ELSEVIER

Brain Research Bulletin 61 (2003) 557–569

BRAIN RESEARCH BULLETIN

www.elsevier.com/locate/brainresbull

Review

Brain anatomy and development in autism: review of structural MRI studies

Paolo Brambilla[a,*], Antonio Hardan[b], Stefania Ucelli di Nemi[c,d], Jorge Perez[a], Jair C. Soares[e,f], Francesco Barale[c,d]

[a] *Biological Psychiatry Unit, IRCCS S. Giovanni di Dio Hospital, Fatebenefratelli, via Pilastroni 4, 25125 Brescia, Italy*
[b] *Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[c] *Department of Psychiatry, IRCCS S. Matteo Hospital, University of Pavia School of Medicine, Pavia, Italy*
[d] *Cascina Rossago' Rehabilitation Center for Autism, Pavia, Italy*
[e] *Department of Psychiatry, University of Texas Health Science Center at San Antonio, TX, USA*
[f] *South Texas VA Health Care System, San Antonio, TX, USA*

Received 8 March 2003; received in revised form 20 June 2003; accepted 27 June 2003

Abstract

Autism is a neurodevelopmental disorder that severely disrupts social and cognitive functions. MRI is the method of choice for in vivo and non-invasively investigating human brain morphology in children and adolescents. The authors reviewed structural MRI studies that investigated structural brain anatomy and development in autistic patients. All original MRI research papers involving autistic patients, published from 1966 to May 2003, were reviewed in order to elucidate brain anatomy and development of autism and rated for completeness using a 12-item check-list. Increased total brain, parieto-temporal lobe, and cerebellar hemisphere volumes were the most replicated abnormalities in autism. Interestingly, recent findings suggested that the size of amygdala, hippocampus, and corpus callosum may also be abnormal. It is conceivable that abnormalities in neural network involving fronto-temporo-parietal cortex, limbic system, and cerebellum may underlie the pathophysiology of autism, and that such changes could result from abnormal brain development during early life. Nonetheless, available MRI studies were often conflicting and could have been limited by methodological issues. Future MRI investigations should include well-characterized groups of autistic and matched healthy individuals, while taking into consideration confounding factors such as IQ, and socioeconomic status.

Keywords: Neuroimaging; Cerebellum; Vermis; Amygdala; Hippocampus; Corpus callosum

1. Introduction

Autism is a complex disease characterized by impairment of social interaction, language, behavior, and cognitive functions [61]. Autistic phenotype is a behavioral syndrome described by the DSM-IV [3] based on the presence of at least 6 of 12 symptoms related to impairment in social interaction, verbal and nonverbal communication deficits, restricted interests, and repetitive behaviors, which are present by the age of 3 years [60]. Clinical features and cognitive impairments persist throughout life and are associated with mental retardation in the majority of patients [50]. Although the causation of autism is still largely unknown, it has been suggested that genetic, developmental, and environmental factors could be involved alone or in combination as possible causal or predisposing effects toward developing autism [7,51,69].

In the last 15 years, several magnetic resonance imaging (MRI) studies examined the brain anatomy in patients with autism in order to identify structural abnormalities. MRI has become the method of choice for investigation of brain morphology, because of its high contrast sensitivity and spatial resolution, in the absence of radiation exposure. This is particularly important in research studies involving children and adolescents [21,40].

The goal of this review was to summarize morphometric brain investigations involving patients with autism, in order to examine structural brain anatomy and development in autism. Additionally, we discussed specific methodological issues that should contribute to improve the design of future MRI investigations in this field.

* Corresponding author. Tel.: +39-030-3501719; fax: +39-030-3533513.
E-mail address: brambillapf@tiscalinet.it (P. Brambilla).

0361-9230/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/j.brainresbull.2003.06.001

2. Methods

We identified all original MRI research papers published in English investigating autistic patients, through a comprehensive Medline search conducted for the period from 1966 to May 2003. A manual search of bibliographic cross-referencing complemented the Medline search. We rated each paper for completeness using a 12-point checklist, divided among three categories, adopted from a checklist developed by Strakowski et al. [70]. The specific 12 items were:

1. Category 1: subjects
   - (i) Patients were evaluated prospectively, specific diagnostic criteria were applied, and demographical data were reported;
   - (ii) Healthy comparison subjects were evaluated prospectively, psychiatric and medical illnesses were excluded, and demographical data were reported;
   - (iii) Important confounds (e.g. age, gender, intelligence quotient, i.e. IQ, handedness, socioeconomic status, height or total brain measures) were controlled either by stratification or statistically;
   - (iv) Sample size per group $\geq$20;
2. Category 2: methods for image acquisition and analysis
   - (v) All neuroanatomic measurements were made blind to group assignment and to subjects' identity;
   - (vi) Measures for brain structures were reported;
   - (vii) MRI slice-thickness $\leq$3 mm and more than one slice were identified and traced;
   - (viii) The imaging technique was clearly described so as to be reproducible;
   - (ix) The measurements were clearly described so as to be reproducible;
   - (x) Regions-of-interest were defined a priori or an exploratory approach was justified;
3. Category 3: results and conclusions
   - (xi) Statistical parameters for significant and important nonsignificant differences were provided;
   - (xii) Conclusions were consistent with results and limitations are discussed.

