self-propelled triangles. In the first type, ToM animations, the movement of the two interacting characters, suggested that one triangle anticipates or manipulates the 'mental state' of the other (i.e. one triangle is trying to trick the other). In the second type, goal-directed action (GD) animations, the interaction between the two triangles evoked description primarily in terms of behavioural interaction (e.g. two triangles dancing together). In the third type, random (Rd) animations, the purposeless movement of the two triangles elicited description without reference to interaction, goals or intentions (e.g. triangles bouncing around). During scanning participants watched these sequences passively and did not have to perform any verbal processing. However, they were asked in between scans to describe what happened in the animations.

Previous behavioural studies, in particular a study by Abell *et al.* (2000) that used the same stimulus materials with somewhat different instructions, led us to expect that the present group of able individuals with autism would show less accurate use of mental state descriptions. At the same time the present group would be expected to have a high success rate on standard tasks of ToM. The argument is that these standard tasks are 'off-line', thus allowing time to work

out the answer by logical inference. Moreover, these tasks are now often trained explicitly. The animations, in contrast, are novel stimuli that have not been trained, and may engage mentalizing 'on-line'. Based on previous imaging studies of mentalizing, we predicted differences in brain activation between the autism and the control group. We expected that the same network associated with mentalizing tasks would be identified as in previous studies: if credence can be given to a mentalizing network, then it needs to be independent of the modality and task used. Compared with previous studies of mentalizing we were not only using different materials, but also a more stringent analytical technique (a random effects model).

## Methods

### Participants

The autism group consisted of 10 adults (mean age 33 years, SD = 7.6) diagnosed on the basis of their developmental history with autistic disorder or Asperger's disorder according to DSM-IV criteria (American Psychiatric Association, 2000). Their high level of functioning was reflected by their education, social independence and employment. All were living semi-independently, seven had completed an undergraduate degree or other further education courses, and eight had a regular job. The control group consisted of 10 subjects recruited from university students and staff (mean age 25 years, SD = 4.8). The two groups did not differ with respect to verbal ability (percentile mean 61, SD = 24 for autism group; mean 76, SD = 11 for controls). We used the Quick Test, a test where words of increasing difficulty have to be matched to one in four pictures (similar to the Peabody test, but standardized for adults) (Ammons and Ammons, 1962). The groups also did not differ with respect to non-verbal ability (percentile mean 73, SD = 30 for autism group; mean 88, SD = 9.4 for controls). To test for non-verbal ability we used the Raven Standard Progressive Matrices (Raven, 1958). The groups also did not differ significantly with respect to the following standard false belief tests: Sally-Ann test (Baron-Cohen *et al.*, 1985), Smarties test (Perner *et al.*, 1989), Ice-Cream story (Perner and Wimmer, 1985), and Birthday Puppy story (Sullivan *et al.*, 1994). Six of the autism group and eight controls passed all four tests, one autistic and two control subjects passed three out of four tests, and three autistic subjects passed only the two first order tests (Sally-Ann and Smarties). The autism group can thus be described as able to pass at least first order false belief tests and as of at least average verbal and non-verbal ability.

Ethical permission to carry out this study was obtained from the Ethics Committee of the National Hospital for Neurology and Neurosurgery, and the Administration of Radioactive Substances Advisory Committee (ARSAC), UK. Informed consent was obtained from each of the participants.

## Materials

Twelve silent animations, lasting 34–45 s each, were shown on a computer screen. All featured a big red triangle and a small blue triangle, moving about on a framed white background. See <http://www.icn.ucl.ac.uk/groups/UF/research/animations.html> for examples. For more details of materials and scoring procedure see Castelli *et al.* (2000). The stimulus parameters of movement change, and presence or absence of an enclosure on the screen, was equated between conditions. The type of movement differed by definition; however, every effort was made to match visual interest across conditions, such as changes in shape and direction of movement.

