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Anatomical Differences in the Mirror Neuron System and Social Cognition Network in Autism

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder associated with impaired social and emotional skills, the anatomical substrate of which is still unknown. In this study, we compared a group of 14 high-functioning ASD adults with a group of controls matched for sex, age, intelligence quotient, and handedness. We used an automated technique of analysis that accurately measures the thickness of the cerebral cortex and generates cross-subject statistics in a coordinate system based on cortical anatomy. We found local decreases of gray matter in the ASD group in areas belonging to the mirror neuron system (MNS), argued to be the basis of empathic behavior. Cortical thinning of the MNS was correlated with ASD symptom severity. Cortical thinning was also observed in areas involved in emotion recognition and social cognition. These findings suggest that the social and emotional deficits characteristic of autism may reflect abnormal thinning of the MNS and the broader network of cortical areas subserving social cognition.

Keywords: autism, cortical thickness, empathy, mirror neuron system

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by debilitating socioemotional impairments, yet its neural substrates remain unknown. ASD affects as many as 1 in 166 children (Fombonne 2003) and is four times more prevalent in boys than in girls. ASD is usually diagnosed between the ages of 2 and 3 years, but early signs may be detectable by 12 months of age (Osterling and Dawson 1994). Defining features of autism include qualitative impairments in communication and reciprocal social interaction as well as repetitive and stereotyped behaviors (APA 1994).

One characteristic of ASD is the lack of empathy and emotional engagement with others (Gillberg 1992; APA 2000). Individuals with ASD have difficulty in relating to others and recognizing their emotions and fail to show the usual empathic reaction when other people demonstrate emotions of fear, pleasure, or pain (Hobson 1993). Lack of empathy in ASD has been quantified with objective test measures, such as the Empathy Quotient Questionnaire (Baron-Cohen and Wheelwright 2004).

A possible neural substrate of empathy is the mirror neuron system (MNS). The MNS was first identified as area F5 of the premotor cortex in the monkey by Rizzolatti, Gallese, and their colleagues (Gallese and others 1996; Rizzolatti, Fadiga, Gallese, and others 1996; Rizzolatti and others 1999), who demonstrated that a set of neurons in this area fired not only when a monkey was moving its own hand or mouth but also when it saw another individual (monkey or human) performing the same action. The activation of the same area of cortex in the observation as well as the execution of a given action led to the concept of an MNS.

Functional evidence for the presence of an MNS in humans comes from several studies using transcranial magnetic stimulation (TMS), electroencephalography (EEG), megnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) methodologies (Fadiga and others 1995, 2005; Grafton and others 1996; Rizzolatti, Fadiga, Matelli, and others 1996; Decety and others 1997; Hari and others 1998; Cochin and others 1999; Decety and Grezes 1999; Iacoboni and others 1999; Nishitani and Hari 2000; Strafella and Paus 2000; Buccino and others 2001; Gangitano and others 2001; Grezes and Decety 2001; Maeda and others 2002; Carr and others 2003; Grezes and others 2003; Leslie and others 2004). Since its discovery, the MNS has been found to be composed of a network of areas, including the pars opercularis of the inferior frontal gyrus (IFG) and its adjacent ventral area (inferior frontal cortex [IFC]), the inferior parietal lobule (IPL), and the superior temporal sulcus (STS), which are activated during the observation and imitation of an action. Insofar as the MNS generates internal representations of actions common to one's self and others, it is likely to be involved in our capacity to understand the actions and experiences of other people. Such an understanding is critical to social–communicative functioning, and accordingly, the MNS has been hypothesized by various researchers to be the basis of "mind reading," imitative learning, and empathy (Gallese 2003; Leslie and others 2004). Several recent functional brain-imaging studies have found evidence of mirror neuron dysfunction in autism (Nishitani and others 2004; Oberman and others 2005; Theoret and others 2005), implicating this neural system in autistic social impairment (Williams and others 2001).

Both the imitation and the attribution of mental states involve translating from another person's perspective into one's own. In addition, imitation requires a shared representation of perceived and executed action, and there is evidence suggesting that the MNS together with the superior parietal lobule serve this function (Iacoboni and others 1999; Williams and others 2001; Decety and others 2002; Heiser and others 2003; Koski and others 2003; Leslie and others 2004; Buxbaum and others 2005). Several studies have found imitative deficits in autism (for review, see Williams and others 2004), including deficits in imitating simple body movements and actions with symbolic meaning (Rogers and Pennington 1991) and in imitating facial expressions of emotion (Hertzig and others 1989; Loveland and others 1994). These deficits are present early in development (Rogers and others 2003). Together, these findings suggest that the basis for imitative and empathic deficits in autism could arise from a dysfunction in the MNS.