When criteria were partially met, 0.5 points were assigned. The aim of this rating was to describe the completeness of published studies with a numeric score in order to aid readers, and was not intended to critique the investigators or the work itself.

3. Brain anatomy in autism: MRI findings

3.1. Posterior fossa

3.1.1. Cerebellar vermis

Courchesne and co-workers [16,52] first reported abnormally reduced areas for neocerebellar vermis lobules VI and VII (superior posterior vermis: declive, folium, and tuber), but not I–V (anterior vermis: lingula, centralis, and culmen) and VIII (inferior posterior vermis: pyramis, uvula, and nodulus), in a sample of children and adult patients with autism ($N = 18$). The authors used as comparison group a retrospective sample of age-matched subjects with non-neurological medical problems ($N = 12$). The same group successively confirmed these findings in larger samples in two different studies, using healthy controls as comparisons [12,14] (Table 1). However, analyses were not adjusted for IQ and total brain measures in any of the these studies. Recently, Carper and Courchesne [8] found significantly reduced vermis lobules VI–VII in mentally and non-mentally retarded autistic male children ($N = 42$) compared to age-matched male healthy controls ($N = 29$), and the difference persisted even after adjusting for total brain volume. However, the two groups of subjects were not matched for IQ and this variable was not used as a covariate in the analysis.

Interestingly, a reduction in vermis lobules I–V [38], VI–VII [38], and VIII–X [36,38,47] were also found in mentally and non-mentally retarded autistic children and adolescents (Table 1). However, the failure to adjust the analyses for potential confounds such as IQ, gender, and brain size may have biased the results of these studies. In fact, in the Levitt et al. study [47] the vermal abnormalities disappeared after adjusting the analyses for IQ. Also, most of the comparisons subjects in the studies by Hashimoto et al. [36,38] were composed of individuals suffering from neurological conditions, non-matched for IQ or gender. However, several replication studies have failed to observe any abnormalities of the vermis lobules I–X in young and adult mentally or non-mentally retarded patients with autism [24,28,29,35,37,41,45,48,53,59,62,66] (Table 1).

Additionally, Courchesne et al. analyzed measurements obtained from subjects included in their original report [16] and in the replication study [14], and found two different sub-groups, one with hypoplasia ($N = 43$) and another with hyperplasia ($N = 6$) of vermal lobules VI–VII [14], suggesting the existence of two distinct subtypes of vermal abnormalities within the autistic population. However, these findings may have been limited by the selection of retrospective medical individuals as control group in the original report, and the failure to adjust the analyses for potential confounders such as IQ, total brain measures, or gender. Nonetheless, providing further support for this hypothesis, a retrospective re-analyses [15] of 78 autistic patients from four MRI studies [14,16,45,58] found that 87% of the patients had hypoplasia and 13% hyperplasia of vermal lobules VI–VII areas. A voxel-based MRI morphometric study found increased vermis pyramis gray matter density (part of the lobules VIII–X) in a small sample of young adults with high-functioning autism ($N = 15$) compared to age-, gender-, and IQ-matched normal controls ($N = 15$) [1] (Table 1).

Table 1
MRI studies of posterior fossa structures, total brain, cortical lobes, and ventricles in autism