## Procedure

Four different examples of each of three types of animation, ToM, GD and Rd, were displayed in a semi-random order over the course of 12 scans. A repeated-measures within-subjects design was used. After each scan subjects were asked: ‘What was happening in this animation?’ Verbal descriptions were recorded and coded with respect to three dimensions: ‘intentionality’ (degree of mental state attribution, range 0–5, with absence of mental state language at one extreme and elaborate use of mental state language at the other); ‘appropriateness’ (0–3, with incorrect at one extreme and highly appropriate at the other); and ‘length’ (0–4, ranging from no response to more than four clauses). Two raters blind to diagnosis independently scored each verbal description after having been trained to use the published set of scoring criteria (Castelli *et al.*, 2000), and their scores were averaged for data analysis. Agreement between the two raters for the intentionality score was good ( $\kappa$  0.92), both across groups and animation types. For ToM animations,  $\kappa$  was 0.96 for each subject group. On the appropriateness score, which was based on two other raters, full agreement was reached except for two descriptions from the autism group. Again an average score was used.

## Neuroimaging data acquisition

All subjects underwent both PET and MRI scanning on the same day. A Siemens VISION (Siemens, Erlangen) operating at 2.0T was used to acquire axial T<sub>1</sub>-weighted structural MRI images for anatomical coregistration. A full description of the H<sub>2</sub><sup>15</sup>O PET activation technique and data analysis can be found elsewhere (Friston, 1997). Regional cerebral blood flow (rCBF) was measured by recording the distribution of radioactivity following the intravenous injection of <sup>15</sup>O-labelled water (H<sub>2</sub><sup>15</sup>O) with a CTI Siemens Ecat HR+ PET scanner (CTI, Knoxville, TN, USA). Twelve scans were acquired per subject.

## Neuroimaging statistical analysis

Data were analysed with statistical parametric mapping (using SPM99 software from the Wellcome Department of

Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab (Mathworks Inc., Sherborn, MA, USA) using standardized procedures (Friston *et al.*, 1995a, b), including realignment for head movements, spatial normalization to the Montreal Neurological Institute template brain (Evans *et al.*, 1994) in the space of Talairach and Tournoux (1988) and smoothing. The smoothing kernel was a 3D Gaussian filter of 16 mm. Condition and subject effects were estimated according to the general linear model at each voxel. To test hypotheses about regionally specific condition effects, these estimates were compared using linear compounds or contrasts. The resulting set of voxel values for each contrast is an SPM of the *t*-statistic.

A random-effects analysis was carried out in order to evaluate common and differential areas of response in the autism and control groups during processing of the three types of animations (Friston and Pocock, 1992). Since in the random effects model the variance estimate is between-subject rather than within-subject, and the degrees of freedom are related to the number of subjects rather than the number of scans, a single mean image of the contrast of interest was first generated for each subject, and then three main analyses were carried out. (i) A main effects analysis allowing for identification of regions that were more activated by ToM than by Rd animations. (ii) A conjunction analysis to identify areas revealed by the main effects where there were significant differences between the autistic and the control groups. Finally, (iii) an analysis of functional connectivity (using the measures available in SPM99 for fixed-effects models) to identify significant differences in connectivity between the two groups.

## Results

### Behavioural data

As shown in Table 1, in both groups the ToM animations evoked more mental state attribution than did GD animations, which in turn evoked more such descriptions than did Rd animations.

The groups did not differ in the ratings of intentionality, appropriateness and length given to their descriptions of Rd and GD animations. For ToM animations, however, the autism group used fewer and less appropriate mental state descriptions than did the controls. Participants with autism tended to refer to the wrong mental states, for instance a description for the animation depicting ‘coaxing’ was: ‘The two triangles are obviously angry with each other—they are fighting’; a description for the animation depicting ‘mocking’, was: ‘... The small triangle is pursuing the large one ... the large one isn’t interested’. Such descriptions deviated from the actual ‘script’ used in the design of the animations and were never given by normal control subjects with one single exception. Strikingly, only two subjects with autism

gave mental state descriptions (each only once in four trials) that were rated as entirely appropriate.

The following examples of descriptions of the animation labelled ‘coaxing’ indicate that linguistic complexity varied markedly. It was not necessary to give complex descriptions to obtain high ratings of intentionality or appropriateness.