One consistent finding in the neuropathology of autism is the presence of enlarged head and brain size (Bailey and others 1993; Davidovitch and others 1996; Woodhouse and others

1996; Lainhart and others 1997; Fidler and others 2000; Fombonne 2000; Miles and others 2000; Aylward and others 2002) that is not present at birth but becomes evident during the first year of life (Lainhart and others 1997; Stevenson and others 1997; Courchesne and others 2001) and that appears to be mostly due to white matter increases (Herbert and others 2003). There is also evidence of a range of cortical abnormalities in autism (Gaffney and Tsai 1987; Berthier and others 1990; Piven and others 1990; Berthier 1994; Bailey and others 1998; Kemper and Bauman 1998), but the findings have shown little consistency. This might be for several reasons, including significant heterogeneity within the syndrome as well as the different ages of the cohorts that have been examined (for review, see Brambilla and others 2003; Palmen and Van Engeland 2004). Most magnetic resonance studies (Abell and others 1999; McAlonan and others 2002, 2005; Boddaert and others 2004; Waiter and others 2004) have used voxel-based morphometry (VBM), a technique that does not give a direct measure of the cortical thickness but instead gives probabilistic information about gray matter volume, which risks partial voluming. VBM studies have found gray matter abnormalities in the inferior frontal (Abell and others 1999; McAlonan and others 2002), parietal (McAlonan and others 2002), and temporal regions, including the STS (Boddaert and others 2004), as well as changes in the basal ganglia, the amygdala, and the cerebellum (Abell and others 1999; McAlonan and others 2002). More recently, McAlonan and others (2005) have shown generalized as well as localized gray matter reduction in the fronto-striatal, parietal, and temporal cortex in high-functioning autistic children, pointing to an early structural abnormality of the "social brain."

In contrast to VBM, direct measures of cortical thickness can reveal subtle cortical differences that are likely to reflect the underlying neuropathological abnormalities. For example, in schizophrenia, cortical thickness measures have proven useful in identifying abnormalities in prefrontal and temporal cortices (Kuperberg and others 2003). Direct measurement of the cortical mantle avoids the risk of introducing confounding factors by normalizing brains of different volumes into a common space and examining voxel intensities that might have been affected by this transformation.

In this study, we used a direct measurement of cortical thickness to examine the gray matter integrity and to explore the anatomical substrate of behavioral symptoms in ASD. This automated method, developed by Fischl and Dale (2000), accurately measures the thickness of the cerebral cortex across the entire brain and generates cross-subject statistics in a coordinate system based on cortical anatomy. The intersubject standard deviation of the thickness measure is less than 0.5 mm, allowing the detection of focal atrophy in small populations or even individual subjects. The reliability and accuracy of this new method have been assessed by within-subject test–retest studies as well as by comparison of cross-subject regional thickness measures with published values. This technique has also been validated with histological (Rosas and others 2002) and manual (Kuperberg and others 2003) measurements. It has been powerful in showing cortical thinning in schizophrenia (Kuperberg and others 2003), Huntington disease (Rosas and others 2002), and aging populations (Salat and others 2004).

Brain size is correlated with sex (Caviness and others 1996; Giedd and others 1996), age (Caviness and others 1996; Giedd and others 1996), intelligence quotient (IQ) (Andreasen and others 1993; Thompson and others 2001; Posthuma and others 2002), and handedness (Witelson and Goldsmith 1991). In order to restrict possible confounds due to these variations, we compared a group of 14 high-functioning ASD young male adults with a group of 14 male normal control (NC) subjects closely matched for age, IQ, and handedness.

Materials and Methods

Participants

Informed consent was obtained for each participant, and all procedures were approved by the Massachusetts General Hospital Internal Review Board. Twenty-eight male subjects (14 ASD and 14 matched controls) closely matched for age (ASD: 33 ± 12 years; NC: 31 ± 9 years; $P < 0.6$, nonsignificant [NS]), IQ (ASD: 113 ± 15; NC: 118 ± 13; $P < 0.4$, NS), and handedness (all right handed) participated in the study.

All participants were diagnosed with autism (8 subjects), Asperger disorder (4 subjects), or pervasive developmental disorder not otherwise specified (2 subjects) by an experienced clinician on the basis of their current presentation and developmental history. The diagnoses were confirmed using the Autism Diagnostic Interview–Revised (ADI-R) (Lord and others 1994) and the Autism Diagnostic Observation Schedule (Lord and others 2000) (see Table 1).

Imaging

Two high-resolution (1.0 × 1.0 × 1.25 mm) structural images were obtained with a magnetization-prepared rapid acquisition with gradient echoes sequence (128 slices, 256 × 256 matrix, echo time [TE] = 3.44 ms; repetition time [TR] = 7.25 ms; flip = 7°) on a 1.5-T Sonata MR scanner (Siemens, Munich, Germany).

Surface Reconstruction and Cortical Thickness Estimation

The 2 scans were motion corrected and averaged to create a single-image volume with high contrast-to-noise. Brain surfaces were reconstructed and inflated as described previously (Dale and others 1999; Fischl and others 1999). Cortical thickness measurements were obtained by reconstructing the gray/white matter boundary (Dale and Sereno 1993; Dale and others 1999; Fischl and others 1999) and the cortical surface. The distance between these 2 surfaces was calculated individually at each point across the cortical mantle (representing a total of ~147 000 vertices in each individual). The maps of cortical thickness were created using spatial intensity gradients across tissue classes and were not restricted to individual voxel intensities, allowing subvoxel resolution and submillimetric difference detection between groups (Fischl and Dale 2000).