Study	Autistic patients	Comparisons	Methods	Findings in autism	Rate
Gaffney et al. [27]	14 DSM III, 10 males	33 retrospective medical controls, 18 males	0.5 T 10 mm thick	Reduced cerebellum area ratios	6.5
	10.9 ± 4.6 years old (4–19)	12.3 ± 4.9 years old (4–19)	IR ≥ 0.84	Enlarged 4th ventricle area ratios	
	IQ: 84.9 ± 27.7 (60–135)	IQ: supposed normal	Area measurements; no covariates		
Gaffney et al. [24,26]	13 DSM III, 10 males	35 retrospective medical controls, 21 males	0.5 T 10 mm thick	Smaller total brainstem and pons areas	8
	11.3 ± 4.7 years old (5–22)	12.0 ± 5.2 years old (4–19)	IR ≥ 0.66	Enlarged 4th ventricle area ratios	
	IQ: 84.9 ± 27.7 (60–135)	IQ: supposed normal	Area measurements; no covariates	No abnormalities in total vermis, cerebrum, cerebellum, midbrain, and medulla oblongata areas	
Courchesne et al. [16]	18 DSM III, 16 males	12 normal (3) or retrospective medical controls (9), 9 males	1.5 T 5 mm thick	Reduced vermis lobule areas VI–VII	7.5
	20.9 years old (6–30)	24.8 years old (9–37)	IR ≥ 0.86	No abnormalities in vermis lobules I–V and VIII areas	
	IQ: 55–108	IQ: supposed normal	Area measurements; no covariates		
Gaffney et al. [25]	13 DSM III, 10 males	33 retrospective medical controls, 18 males	0.5 T 10 mm thick	Enlarged anterior ventricular horns and lateral ventricle areas	8
	4–19 years old	4–19 years old	IR ≥ 0.84		
	IQ: 84.9 ± 26.7 (65–139)	IQ: supposed normal	Area measurements; total brain covariated		
Garber et al. [29], Ritvo and Garber [62]	15 DSM III, 11 males	15 age- and sex-matched normal controls	1.5 T 5 mm thick	No abnormalities in vermis lobule and 4th ventricle sizes	9.5
	11.6 ± 4.1 years old (5–19)	IQ: supposed normal	IR ≥ 0.92		
	IQ > 70: 5 patients		Area and volume measurements; IQ covariated		
	IQ < 70: 10 patients				
Murakami et al. [52]	10 DSM III, 8 males	8 normal (3) or retrospective medical controls (5), 7 males	1.5 T 5 mm thick	Reduced vermis lobule VI–VII areas and cerebellar hemisphere cross-sectional areas	8
	23.0 ± 7.1 years old (14–39)	28.2 ± 6.0 years old (19–37)	IR ≥ 0.96	No abnormalities in vermis lobules I–V	
	IQ: 86 ± 22	IQ: supposed normal	Area measurements; no covariates		
Hsu et al. [44]	34 DSM III, 27 males	44 healthy (35) or medical controls (9), 40 males	1.5 T 5 mm thick	No abnormalities in pons and midbrain areas	9.5
	18.9 years old (2–39)	19.8 years old (3–39)	IR ≥ 0.83		
	IQ: 82.6 ± 15.5	IQ: 113 ± 11.4	Area measurements; no covariates		
Nowell et al. [53]	53 retrospective DSM III, 45 males	32 retrospective pediatric patients	0.5 T 10 mm thick	No abnormalities in vermis lobules VI–VII and 4th ventricle sizes	6
	9 years old (2–22)	8.5 years old (1–17)	IR not reported		
	IQ ≤ 80	IQ: supposed normal	Height measurements; no covariates		
Garber and Ritvo [28]	12 DSM III, 9 males	12 normal controls, 8 males	1.5 T 5 mm thick	No abnormalities in vermis lobules I–VII, pons, 4th ventricle, and total cerebral areas	8.5
	27.2 ± 5.3 years old (18–38)	26.4 ± 3.6 years old (21–35)	IR ≥ 0.91		
	IQ: middle-to-high functioning	IQ: normal or higher	Area measurements; no covariates		
Hashimoto et al. [35]	12 DSM III-R, 8 males	14 retrospective neurologic controls, 9 males	0.5 T 5 mm thick	Smaller midbrain and medulla oblongata areas and ratios	7.5
	6.6 ± 1.5 years old (5–10)	7.4 ± 1.8 years old (5–10)	IR ≥ 0.98	No abnormalities in vermis lobules I–X and pons areas	
	IQ: 49.0 ± 14.6 (33–73)	IQ: supposed normal	Area measurements; no covariates		

Table 1 (*Continued*)