**Table 1** Ratings of participants’ descriptions [mean (SD)]

SCORE type (range) and group	Animation type		
	ToM	GD	Rd
Intentionality (0–5)			
Autism	2.9 (0.6)*	2.4 (0.7)	0.8 (0.7)
Control	4.3 (0.4)	2.4 (0.2)	0.5 (1.0)
Appropriateness (0–3)			
Autism	0.5 (0.2)*	1.3 (0.2)	1.5 (0.5)
Control	1.7 (0.2)	1.7 (0.3)	1.8 (0.4)
Length (0–4)			
Autism	2.5 (1.2)	2.1 (1.3)	2.0 (1.0)
Control	2.8 ( 1.1)	1.9 (0.9)	1.6 (0.8)

\*Significant difference (autism versus controls) at  $P < 0.001$ . The spontaneous descriptions for ToM animations were rated as reflecting less mental state attribution (intentionality score) for the autism group than the control group ( $Z = 3.6, P < 0.001$ ), and as reflecting less appropriate understanding of the story line (appropriateness score) for the autism group than the control group ( $Z = 3.8, P < 0.001$ ). No other group differences were significant. In the controls, intentionality score was higher for ToM than for GD animations ( $Z = 3.7, P < 0.0001$ ), and higher for GD than Rd animations ( $Z = 3.7, P < 0.0001$ ). The autism group also differentiated ToM and GD animations in terms of intentionality score ( $Z = 2.3, P < 0.05$ ), but described GD animations more appropriately than ToM animations ( $Z = 2.7, P < 0.01$ ).

High scores were given to the following example from the autism group: ‘The big triangle was trying to make the little one go out, but he doesn’t want to’; and to the following example from the normal group: ‘Triangles cuddling inside the house. Big wanted to persuade little to get out. He didn’t want to ... cuddling again’. Low scores for both intentionality and appropriateness were given to the following example from the autism group: ‘They are rubbing noses and caressing each other and they ended up holding hands’. A low score for appropriateness, but high score for intentionality was given to the following example from the autism group: ‘The two triangles were fighting each other. They obviously ... didn’t like each other ... they were ... one was following another to suggest ... fight each other ... and occasionally they ... later they clashed. It was quite ... the other one ... they were not getting on very well. They were obviously angry with each other’.

**Neuroimaging data**

*Random effects analysis of ToM compared with Rd animations*

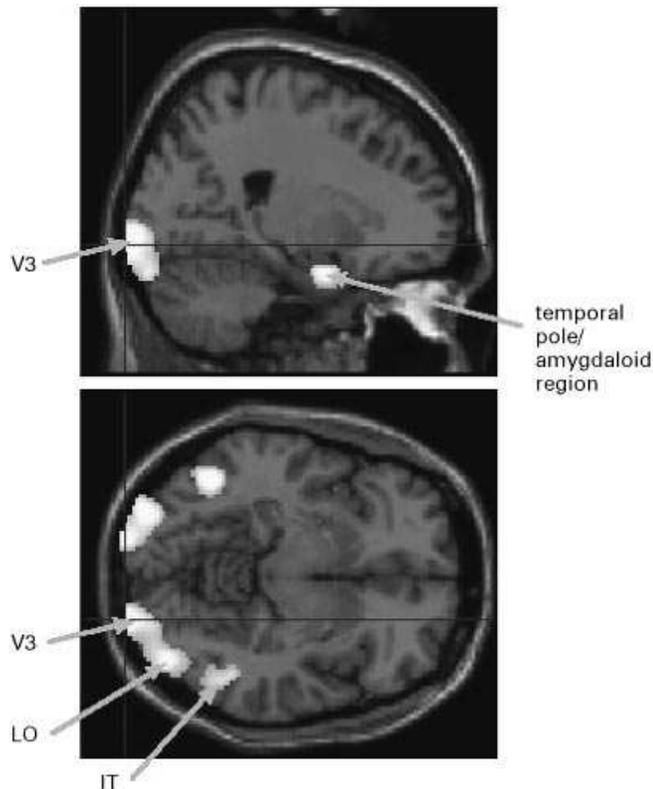
A network of brain regions for all subjects combined showed higher activity during ToM compared with Rd animations (see Table 2 and Figs 1–3). These regions comprised: basal temporal area (inferior temporal gyrus extending to anterior fusiform gyrus and temporal pole adjacent to amygdala), superior temporal sulcus (STS) at the temporo-parietal junction, extrastriate cortex (inferior occipital gyrus), and medial prefrontal cortex (SFG).