Statistical Analysis

Data were then aligned according to cortical folding (Dale and others 1999) and smoothed on the surface tessellation, using an iterative nearest neighbor procedure. Smoothing was restricted to the cortical surface, thus avoiding the averaging of data across sulci or outside the

Table 1
ADI-R and ADOS scores of each participant in the ASD group

	ADI-R			ADOS			
	Communication	Social	Repetitive behaviors	Communication	Social	Total	Clinical diagnosis
Subject 1	5	13	1	2	9	11	PDD
Subject 2	14	24	2	2	6	8	Autism
Subject 3	12	15	2	2	6	8	Asperger
Subject 4	7	15	5	3	5	8	Autism
Subject 5	20	27	11	7	13	20	Autism
Subject 6				2	6	8	PDD
Subject 7	13	12	2	3	8	11	Asperger
Subject 8	7	15	2	1	5	6	Asperger
Subject 9	8	16	6	3	5	8	Autism
Subject 10	16	22	8	3	10	13	Autism
Subject 11	14	26	6	2	8	10	Autism
Subject 12	10	14	2	3	3	6	Autism
Subject 13	7	15	5	1	5	6	Asperger
Subject 14	11	18	8	2	6	8	Autism

Note: ADOS, Autism Diagnostic Observation Schedule; PDD, pervasive developmental disorder.

gray matter (Dale and others 1999). This method has the advantage of matching morphologically homologous cortical areas based on the main gyri/sulci patterns with minimal metric distortion. Per voxel *t*-tests were then calculated between groups for the smoothed values on the target surface.

In addition, definition of the regions of interest (ROIs) was performed by the detection of contiguous regions of statistical significance ($P < 0.01$) in the maps described above. These areas of regional thinning were used to create ROIs on a standard brain that were mapped back to each individual subject using spherical morphing to find homologous regions across subjects. A mean thickness score over each location was calculated for each subject. These scores were used to perform a *t*-test between the 2 groups for each ROI. Spearman rank-order correlation coefficients were computed to assess the degree of relationship between cortical thickness and behavioral (social and communication) symptoms as measured with ADI-R scores. Cortical locations were defined according to Duvernoy (1999)

Results

Several areas were significantly thinner in the autism group, including the IFG pars opercularis, IPL, and STS (Fig. 1). These areas are part of the network argued to be the basis of imitative and empathic behavior (e.g., Iacoboni and others 1999; Buccino and others 2001; Rizzolatti and Craighero 2004).

Thinning was also present in areas involved in facial expression production and recognition (face regions in sensory and motor cortex and in middle temporal gyrus) and in areas involved in social cognition (prefrontal cortex, anterior cingulate, medial parietal cortex, supramarginal gyrus, and middle and inferior temporal cortex).

There was no difference between groups in the remaining areas of the cortex. Cortical thinning was not associated with IQ scores in any of the areas of the MNS.

Significant associations between cortical thinning and autism symptom severity were found in—and nearly restricted to—all the areas constituting the MNS. Specifically, ADI-R combined social and communication diagnostic algorithm scores, which are based on the parental report of an individual's behaviors between the ages of 4 and 5 years, were correlated with cortical thinning bilaterally in the IFG pars opercularis, IPL, and right STS (see Table 2). The other areas that showed correlations with ADI-R symptoms were the right superior parietal lobule, involved in action observation and imitation (e.g., Buccino and others 2001); the inferior occipital gyrus, involved in face perception (e.g., Haxby and others 2000); and the supramarginal gyrus, involved in phonological processing (e.g., Celsis and others 1999).

Discussion

With this direct measurement of cortical mantle thickness, we found significant thinning of areas belonging to the MNS (IFC, IPL, and STS) and of other areas involved in social cognition in individuals with ASD. The MNS couples action perception and action production. This shared-representation model may also apply to the domain of emotion. Empathy can be defined as a phenomenon in which the perception of another's state activates one's own corresponding representation, which in turn activates somatic and autonomic responses. The MNS is arguably the basis of mind reading and empathy (Leslie and others 2004) and as such may well be implicated in the neuropathology of autism. Lack of empathy and emotional engagement with others is indeed one of the defining characteristics and very early signs of autism (Charman and others 1997; Baron-Cohen and Wheelwright 2004).

Our finding of thinning of the STS in individuals with ASD is consistent with robust evidence of abnormal processing of eye gaze in autism (Mundy and others 1986; Phillips and others 1992; Baron-Cohen and others 1997; Leekam and others 1998; Ristic and others 2002; Pelphrey and others 2005). In healthy individuals, observation of gaze direction is associated with STS activation (Perrett and others 1992; Puce and others 1998; Wicker and others 1998; Hoffman and Haxby 2000; Pelphrey and others 2003, 2004). STS is sensitive to the intention or goal directedness of a gaze shift (Pelphrey and others 2003), and the right STS is preferentially involved in the processing of social information conveyed by shifts in eye gaze (Pelphrey and others 2004). Deficits of activation of STS in ASD have been found in a variety of tasks involving attribution of intentions on the basis of shifts of gaze, body movements, or geometric figure movement (Baron-Cohen and others 1999; Castelli and others 2002; Mosconi and others 2005; Pelphrey and others 2005). Our findings of cortical thinning in the right STS of ASD are also in line with findings of volumetric differences (Boddaert and others 2004) and sulcal displacement (Levitt and others 2003) of STS in children with ASD.