Study	Autistic patients	Comparisons	Methods	Findings in autism	Rate
Hashimoto et al. [36]	21 DSM III-R, 15 males 4.3 ± 1.7 years old (2–7) IQ: 64.2 ± 24.0 (20–129)	24 retrospective neurologic controls, 14 males 3.9 ± 2.0 years old (2–7) IQ: 108.5 ± 8.6 (94–123)	0.5 T 5 mm thick IR ≥ 0.98 Area measurements; no covariates	Smaller midbrain, pons, medulla oblongata, and vermis lobule VIII–X areas	8
Holttum et al. [41]	18 male DSM III-R 20.2 ± 8.1 years old (11.7–41.0) IQ: 94.5 ± 12.2 (74–116)	18 male healthy controls 20.2 ± 8.3 years old (11.9–41.7) IQ: 95.2 ± 12.1 (72–115)	1.5 T 3 mm thick IR ≥ 0.75 Area measurements; total brain covariate	No abnormalities in vermis lobules I–X and 4th ventricle areas	9.5
Kleiman et al. [45]	13 DSM III-R, 10 males 7.7 ± 5.7 years old (2.7–16.8) IQ: 48 (20–71)	26 retrospective neurologic controls 7.0 years old (1 month–12.5) IQ: supposed normal	1.0 T 3–8 mm thick IR ≥ 0.95 Area measurements; age and sex covariated	No abnormalities in vermis lobules I–VII, pons, and 4th ventricle areas	8
Piven et al. [58]	15 male DSM III-R 27.7 ± 10.7 years old (8–53) IQ: 92.5 ± 23.4 (60–130) IQ < 70: 4 patients IQ > 70: 11 patients	Group I: 15 male controls 30.3 ± 8.9 years old (18–47) IQ: 99.9 ± 26.4 (64–130) Group II: 15 normal male controls 28.8 ± 5.6 years old (18–36) IQ: 130 ± 0.0	1.5 T 3 mm thick IR ≥ 0.95 Area measurements IQ; total brain, and age covariated	No abnormalities in vermis lobules VI–VII, pons, and 4th ventricle areas Enlarged midsagittal brain areas	10
Hashimoto et al. [37]	12 DSM III-R, 11 males 6.1 ± 3.2 years old (2–12) IQ: 99.2 ± 18.1 (80–129)	24 retrospective neurologic controls, 21 males 5.9 ± 3.2 years old (2–12) IQ: 105.9 ± 9.8 (91–125)	0.5 T 5 mm thick IR ≥ 0.98 Area measurements; no covariates	Smaller midbrain and medulla oblongata areas No abnormalities in vermis lobules I–X and pons areas	7.5
Courchesne et al. [14]	50 DSM III, 41 males 16.5 years old (2–40) IQ < 70: 27 patients IQ > 70: 22 patients	53 healthy (41) or medical controls (12), 43 males 17 years old (3–39) IQ: supposed normal	1.5 T 5 mm thick IR ≥ 0.90 Area measurements; no covariates	Hypoplasia and hyperplasia subtypes for vermis lobules VI–VII	9.5
Hashimoto et al. [38]	102 DSM III-R, 76 males 6.1 ± 4.7 years old (1–20) IQ: 59.5 ± 25.0 (10–129)	112 healthy (41) or retrospective neurologic controls (71), 65 males 7.1 ± 5.4 years old (1–20) IQ: 99.2 ± 18.1 (80–129)	0.5 and 1.5 T 5–7 mm thick IR ≥ 0.98 Area measurements; no covariates	Reduced total brainstem, pons, midbrain, medulla oblongata and vermis lobules I–X areas	9.5
Piven et al. [55]	22 males, DSM III-R 18.4 ± 4.5 years old (13–29) IQ: 90.8 ± 22.0 (52–136)	20 males healthy controls 21.6 ± 3.5 years old (14–28) IQ: 103.4 ± 9.9 (80–122)	1.5 T 1.5 mm thick IR ≥ 0.98 Volume measurements; height and IQ covariated	Increased total brain volumes No abnormalities in lateral ventricle volumes	12
Piven et al. [54]	35 DSM III-R, 26 males 18.4 ± 4.5 years old (12–29) IQ: 91.0 ± 19.8 (52–136)	36 healthy controls, 20 males 20.2 ± 3.8 years old (13–28) IQ: 102.1 ± 12.8 (72–135)	1.5 T 1.5 mm thick IR ≥ 0.95 Volume measurements; height and IQ covariated	Increased temporal, parietal, occipital lobe volumes No abnormalities in frontal lobe volumes	11.5
Schaefer et al. [66]	13 retro or prospective DSM III-R, 7 males 5.9 years old IQ < 70	125 retro or prospective normal controls 0–90 years old IQ: supposed normal	Tesla not reported 3–5 mm thick IR ≥ 0.95 Area measurements; age covariated	No abnormalities in vermis lobules VI–VII areas	8

Table 1 (*Continued*)