Figures 1–3 show the peaks of increased activity when watching ToM relative to Rd animations in these four

**Table 2** Regional cerebral blood flow activation common to autism and control groups while processing ToM animations compared with Rd animations

Foci of common activation	Left/right/medial	Coordinates			(Z score) $P <$
		x	y	z	
Basal temporal area					
ITG (BA 37)	L	<b>-46</b>	<b>-60</b>	<b>-10</b>	<b>(5.5) 0.002</b>
FuG (BA 20)	L	-38	-14	-30	(4.5) 0.0001
TmP/Am (BA 38)	R	42	6	-28	(4.2) 0.0001
Temporo-parietal junction					
STS (BA 22)	R	<b>64</b>	<b>-48</b>	<b>16</b>	<b>(5.6) 0.001</b>
STS (BA 21/22)	L	<b>-58</b>	<b>-52</b>	<b>4</b>	<b>(5.4) 0.003</b>
Extrastriate cortex					
IOcG (BA 18; V3)	R	<b>22</b>	<b>-104</b>	<b>-8</b>	<b>(5.0) 0.015</b>
IOcG (BA 18; V3)	L	<b>-18</b>	<b>-106</b>	<b>-10</b>	<b>(5.0) 0.02</b>
IOcG (BA18; LO)	R	<b>42</b>	<b>-82</b>	<b>-8</b>	<b>(4.8) 0.04</b>
IOcG (BA18; LO)	L	<b>-26</b>	<b>-94</b>	<b>-12</b>	<b>(4.8) 0.03</b>
Prefrontal area					
SFG (BA9)	M	10	54	30	(3.4) 0.0001

Z scores ( $P$ -value  $< 0.05$  corrected for multiple comparisons in bold;  $P$ -value  $< 0.001$  uncorrected in light type). Brain regions are identified by name and by putative Brodmann area (BA). LO = lateral occipital complex; ITG = inferior temporal gyrus; TmP/Am = temporal pole adjacent to amygdala; FuG = fusiform gyrus; STS = superior temporal sulcus; IOcG = inferior occipital gyrus; SFG = superior frontal gyrus.



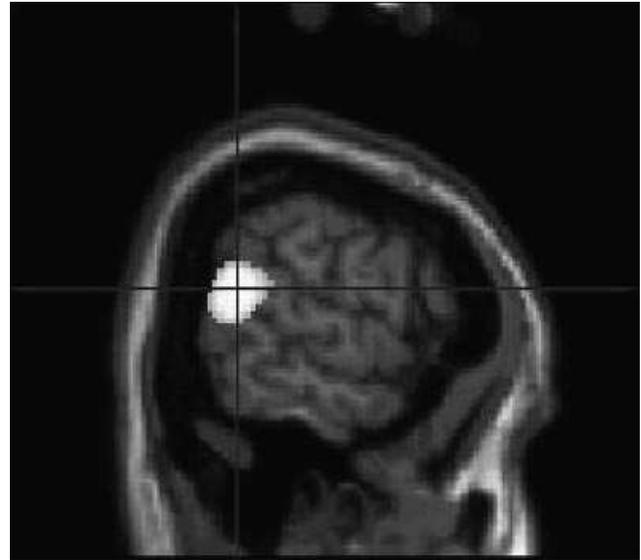
**Fig. 1** Greater activation in occipital and temporal pole/ amygdaloid regions while watching ToM animations (top: sagittal view; bottom: horizontal view).  $n = 20$ , both groups combined. LO = lateral occipital complex; IT = inferior temporal gyrus. This figure can be viewed in colour as supplementary material at Brain Online.

regions. The activated areas reported as main effects for processing ToM compared with Rd animations consisted of voxels that survived a voxel-wise multiple comparison correction of  $P < 0.05$ . While activation in prefrontal cortex ( $P < 0.0001$  uncorrected) did not meet this strict criterion, it was specifically predicted on the basis of previous studies of mentalizing. The activity associated with GD animations was intermediate between ToM and Rd animations.

Within the network defined above, direct comparison between the groups (see Table 3) revealed significantly reduced activation in autism subjects in the following regions: basal temporal area, STS and medial prefrontal area. The extrastriate regions were activated to the same extent in both groups. This pattern is illustrated in Fig. 4.