Thinning was also observed bilaterally in the superior parietal lobule, an area involved in imitation (Buxbaum and others 2005; Chaminade and others 2005), a function that has been shown to

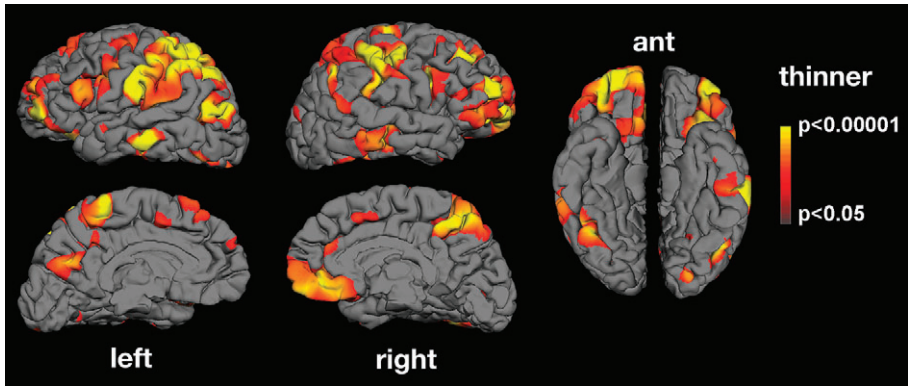

Figure 1. Mean thickness difference significance maps. Lateral, medial, and ventral views of the brain showing areas presenting cortical thinning in the autism group compared with normal controls. No area showed cortical thickening. Significant thinning was found in areas belonging to the MNS as well as in areas involved in facial expression production and recognition, imitation, and social cognition.

Table 2
Areas of significant cortical thinning in autism compared with matched controls

	BA	Hemi	Thickness (mm), mean (SEM)		*t*-Test	Correlation with ADI-R symptoms (Spearman *r*; *P*)
			ASD	Controls		
Mirror system						
IFG pars opercularis	44	rh	1.98 (0.04)	2.17 (0.04)	***	−0.32; ≤0.1
		lh	2.14 (0.07)	2.41 (0.06)	**	−0.57; ≤0.05
IPL	39	rh	2.11 (0.06)	2.49 (0.07)	***	−0.67; ≤0.01
		lh	2.06 (0.03)	2.26 (0.05)	***	−0.42; ≤0.1
STS	22	rh	2.05 (0.09)	2.39 (0.05)	**	0.40; ≤0.1
Face-related areas						
Precentral gyrus (motor face area)	4	rh	1.85 (0.02)	1.96 (0.03)	**	NS
		lh	2.11 (0.06)	2.36 (0.06)	**	NS
Postcentral gyrus (sensory face area)	SI	rh	1.96 (0.03)	2.16 (0.03)	***	NS
		lh	2.03 (0.03)	2.24 (0.03)	***	NS
Inferior occipital gyrus	19	rh	2.07 (0.08)	2.31 (0.06)	*	NS
		lh	1.90 (0.06)	2.22 (0.05)	***	−0.59; ≤0.05
Social cognition						
Orbitofrontal cortex	11	rh	2.25 (0.04)	2.50 (0.05)	***	NS
		lh	2.52 (0.07)	2.76 (0.06)	**	NS
Prefrontal cortex	10	rh	1.88 (0.03)	2.10 (0.04)	***	NS
		lh	2.07 (0.03)	2.34 (0.04)	***	NS
Anterior cingulated	24 + 32	rh	1.88 (0.05)	2.24 (0.05)	***	NS
IFG pars triangularis	45	rh	1.96 (0.11)	2.25 (0.11)	*	NS
Superior frontal gyrus	8	rh	1.97 (0.05)	2.22 (0.03)	***	NS
		lh	2.00 (0.04)	2.16 (0.04)	**	NS
Supramarginal gyrus	40	rh	2.34 (0.04)	2.58 (0.06)	**	0.51; ≤0.05
		lh	2.20 (0.06)	2.51 (0.05)	***	NS
Inferior temporal gyrus	37	rh	2.20 (0.06)	2.45 (0.09)	*	NS
Middle temporal gyrus	21	rh	2.39 (0.08)	2.74 (0.06)	**	NS
		lh	2.40 (0.06)	2.76 (0.04)	***	NS
Middle occipital gyrus	19	lh	2.09 (0.03)	2.29 (0.02)	***	NS
Superior parietal lobule	7a	rh	1.97 (0.05)	2.18 (0.03)	**	NS
		lh	1.86 (0.03)	2.06 (0.03)	***	NS
Medial parietal cortex	7b	lh	2.07 (0.10)	2.41 (0.10)	*	NS
Imitation						
Superior parietal lobule	7b	rh	1.88 (0.04)	2.12 (0.05)	***	−0.53; ≤0.05
		lh	1.87 (0.03)	2.13 (0.04)	***	

Note: BA, Brodmann area. All the areas that belong to the MNS are affected. Other areas presenting cortical thinning are involved in facial expression production and understanding, social cognition, and imitation. Thinning was specific to these regions, and no group differences were found in the rest of the cortex. Hemi = hemisphere. Rh = right hemisphere. Lh = left hemisphere. *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.

be impaired as early as 34 months of age in children with autism (Rogers and others 2003). Other areas of cortical thinning included the face regions of the motor and premotor cortex bilaterally, the right face somatosensory cortex, and the middle temporal gyrus. These areas are involved in emotion production and recognition. Damage to these areas results in deficits in facial expression recognition, consistent with the fact that deficits in production and recognition of emotion reliably co-occur (e.g., Adolphs and others 1996). These findings could cast light on the abnormalities shown by individuals with ASD in facial expression recognition.