Study	Autistic patients	Comparisons	Methods	Findings in autism	Rate
Ciesielski et al. [10]	9 DSM III-R, 5 males 16.8 years old (10–23) IQ: 77–109	10 healthy controls, 7 males 16.6 years old (12–26) IQ: 106–132	1.5 T 5 mm thick IR $\geq$ 0.92 Area measurements; IQ covariated	No abnormalities in vermis lobules I–VII and pons areas	8
Piven et al. [59]	35 DSM II-R, 26 males 18.0 $\pm$ 4.5 years old (12–29) IQ: 91.0 $\pm$ 19.8 (52–136) IQ < 70: 4 patients IQ > 70: 31	36 healthy controls, 20 males 20.2 $\pm$ 3.8 years old (13–28) IQ: 102.0 $\pm$ 12.8 (72–135)	1.5 T 1.5 mm thick IR $\geq$ 0.90 Area and volume measurements; total brain, IQ, and sex covariated	No abnormalities in total cerebellum and vermis lobules I–VII sizes	11.5
Abell et al. [1]	15 DSM IV, 12 males 28.9 $\pm$ 6.6 years old IQ: 42.5 $\pm$ 6.6 (max: 50)	15 normal controls, 12 males 25.4 $\pm$ 3.1 years old IQ: 45.2 $\pm$ 2.9 (max: 50)	2 T 1 mm^3 voxels; voxel-based MRI gray matter density	Increased cerebellar hemisphere and pyramis, right inferior and left middle temporal gyrus gray matter densities Decreased right paracingulate sulcus, left occipito-temporal cortex, and left inferior frontal gyrus gray matter densities	9
Aylward et al. [5]	14 male ADI 20.5 $\pm$ 1.8 years old (11–37) IQ: 106.4 $\pm$ 11.7	14 male healthy controls 20.3 $\pm$ 1.7 years old (11–38) IQ: 108.5 $\pm$ 12.6	1.5 T 1.5 mm thick IR $\geq$ 0.99 Volumes measurements; no covariates	No abnormalities in total brain volume	10.5
Levitt et al. [47]	8 DSM IV 12.5 $\pm$ 2.2 years old (9.8–16.0) IQ: 83.3 $\pm$ 11.9	21 healthy controls 12.0 $\pm$ 2.8 years old (7.9–16.8) IQ: 114.9 $\pm$ 11.0	1.5 T 1.4 mm thick IR $\geq$ 98 Area measurements; IQ covariated	No abnormalities for vermis lobules I–X areas	8
Manes et al. [48]	27 DSM IV, 22 males 14.3 $\pm$ 6.8 years old Mental age: 4.6 $\pm$ 5.6	17 healthy controls 11 males, 11.8 $\pm$ 5.0 years old Mental age: 4.5 $\pm$ 2.7	1.5 T 5 mm thick IR $\geq$ 0.95 Area measurements; brain area covariated	No abnormalities in vermis lobules I–X areas	10
Carper and Courchesne [8]	42 male DSM IV 5.4 $\pm$ 1.7 years old (3.1–9.1) IQ: 79.5 $\pm$ 22.3	29 male healthy controls 6.0 $\pm$ 1.8 years old (3.4–9.0) IQ: 114.0 $\pm$ 12.0	1.5 T 3–4 mm thick IR not reported Area and volume measurements; total brain covariated	Reduced vermis lobules VI–VII areas Inverse correlation between vermis lobules VI–VII areas and frontal cortex volumes No abnormalities in frontal lobe volumes	10.5
Elia et al. [20]	22 male retarded DSM IV 10.9 $\pm$ 4.0 years old (4.7–16.6) IQ < 70	11 male normal controls 10.9 $\pm$ 2.9 years old (5.3–14.6) IQ: supposed normal	0.5 T 5 mm thick IR not reported Area measurements; no covariates	No abnormalities in total vermis, vermis lobules VI–VII, pons, midbrain, and cerebrum areas	7.5
Haznedar et al. [39]	17 DSM IV, 15 males 27.7 $\pm$ 11.3 years old IQ: 55–125	17 healthy controls, 15 males 28.8 $\pm$ 9.4 years old IQ: 88–136	1.5 T axial 1.2 mm thick IR $\geq$ 0.87 Volume measurements; total brain covariated	Reduced right anterior cingulate gyrus volumes No abnormalities in brain, left anterior cingulate gyrus, and left and right posterior cingulate gyrus volumes	9.5
Howard et al. [43]	10 male DSM IV 15.8–40.3 years old IQ > 70	10 male healthy controls age-, gender-, IQ-matched	1.5 T 1.6 mm thick IR $\geq$ 0.80 Volume measurments; intracranium covariated	Enlarged lateral ventricle and intracranium volumes No abnormalities in temporal lobe volumes	10

Table 1 (*Continued*)