### Connectivity analysis

We hypothesized that the extrastriate region, which the autism group activated as strongly as controls while watching ToM in contrast to Rd animations, was not interacting appropriately with the rest of the larger mentalizing network, which showed reduced activation. We therefore investigated the connectivity of this region with the rest of the brain using the measures of functional connectivity available in SPM for



**Fig. 2** Greater activation in superior temporal sulcus while watching ToM animations ( $n = 20$ , both groups combined). This figure can be viewed in colour as supplementary material at Brain Online.



**Fig. 3** Greater activity in medial prefrontal cortex while watching ToM animations ( $n = 20$ , both groups combined). This figure can be viewed in colour as supplementary material at Brain Online.

fixed effects models (see Table 4). The extrastriate region showed significantly less connectivity with the STS in the autism group.

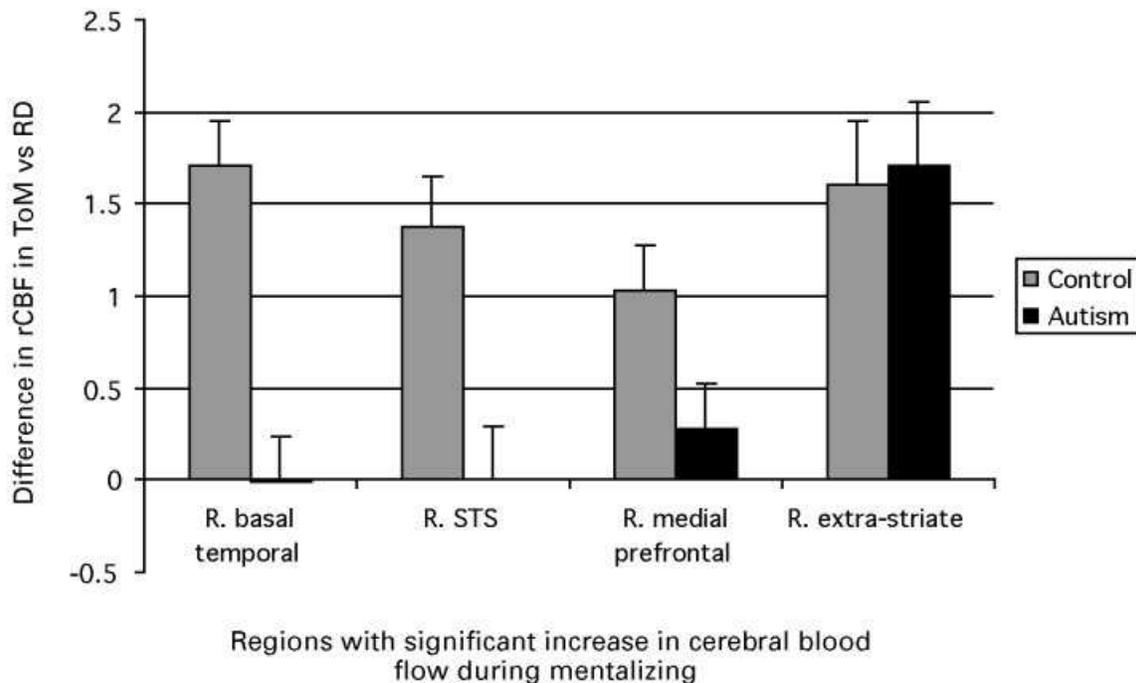
### Discussion

The claim that individuals with autism spectrum disorders, regardless of general intelligence, have an impairment in the attribution of mental states, has been confirmed once again.

**Table 3** Peaks of reduced activation in the autism group relative to the control group, during perception of ToM animations versus Rd animations

Foci of reduced activation	Left/right/ medial	Coordinates			(Z score)
		x	y	z	P <
Basal temporal area					
FuG (BA20)	L	<b>-38</b>	<b>-14</b>	<b>-26</b>	<b>(5.3) 0.004</b>
TmP/Am (BA38)	R	<b>42</b>	<b>6</b>	<b>-28</b>	<b>(6.2) 0.0001</b>
Temporo-parietal junction					
STS (BA 22/40)	R	<b>52</b>	<b>-46</b>	<b>24</b>	<b>(4.8) 0.04</b>
STS (BA 21)	L	<b>-66</b>	<b>-52</b>	<b>8</b>	<b>(4.9) 0.02</b>
Prefrontal area					
SFG (BA 9)	M	-4	56	22	(4.5) 0.0001

Analysis was restricted to the areas shown in Table 3 ( $P < 0.05$  corrected for multiple comparisons is shown in bold;  $P < 0.001$  uncorrected is shown in light type).