Additional areas of cortical thinning were found in the lateral, medial, and ventral prefrontal cortex, the anterior cingulate, the medial parietal cortex, and the supramarginal gyrus. These regions have critical functions in social cognition (Brothers 1990), and functional imaging in autism has suggested altered functionality in these regions (Baron-Cohen and others 1999). For example, reduced medial prefrontal dopaminergic activity and reduced glucose metabolism in the anterior cingulate gyrus have been reported (Schultz and Klin 2002), and medial prefrontal cortex activation has been reported for tasks involving the attribution of mental states in NCs (Fletcher and others 1995) but not in ASD subjects (Happe and others 1996).

The cortical thickness differences observed might be due to primary developmental histopathological abnormalities, including defective neuronal proliferation or migration (Rorke 1994), cell density, and microcolumnar changes (Casanova and others 2002). Alternatively, or in combination, the cortical thinning we observed in ASD could be a secondary consequence of a lack of input to specific brain areas resulting either from abnormal subcortical or cortical function or from primary white matter abnormalities. The latter possibility is consistent with recent findings of reduced cortical connectivity in ASD (Belmonte and others 2004; Just and others 2004; Welchew and others 2005).

The correlation of MNS thinning with ADI-R scores, based on symptoms reported for the preschool years, may indicate that MNS abnormalities are already present in early childhood. This possibility is supported by recent data from McAlonan and others (2005), who found changes in gray matter volumes in high-functioning children with autism. Early dysfunction of the MNS could generate abnormal development of other areas of the social brain and result in several of the clinical features that characterize autism, including the failure to develop reciprocal social and emotional abilities. Indeed, if social understanding has its basis in experiential sharing, a function sustained by the MNS, autistic symptoms could be seen as developing as a consequence of a lack of mimicry and empathic activity caused by an underlying failure of the MNS system. Future studies using in vivo magnetic resonance spectroscopy imaging, a method allowing the characterization of a cell population involved in pathological processes (e.g., Cheng and others 2002), might clarify the underlying neuropathological change in autism, and diffusion studies will cast light on the anatomical connectivity in ASD brains.

Our technique is limited to measures of the cortex and does not allow us to examine potentially affected subcortical structures that play a pivotal role in the social brain, such as the amygdala and the basal ganglia (Baron-Cohen and others 2000; Hrdlicka and others 2005; McAlonan and others 2005). In addition, the present findings cannot determine whether the anatomical differences observed are a cause or a consequence of behavioral abnormalities, which will need to be resolved by longitudinal studies. More studies are needed to finely probe the functional integrity of this network in ASD and to investigate the associations among cortical thickness changes, brain-activation patterns, and the severity of the behavioral manifestations of autism. Finally, studies of neurofunctional changes in children receiving skills training in imitation and emotional decoding may help to further specify the cerebral bases of empathic behavior as well as to determine the degree of plasticity in this neural system.

Notes

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References

Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, Happe F, Frith C, Frith U. 1999. The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. Neuroreport 10:1647–1651.

Adolphs R, Damasio H, Tranel D, Damasio AR. 1996. Cortical systems for the recognition of emotion in facial expressions. J Neurosci 16:7678–7687.

Andreasen NC, Flaum M, Swayze V II, O'Leary DS, Alliger R, Cohen G, Ehrhardt J, Yuh WT. 1993. Intelligence and brain structure in normal individuals. Am J Psychiatry 150:130–134.

[APA] American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders (DSM-IV). Washington, DC: American Psychiatric Association.

[APA] American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders, DSM-IV-TR. Washington, DC: American Psychiatric Association.

Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. 2002. Effects of age on brain volume and head circumference in autism. Neurology 59:175–183.

Bailey A, Luthert P, Bolton P, Le Couteur A, Rutter M, Harding B. 1993. Autism and megalencephaly. Lancet 341:1225–1226.

Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, Rutter M, Lantos P. 1998. A clinicopathological study of autism. Brain 121(Pt 5):889–905.

Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SC. 2000. The amygdala theory of autism. Neurosci Biobehav Rev 24:355–364.

Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simmons A, Williams SC. 1999. Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci 11:1891–1898.

Baron-Cohen S, Wheelwright S. 2004. The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. J Autism Dev Disord 34:163–175.

Baron-Cohen S, Wheelwright S, Jolliffe T. 1997. Is there a "language of the eyes"? Evidence from normal adults and adults with autism or Asperger syndrome. Vis Cogn 4:311–331.

Belmonte MK, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ. 2004. Autism and abnormal development of brain connectivity. J Neurosci 24:9228–9231.

Berthier ML. 1994. Corticocallosal anomalies in Asperger's syndrome. AJR Am J Roentgenol 162:236–237.

Berthier ML, Starkstein SE, Leiguarda R. 1990. Developmental cortical anomalies in Asperger's syndrome: neuroradiological findings in two patients. J Neuropsychiatry Clin Neurosci 2:197–201.

Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet MH, Barthelemy C, Mouren MC, Artiges E, Samson Y, Brunelle F, Frackowiak RS, Zilbovicius M. 2004. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. Neuroimage 23:364–369.

Brambilla P, Hardan A, di Nemi SU, Perez J, Soares JC, Barale F. 2003. Brain anatomy and development in autism: review of structural MRI studies. Brain Res Bull 61:557–569.

Brothers L. 1990. The neural basis of primate social communication. Motiv Emotion 14:81–91.

Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, Seitz RJ, Zilles K, Rizzolatti G, Freund HJ. 2001. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur J Neurosci 13:400–404.

Buxbaum LJ, Kyle KM, Menon R. 2005. On beyond mirror neurons: internal representations subserving imitation and recognition of skilled object-related actions in humans. Brain Res Cogn Brain Res 25:226–239.

Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci USA 100:5497–5502.

Casanova MF, Buxhoeveden DP, Switala AE, Roy E. 2002. Minicolumnar pathology in autism. Neurology 58:428–432.

Castelli F, Frith C, Happe F, Frith U. 2002. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain 125:1839–1849.

Caviness VS Jr, Kennedy DN, Richelme C, Rademacher J, Filipek PA. 1996. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. Cereb Cortex 6:726–736.

Celsis P, Boulanouar K, Doyon B, Ranjeva JP, Berry I, Nespoulous JL, Chollet F. 1999. Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. Neuroimage 9:135–144.

Chaminade T, Meltzoff AN, Decety J. 2005. An fMRI study of imitation: action representation and body schema. Neuropsychologia 43:115–127.

Charman T, Swettenham J, Baron-Cohen S, Cox A, Baird G, Drew A. 1997. Infants with autism: an investigation of empathy, pretend play, joint attention, and imitation. Dev Psychol 33:781–789.

Cheng LL, Newell K, Mallory AE, Hyman BT, Gonzalez RG. 2002. Quantification of neurons in Alzheimer and control brains with ex vivo high resolution magic angle spinning proton magnetic resonance spectroscopy and stereology. Magn Reson Imaging 20:527–533.

Cochin S, Barthelemy C, Roux S, Martineau J. 1999. Observation and execution of movement: similarities demonstrated by quantified electroencephalography. Eur J Neurosci 11:1839–1842.

Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY. 2001. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology 57:245–254.

Dale AM, Fischl B, Sereno MI. 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194.

Dale AM, Sereno MI. 1993. Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. J Cogn Neurosci 5:162–176.

Davidovitch M, Patterson B, Gartside P. 1996. Head circumference measurements in children with autism. J Child Neurol 11:389–393.

Decety J, Chaminade T, Grezes J, Meltzoff AN. 2002. A PET exploration of the neural mechanisms involved in reciprocal imitation. Neuroimage 15:265–272.

Decety J, Grezes J. 1999. Neural mechanisms subserving the perception of human actions. Trends Cogn Sci 3:172–178.

Decety J, Grezes J, Costes N, Perani D, Jeannerod M, Procyk E, Grassi F, Fazio F. 1997. Brain activity during observation of actions. Influence of action content and subject's strategy. Brain 120:1763–1777.

Duvernoy HM. 1999. The human brain: surface, three-dimensional sectional anatomy with MRI, and blood supply. Wien: Springer Verlag.

Fadiga L, Craighero L, Olivier E. 2005. Human motor cortex excitability during the perception of others' action. Curr Opin Neurobiol 15:213–218.

Fadiga L, Fogassi L, Pavesi G, Rizzolatti G. 1995. Motor facilitation during action observation: a magnetic stimulation study. J Neurophysiol 73:2608–2611.

Fidler DJ, Bailey JN, Smalley SL. 2000. Macrocephaly in autism and other pervasive developmental disorders. Dev Med Child Neurol 42:737–740.

Fischl B, Dale AM. 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 97:11050–11055.

Fischl B, Sereno MI, Dale AM. 1999. Cortical surface-based analysis II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9:195–207.

Fletcher PC, Happe F, Frith U, Baker SC, Dolan RJ, Frackowiak RS, Frith CD. 1995. Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. Cognition 57:109–128.

Fombonne E. 2000. Is a large head circumference a sign of autism? J Autism Dev Disord 30:365.

Fombonne E. 2003. Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord 33:365–382.

Gaffney GR, Tsai LY. 1987. Magnetic resonance imaging of high level autism. J Autism Dev Disord 17:433–438.

Gallese V. 2003. The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. Psychopathology 36:171–180.

Gallese V, Fadiga L, Fogassi L, Rizzolatti G. 1996. Action recognition in the premotor cortex. Brain 119:593–609.

Gangitano M, Mottaghy FM, Pascual-Leone A. 2001. Phase-specific modulation of cortical motor output during movement observation. Neuroreport 12:1489–1492.

Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL. 1996. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb Cortex 6:551–560.

Gillberg CL. 1992. The Emanuel Miller Memorial Lecture 1991. Autism and autistic-like conditions: subclasses among disorders of empathy. J Child Psychol Psychiatry Allied Discip 33:813–842.

Grafton ST, Arbib MA, Fadiga L, Rizzolatti G. 1996. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. Exp Brain Res 112:103–111.

Grezes J, Armony JL, Rowe J, Passingham RE. 2003. Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. Neuroimage 18:928–937.