Study	Autistic patients	Comparisons	Methods	Findings in autism	Rate
Courchesne et al. [12]	60 male DSM IV	52 male healthy controls	1.5 T 3–4 mm thick	In 2–4 years old autistic patients	11.5
	6.2 ± 3.5 years old (2–16)	2–16 years old	IR = 0.99	Larger cerebellar white matter and brain volumes	
	IQ: 40–90	IQ: 86–132	Area and volume measurements; no covariates	Reduced vermis lobules VI–VII cross-sectional areas	
Hardan et al. [32]	22 male ADI	22 male healthy controls	1.5 T 3–5 mm thick	Enlarged total cerebellum and cerebellar hemisphere volumes	12
	22.4 ± 10.1 years old (12.2–51.8)	22.4 ± 10.0 years old (12.9–52.2)	IR ≥ 0.92	No abnormalities in total vermis, vermis lobules I–X, total brainstem, pons, midbrain, and medulla oblongata sizes	
	IQ: 100.4 ± 14.7 (83–136)	IQ: 100.5 ± 14.2 (72–131)	Area and volume measurements; total brain covariated		
Hardan et al. [34]	16 male ADI	22 male healthy controls	1.5 T 5 mm thick	Increased total brain and 3rd ventricle volumes	10.5
	22.2 ± 10.1 years old	22.4 ± 10.0 years old	IR ≥ 0.95	No abnormalities in 4th and lateral ventricle volumes	
	IQ: 102.8 ± 15.2	IQ: 101.2 ± 13.9	Volume measurements; intracranium covariated		
Aylward et al. [4]	67 ADI, 58 males	83 healthy controls, 76 males	1.5 T 1.5 mm thick	In 8–12 years old autistic patients: increased brain volume	11.5
	18.8 ± 10.0 years old	18.9 ± 10.0 years old	IR = 0.99	In all patient sample: increased head circumference	
	IQ: 102.7 ± 15.5	IQ: 107.0 ± 12.5	Volume measurements; height and sex covariated		
Carper et al. [9]	38 male DSM IV and ADI	39 male healthy controls	1.5 T 3 mm thick	In 2–4 years old autistic patients: larger frontal and parietal white matter and frontal and temporal gray matter volumes	11.5
	5.7 ± 2.2 years old (3–10)	6.5 ± 2.5 years old (2–12)	IR not reported		
	IQ: >70 in 26 patients <70 in 12 patients	IQ > 80	Volume measurements; no covariates		
Rojas et al. [63]	15 DSM IV and ADI, 13 males	15 healthy controls, 13 males	1.5 T 1.7 mm thick	Reduced left planum temporale	10.5
	29.9 ± 9.0 years old (19–47)	30.4 ± 9.3 years old (17–47)	IR ≥ 0.86	No abnormalities in right planum temporale and both Heschl's girus volumes	
	IQ: 94.9 ± 21.6 (62–133)	IQ: 124.8 ± 7.98 (113–142)	Volume measurements; total brain covariated		
Sparks et al. [68]	29 DSM IV and ADI, 26 males	26 healthy controls, 18 males	1.5 T 1.5–2 mm thick	Enlarged total brain volumes	11
	3.9 ± 0.4 years old (3.2–4.5)	3.9 ± 0.5 years old (3.0–4.7)	IR ≥ 0.83	No abnormalities in cerebellum volumes	
	IQ: < 80 for most patients	IQ: supposed normal	Volume measurements; age, sex, and total brain covariated		

IQ: intelligence quotient; IR: inter-rater reliability; ADI: Autism Diagnostic Interview.

3.1.2. Cerebellar hemispheres

Decreased cerebellar areas have been reported in children and adult autistic patients in two small MRI studies [27,52]. However, these studies were limited by the use of one 5–10 mm thick image, the lack of adjustment for IQ, and the comparison with retrospective samples of medical controls. Also, Gaffney et al. failed to replicate their findings in a subsequent study [26]. On the contrary, enlarged total [32,59,68], gray [1], and white matter [12] volumes in cerebellum have been shown by several well-designed controlled MRI studies in children and young adult individuals with autism, mostly moderate-to-high-functioning (Table 1). However, in the studies by Piven et al. [59] and by Sparks et al. [68] cerebellar enlargement was not detected after controlling for total brain volume, IQ, or gender.

3.1.3. Brainstem

Smaller areas of brainstem sub-regions have also been reported by three different research groups in mentally and non-mentally retarded juvenile and young adult patients with

autism [10,24,36–38]. However, in the study by Ciesielski et al. [10] the anatomical abnormalities disappeared after controlling for IQ, whereas the other studies did not adjust their findings for total brain size and IQ measures. Furthermore, Hashimoto et al. [36–38] included in their comparison group individuals who had the MRI study conducted for headache or head trauma. Additionally, several controlled MRI studies found no anatomical abnormalities in brainstem in mentally or non-mentally retarded young and adult individuals with autism [20,28,32,35,44,45,58] (Table 1).

3.2. Total brain and cortical lobes

Enlarged total brain area [58] and volume [4,12,34,43, 55,68] have been reported in juvenile and adult male individuals with autism, after adjusting for height, IQ, and intra-cranial volume (ICV). This observation in combination