**Fig. 4** Comparison of activations in critical mentalizing regions in control and autistic groups, in the four regions that were activated more strongly during mentalizing. This figure can be viewed in colour as supplementary material at Brain Online.

Able individuals with high-functioning autism or Asperger syndrome gave fewer and less accurate interpretations of animations that elicited mentalizing. Normal participants were highly accurate in inferring the putative mental states of triangles without facial expressions or other human cues from movement cues alone. These data parallel those obtained in previous behavioural studies, and suggest that continuing impairments in individuals with autism can be revealed in characteristic inaccuracies in mental state attribution to animated shapes (Abell *et al.*, 2000; Bowler and Thommen, 2000; Klin, 2000).

Precisely as in previous studies of mentalizing that used a variety of stimuli (Fletcher *et al.*, 1995; Goel *et al.*, 1995;

**Table 4** Connectivity analysis

Foci of significant connectivity coordinates: x, y, z	(Z score)	P <
IOcG		
STS		
24, -100, -10	66, -46, 4	<b>(5.05) 0.004</b> voxel level
	68, -56, 18	(3.44) 0.001 uncorrected
	-68, -46, 0	(3.29) 0.001 uncorrected

The right extrastriate cortex (volume of interest of 6 mm radius) shows reduced connectivity with superior temporal sulcus in the autistic group compared with the control group.

Brunet *et al.*, 2000; Castelli *et al.*, 2000; Gallagher *et al.*, 2000; Vogeley *et al.*, 2001), greater activation during mentalizing was seen in medial prefrontal cortex, temporal poles and STS. These cortical regions, which are found consistently, can be considered the rudiments of the mentalizing network of the brain, independent of task and modality. New to this study, and probably task specific, were activations observed during mentalizing in extrastriate regions of occipital cortex. The more medial and posterior of these extrastriate regions can probably be identified with V3 in the visual cortex, while the more lateral may be part of the lateral occipital complex (LO; S. Zeki, personal communication). Area V3 is responsive to form and motion (Zeki, 1978; Felleman and van Essen, 1987) and has inputs dominated by the magnocellular processing stream (Felleman *et al.*, 1997), while area LO is involved in the early stages of object recognition (Malach *et al.*, 1995). The greater activation of these regions suggests that the ToM animations were more visually demanding despite our attempts to control for physical characteristics of the stimuli across conditions. However, the basic movement parameters seem to have been well controlled since ToM animations did not elicit more activity in V5/MT, the visual movement area.

Our able participants with high-functioning autism showed less activation than controls in three components of the mentalizing network: bilateral superior temporal sulcus at the temporo-parietal junction, the basal temporal area (left fusiform gyrus and right temporal pole adjacent to amygdala) and the medial prefrontal cortex. This last component also showed reduced activation in autism during ToM story comprehension in an earlier study by Happé *et al.* (1996), while lack of amygdala activation was found by Baron-Cohen *et al.* (1999) during a mentalizing task that involved eye gaze interpretation. Reduced activation in the region of the amygdala was also observed in subjects with autism while they processed facial expressions implicitly (Critchley *et al.*, 2000).

Given that the subjects with autism were impaired in making correct mental state attributions, one might expect to see a general reduction in activity associated with the mental state scenarios. Although a reduction was seen in areas previously associated with mentalizing, however, we did not see a reduction of activity in the extrastriate regions that in the present study were specifically associated with ToM animations. The greater activity in these early visual processing areas probably reflects the greater visual complexity of the mental state scenarios, since aspects of motion perception and velocity discrimination depend on intact extrastriate cortex (Plant and Nakayama, 1993). In these early visual processing stages, brain activity in our subjects with autism, just as in controls, was greater for the mental state scenarios. However, despite the detection of greater visual complexity by the autism group, this information failed to reach the multi-modal brain systems that are associated with mentalizing, regardless of task. In particular there was reduced connectivity between extrastriate regions and STS. While we found reduced

activation in STS, basal temporal and medial prefrontal regions for the autism group, we did not find weaker connectivity between them. This could be because PET is not sufficiently sensitive, with only 12 observations available for each subject. Functional MRI would be a more appropriate technique for connectivity analysis in the future. However, to gain full advantage from this, new and shorter animation sequences would have to be developed.