Grezes J, Decety J. 2001. Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. Hum Brain Mapp 12:1–19.

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

Hari R, Forss N, Avikainen S, Kirveskari E, Salenius S, Rizzolatti G. 1998. Activation of human primary motor cortex during action observation: a neuromagnetic study. Proc Natl Acad Sci USA 95:15061–15065.

Haxby JV, Hoffman EA, Gobbini MI. 2000. The distributed human neural system for face perception. Trends Cogn Sci 4:223–233.

Heiser M, Iacoboni M, Maeda F, Marcus J, Mazziotta JC. 2003. The essential role of Broca's area in imitation. Eur J Neurosci 17:1123–1128.

Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, Hodgson J, Adrien KT, Steele S, Makris N, Kennedy D, Harris GJ, Caviness VS Jr. 2003. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 126:1182–1192.

Hertzig ME, Snow ME, Sherman M. 1989. Affect and cognition in autism. J Am Acad Child Adolesc Psychiatry 28:195–199.

Hobson RP. 1993. Autism and the development of mind. East Sussex, UK: Lawrence Erlbaum Associates Ltd.

Hoffman EA, Haxby JV. 2000. Distinct representations of eye gaze and identity in the distributed human neural system for face perception. Nat Neurosci 3:80–84.

Hrdlicka M, Dudova I, Beranova I, Lisy J, Belsan T, Neuwirth J, Komarek V, Faladova L, Havlovicova M, Sedlacek Z, Blatny M, Urbanek T. 2005. Subtypes of autism by cluster analysis based on structural MRI data. Eur Child Adolesc Psychiatry 14:138–144.

Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G. 1999. Cortical mechanisms of human imitation. Science 286:2526–2528.

Just MA, Cherkassky VL, Keller TA, Minshew NJ. 2004. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain 127:1811–1821.

Kemper TL, Bauman M. 1998. Neuropathology of infantile autism. J Neuropathol Exp Neurol 57:645–652.

Koski L, Iacoboni M, Dubeau MC, Woods RP, Mazziotta JC. 2003. Modulation of cortical activity during different imitative behaviors. J Neurophysiol 89:460–471.

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B. 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 60:878–888.

Lainhart JE, Piven J, Wzorek M, Landa R, Santangelo SL, Coon H, Folstein SE. 1997. Macrocephaly in children and adults with autism. J Am Acad Child Adolesc Psychiatry 36:282–290.

Leekam SR, Hunnisett E, Moore C. 1998. Targets and cues: gaze-following in children with autism. J Child Psychol Psychiatry Allied Discip 39:951–962.

Leslie KR, Johnson-Frey SH, Grafton ST. 2004. Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage 21:601–607.

Levitt JG, Blanton RE, Smalley S, Thompson PM, Guthrie D, McCracken JT, Sadoun T, Heinichen L, Toga AW. 2003. Cortical sulcal maps in autism. Cereb Cortex 13:728–735.

Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, Pickles A, Rutter M. 2000. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30:205–223.

Lord C, Rutter M, Le Couteur A. 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.

Loveland KA, Tunali-Kotoski B, Pearson DA, Brelsford KA, Ortegon J, Chen R. 1994. Imitation and expression of facial affect in autism. Dev Psychopathol 6:433–444.

Maeda F, Kleiner-Fisman G, Pascual-Leone A. 2002. Motor facilitation while observing hand actions: specificity of the effect and role of observer's orientation. J Neurophysiol 87:1329–1335.

McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, Yip L, Murphy DG, Chua SE. 2005. Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. Brain 128:268–276.

McAlonan GM, Daly E, Kumari V, Critchley HD, van Amelsvoort T, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F, Howlin P, Murphy DG. 2002. Brain anatomy and sensorimotor gating in Asperger's syndrome. Brain 125:1594–1606.

Miles JH, Hadden LL, Takahashi TN, Hillman RE. 2000. Head circumference is an independent clinical finding associated with autism. Am J Med Genet 95:339–350.

Mosconi MW, Mack PB, McCarthy G, Pelphrey KA. 2005. Taking an "intentional stance" on eye-gaze shifts: a functional neuroimaging study of social perception in children. Neuroimage 27:247–252.

Mundy P, Sigman M, Ungerer J, Sherman T. 1986. Defining the social deficits of autism: the contribution of non-verbal communication measures. J Child Psychol Psychiatry Allied Discip 27:657–669.

Nishitani N, Avikainen S, Hari R. 2004. Abnormal imitation-related cortical activation sequences in Asperger's syndrome. Ann Neurol 55:558–562.

Nishitani N, Hari R. 2000. Temporal dynamics of cortical representation for action. Proc Natl Acad Sci USA 97:913–918.

Oberman LM, Hubbard EM, McCleery JP, Altschuler EL, Ramachandran VS, Pineda JA. 2005. EEG evidence for mirror neuron dysfunction in autism spectrum disorders. Brain Res Cogn Brain Res 24:190–198.

Osterling J, Dawson G. 1994. Early recognition of children with autism: a study of first birthday home videotapes. J Autism Dev Disord 24:247–257.

Palmen SJ, Van Engeland H. 2004. Review on structural neuroimaging findings in autism. J Neural Transm 111:903–929.