Table 2
MRI studies of amygdala and hippocampus in autism

Study	Autistic patients	Comparisons	Methods	Findings in autism	Rate
Saitoh et al. [64]	33 DSM III-R, 30 males 13.8 ± 9.1 years old (5.9–42.2) IQ > 70: 21 patients IQ < 70: 12 patients	23 healthy controls, 19 males 13.3 ± 8.1 years old (6.2–42.7) IQ: supposed normal	1.5 T 5 mm thick IR ≥ 0.96 Area measurements; no covariates	No abnormalities in posterior hippocampal cross-sectional areas	10
Piven et al. [57]	35 DSM III-R, 26 males 18.0 ± 4.5 years old (12–29) IQ: 91.0 ± 19.8 (52–136)	36 healthy controls, 20 males 20.2 ± 3.8 years old (13–28) IQ: 102.1 ± 12.8 (72–135)	1.5 T 1.5 mm thick IR ≥ 0.90 Volume measurements; total brain, IQ, and sex covariates	No abnormalities in hippocampus volume	11.5
Abell et al. [1]	15 DSM IV, 12 males 28.9 ± 6.6 years old IQ: 42.5 ± 6.6 (max: 50)	15 normal controls, 12 males 25.4 ± 3.1 years old IQ: 45.2 ± 2.9 (max: 50)	2.0 T 1 mm^3-voxels voxel-based MRI gray matter density	Increased left amygdala gray matter density	9
Aylward et al. [5]	14 male ADI 20.5 ± 1.8 years old (11–37) IQ: 106.4 ± 11.7	22 male healthy controls 22.4 ± 10.0 years old (11–38) IQ: 108.5 ± 12.6	1.5 T 1.5 mm thick IR ≥ 0.88 Volume measurements; total brain and height covariated	Bilaterally reduced amygdala and hippocampus volumes	10.5
Haznedar et al. [39]	17 DSM IV, 15 males 27.7 ± 11.3 years old IQ: 55–125	17 healthy controls, 15 males 28.8 ± 9.4 years old IQ: 88–136	1.5 T 1.2 mm thick IR ≥ 0.81 Volume measurements; total brain covariated	No abnormalities in amygdala or hippocampus volumes	9.5
Howard et al. [43]	10 male DSM IV 15.8–40.3 years old IQ > 70	10 male healthy controls age-, gender-, IQ-matched	1.5 T 1.6 mm thick IR ≥ 0.80 Volume measurements; intracranium covariated	Bilaterally enlarged amygdala volumes No abnormalities in hippocampal and parahippocampal volumes	10
Saitoh et al. [65]	59 ADI, 52 males 11.2 ± 9.2 years old (2.4–42) IQ: 41–135	51 healthy controls, 40 males 11.4 ± 8.0 years old (2.3–43) IQ: 88–150	1.5 T 5 mm thick IR ≥ 0.96 Area measurements; total brain covariated	Reduced hipppocampal area dentate cross-sectional areas No abnormalities in subiculum + hippocampal CA1–CA3 cross sectional areas	10
Sparks et al. [68]	29 DSM IV and ADI, 26 males 3.9 ± 0.4 years old (3.2–4.5) IQ: < 80 for most patients	26 healthy controls, 18 males 3.9 ± 0.5 years old (3.0–4.7) IQ: supposed normal	1.5 T 1.5–2 mm thick IR ≥ 0.83 Volume measurements; age, sex, and total brain covariated	Enlarged right amygdala in male patients No abnormalities in both hippocampal and left amygdala volumes	11

IQ: intelligence quotient; IR: inter-rater reliability; ADI: Autism Diagnostic Interview.

with increased fronto-occipital circumference appears to be one of the most consistent neurobiologic findings in autism [4,6,18,22,23,31,46,49]. However, other studies did not find any abnormal total brain area [20,26,28] or volumes [5,39] in mentally or non-mentally retarded patients with autism, predominantly males (Table 1). Nonetheless, these negative studies did not take IQ, gender, or ICV into account (except in Haznedar et al. [39]), and in three of them total brain areas were measured by analyzing a single 5–10 mm thick image slice [20,26,28].

Abnormally enlarged volumes of frontal, temporal, and parietal lobes [9,54], and increased gray matter density in the inferior and middle temporal gyri [1] have been reported in juvenile and young male adult mentally and non-mentally retarded individuals with autism, before and after adjusting for TBV, height, and IQ (Table 1). However, qualitative signs of superior parietal cortical volume loss (7/21 autistic patients) [13] and abnormally decreased volumes of right cingulate [1,39], left occipito-temporal cortex, and left inferior frontal gyrus [1] have been shown in adolescent and young adult patients with autism. Nonetheless, normal frontal [8,54] and occipital lobe volumes [9] were also reported by controlled MRI investigations.

Interestingly, Rojas et al. [63] recently showed that planum temporale in adults with autistic disorder lacks of the normal asymmetry, being abnormally reduced in the left side. Planum temporal is a structure located on the superior surface of the temporal lobe and roughly corresponding with the receptive speech area, playing a crucial role in the functional asymmetry of language skill. Therefore, the authors suggested that the absence of planum temporale asymmetry in autism may be due to early neurodevelopmental disturbance, possibly impairing language acquisition and competency.

3.3. Ventricles

Gaffney et al. [26,27] reported abnormally enlarged 4th ventricle in autism, whereas most controlled MRI reports did not [28,29,34,41,45,53,58]. Lateral ventricle sizes in patients with autism have been reported enlarged in one controlled MRI study [43], and normal in two others [34,55]. Only one controlled MRI study examined 3rd ventricle in autism, showing abnormally increased volumes [34] (Table 1).