The finding of weak connectivity between STS and V3 regions in autism, given PET's insensitivity together with reduced activation in STS, must be regarded as highly significant. The role of STS in mentalizing may be specifically linked to the processing of real or potential motion of other agents. This region has also been activated in a number of studies when subjects observed biological motion (Bonda *et al.*, 1996; Puce *et al.*, 1998; Allison *et al.*, 2000). The region is probably the homologue of the superior temporal polysensory area (STP) in the macaque. STP contains cells with large receptive fields, which also respond to biological motion (Bonda *et al.*, 1996). This region of STS is one of the major targets of extrastriate visual areas and 'is in a unique position to integrate motion, spatial and object information' (Boussaoud *et al.*, 1990). In addition, in the macaque, STS also has strong reciprocal connections with the basolateral amygdala and adjacent regions of temporal pole (Amaral *et al.*, 1992).

How can we explain the reduced activation in STS and its relationship to normal activation in V3 in autism? In the present study, individuals with autism showed less activation in STS while watching scripted versus random animations. In the study of Schultz *et al.* (2000), individuals with autism showed less activation in FFA while looking at faces compared with objects. In our task the motion of agents has to be processed, which concerns STS, and in Schultz *et al.*'s task faces have to be processed, which concerns FFA. It seems plausible that both these more specialized regions are failing to get information from regions earlier in the visual processing stream, which process more general attributes of objects and movements. Schultz *et al.* (2000) proposed that in autism the processing of facial information may be compromised due to weak feedback connections from amygdala to fusiform gyrus, which in turn they attribute to the developmental effects of lack of signals for the emotional importance of faces. In our study, the difficulty experienced by the autism group in understanding ToM animations may have occurred because important information about the motion of the triangles was failing to be transmitted from V3 to STS. Two reasons may be considered for this transmission failure.

One possibility is a bottom-up failure of feed-forward visual signals reaching STS from V3. However, such an explanation would pre-suppose a different physiological reason for each study where reduced activation and transmission failure is found. Another possibility is a top-down failure of feedback signals reaching STS from the anterior components of the mentalizing system. Top-down feedback is

known to alter connectivity (Friston and Büchel, 2000). Amygdala, temporal pole or medial prefrontal cortex could be the sources of this problem. These anterior components normally enhance attention towards the signals being processed (i.e. increase connectivity between STS and earlier regions in the visual processing stream) and are thus able to signal their social significance. This is in line with the suggestion of Allison *et al.* (2000) that amygdalar feedback induces attentional amplification of STS activity evoked by salient social stimuli. We propose, therefore, that in the present study a lack of feedback from temporal pole and/or medial prefrontal cortex to STS results in the transmission failure between V3 and STS, and thus in an inability to recognize the social significance of the moving triangles. This top-down modulation hypothesis has the advantage of parsimony as it suggests a common pathology, which can also account for results from other studies.

Further support for the plausibility of the hypothesis comes from a study using single cell recording. Sugase *et al.* (1999) measured activity in cells in the inferior temporal cortex, while macaque monkeys looked at faces or geometrical shapes. The initial activity in the cells simply reflected whether the monkey was seeing a face or a shape, while the later occurring activity also distinguished between facial expressions. The authors suggest that these different processing modes over time reflect intra-area contributions and feedback from higher-level processing areas, necessary for the finer grain analysis of expressions. Likewise, in humans, as shown with intracranial event related potentials, context can enhance visual processing by late top-down modulation of temporally earlier activity in visual cortex (Olson *et al.*, 2001).

In conclusion, we hypothesize that weaker connectivity between V3 and STS in autism may reflect a lack of top-down modulation from more anterior regions such as the amygdala and surrounding temporal pole and/or medial prefrontal cortex, which would normally enhance attention to the incoming visual stimuli transmitted from V3. For reasons yet to be determined, such top-down modulation does not seem to occur in autism, and as a consequence the social meaning of movements is more difficult to perceive.

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