Pelphrey KA, Morris JP, McCarthy G. 2005. Neural basis of eye gaze processing deficits in autism. Brain 128:1038–1048.

Pelphrey KA, Singerman JD, Allison T, McCarthy G. 2003. Brain activation evoked by perception of gaze shifts: the influence of context. Neuropsychologia 41:156–170.

Pelphrey KA, Viola RJ, McCarthy G. 2004. When strangers pass: processing of mutual and averted social gaze in the superior temporal sulcus. Psychol Sci 15:598–603.

Perrett DI, Hietanen JK, Oram MW, Benson PJ. 1992. Organization and functions of cells responsive to faces in the temporal cortex. Philos Trans R Soc Lond B Biol Sci 335:23–30.
Phillips W, Baron-Cohen S, Rutter M. 1992. The role of eye contact in the detection of goals: evidence from normal toddlers and children with autism or mental handicap. Dev Psychopathol 4:375–383.
Piven J, Berthier ML, Starkstein SE, Nehme E, Pearlson G, Folstein S. 1990. Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. Am J Psychiatry 147:734–739.
Posthuma D, De Geus EJ, Baare WF, Hulshoff Pol HE, Kahn RS, Boomsma DI. 2002. The association between brain volume and intelligence is of genetic origin. Nat Neurosci 5:83–84.
Puce A, Allison T, Bentin S, Gore JC, McCarthy G. 1998. Temporal cortex activation in humans viewing eye and mouth movements. J Neurosci 18:2188–2199.
Ristic J, Friesen CK, Kingstone A. 2002. Are eyes special? It depends on how you look at it. Psychon Bull Rev 9:507–513.
Rizzolatti G, Craighero L. 2004. The mirror-neuron system. Annu Rev Neurosci 27:169–192.
Rizzolatti G, Fadiga L, Fogassi L, Gallese V. 1999. Resonance behaviors and mirror neurons. Arch Ital Biol 137:85–100.
Rizzolatti G, Fadiga L, Gallese V, Fogassi L. 1996. Premotor cortex and the recognition of motor actions. Brain Res Cogn Brain Res 3:131–141.
Rizzolatti G, Fadiga L, Matelli M, Bettinardi V, Paulesu E, Perani D, Fazio F. 1996. Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp Brain Res 111:246–252.
Rogers RD, Pennington BF. 1991. A theoretical approach to the deficits in infantile autism. Dev Psychopathol 3:137–162.
Rogers SJ, Hepburn SL, Stackhouse T, Wehner E. 2003. Imitation performance in toddlers with autism and those with other developmental disorders. J Child Psychol Psychiatry Allied Discip 44:763–781.
Rorke LB. 1994. A perspective: the role of disordered genetic control of neurogenesis in the pathogenesis of migration disorders. J Neuropathol Exp Neurol 53:105–117.
Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van Der Kouwe A, Jenkins BG, Dale AM, Fischl B. 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 58:695–701.
Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, Morris JC, Dale AM, Fischl B. 2004. Thinning of the cerebral cortex in aging. Cereb Cortex 14:721–730.
Schultz RT, Klin A. 2002. Genetics of childhood disorders: XLIII. Autism, part 2: neural foundations. J Am Acad Child Adolesc Psychiatry 41:1259–1262.
Stevenson RE, Schroer RJ, Skinner C, Fender D, Simensen RJ. 1997. Autism and macrocephaly. Lancet 349:1744–1745.
Strafella AP, Paus T. 2000. Modulation of cortical excitability during action observation: a transcranial magnetic stimulation study. Neuroreport 11:2289–2292.
Theoret H, Halligan E, Kobayashi M, Fregni F, Tager-Flusberg H, Pascual-Leone A. 2005. Impaired motor facilitation during action observation in individuals with autism spectrum disorder. Curr Biol 15:R84–R85.
Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, Lonnqvist J, Standertskjold-Nordenstam CG, Kaprio J, Khaledy M, Dail R, Zoumalan CI, Toga AW. 2001. Genetic influences on brain structure. Nat Neurosci 4:1253–1258.
Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A. 2004. A voxel-based investigation of brain structure in male adolescents with autistic spectrum disorder. Neuroimage 22: 619–625.
Welchew DE, Ashwin C, Berkouk K, Salvador R, Suckling J, Baron-Cohen S, Bullmore E. 2005. Functional disconnectivity of the medial temporal lobe in Asperger's syndrome. Biol Psychiatry 57:991–998.
Wicker B, Michel F, Henaff MA, Decety J. 1998. Brain regions involved in the perception of gaze: a PET study. Neuroimage 8:221–227.
Williams JH, Whiten A, Singh T. 2004. A systematic review of action imitation in autistic spectrum disorder. J Autism Dev Disord 34:285–299.
Williams JH, Whiten A, Suddendorf T, Perrett DI. 2001. Imitation, mirror neurons and autism. Neurosci Biobehav Rev 25:287–295.
Witelson SF, Goldsmith CH. 1991. The relationship of hand preference to anatomy of the corpus callosum in men. Brain Res 545:175–182.
Woodhouse W, Bailey A, Rutter M, Bolton P, Baird G, Le Couteur A. 1996. Head circumference in autism and other pervasive developmental disorders. J Child Psychol Psychiatry Allied Discip 37:665–671.