3.4. Hippocampus and amygdala

Decreased hippocampal measures have been found in juvenile and adult male patients with autism, mostly high-functioning [5,65] when compared to age- and gender-matched healthy controls, even after total brain adjustment. However, several controlled MRI studies have reported no abnormalities in this region in mentally and non-mentally retarded male individuals with autism [39,43,57,64,68] (Table 2). Enlarged amygdala volumes have been described in adolescent and adult patients with autism, mostly high-functioning males [1,43,68], but not in all studies [5,39] (Table 2).

3.5. Basal ganglia and thalamus

Abnormally reduced areas of lenticular nucleus [25] and increased caudate volumes [67] have been reported in autism. No abnormalities in size of thalamus and caudate [25], and putamen and globus pallidus [67] were reported (Table 3). Interestingly, caudate volumes significantly correlated with ritualistic-repetitive behaviors in the study by Sears et al. [67], suggesting that it may be part of an

Table 3
MRI studies of basal ganglia and thalamus in autism

Study	Autistic patients	Comparisons	Methods	Findings in autism	Rate
Gaffney et al. [25]	13 DSM III, 10 males 4–19 years old IQ: 84.9 ± 26.7 (65–139)	33 retrospective medical controls, 18 males 4–19 years old IQ: supposed normal	0.5 T 10 mm thick IR ≥ 0.84 Area measurements; total brain covariated	Reduced right lenticular nucleus areas No abnormalities in caudate, left lenticular, and thalamus areas	8
Sears et al. [67]	35 DSM III-R, 26 males 18.4 ± 4.5 years old (12–29) IQ: 91.0 ± 19.8 (52–136)	36 healthy controls, 20 males 20.2 ± 3.8 years old (13–28) IQ: 102.1 ± 12.8 (72–135)	1.5 T 1.5 mm thick IR ≥ 0.74 Area measurements; total brain covariated	No abnormalities in caudate, putamen, and globus pallidus volumes	12
Sears et al. [67]	13 male DSM III-R 27.7 ± 10.7 years old IQ: 92.5 ± 23.4 (60–130)	25 male control Group I: 18–47 years old IQ: 64–130	1.5 T 3 mm thick IR not reported Volume measurements; total brain and IQ covariated	Enlarged caudate volumes	10.5
Tsatsanis et al. [71]	12 male DSM IV and ADI 21.0 ± 10.4 years old (11.3–37.9) IQ: 106.4 ± 18.3 (82–141)	12 male healthy controls 18.1 ± 6.3 years old (10.7–29.5) IQ: 108.8 ± 15.6 (87–138)	1.5 T 1.2 mm thick IR ≥ 0.93 Total brain covariated	Reduced thalamic volumes in patients with high total brain volumes	10.5

IQ: intelligence quotient; IR: inter-rater reliability; ADI: Autism Diagnostic Interview.

Table 4
MRI studies of corpus callosum in autism

Study	Autistic patients	Comparisons	Methods	Findings in autism	Rate
Gaffney et al. [27]	13 DSM III, 10 males	35 retrospective medical controls, 21 males	0.5 T 10 mm thick	No abnormalities in total corpus callosum areas	8
	11.3 ± 4.7 years old (5–22)	12.0 ± 5.2 years old (4–19)	IR ≥ 0.94		
	IQ: 84.9 ± 27.7 (60–135)	IQ: supposed normal	Area measurements; no covariates		
Egaas et al. [19]	51 DSM III-R, 45 males	51 healthy controls, 45 males	1.5 T 4–5 mm thick	Reduced total and posterior callosal sub-region areas	9.5
	15.5 ± 10.0 years old (3–42)	15.5 ± 9.9 years old (3–45)	IR ≥ 0.99		
	IQ > 70: 35 patients IQ < 70: 16 patients	IQ: supposed normal	Area measurements; no covariates		
Piven et al. [56]	35 DSM III-R, 26 males	36 healthy controls, 20 males	1.5 T 1 mm thick	Reduced middle and posterior callosal sub-region areas	11.5
	18.0 ± 4.5 years old (12–29)	20.2 ± 3.8 years old (13–28)	IR ≥ 0.90		
	IQ: 91.0 ± 19.8 (52–136)	IQ: 102.1 ± 12.8 (72–135)	Area measurements; total brain, IQ, and sex covariated		
Manes et al. [48]	27 DSM IV, 22 males	17 healthy controls, 11 males	1.5 T 5 mm thick	Reduced total, genu, body, and isthmus areas	10
	14.3 ± 6.8 years old	11.8 ± 5.0 years old	IR ≥ 0.98		
	Mental age: 4.6 ± 5.6	Mental age: 4.5 ± 2.7	Area measurements; total brain and IQ covariated		
Elia et al. [20]	22 male DSM IV	11 male normal controls	0.5 T 5 mm thick	No abnormalities in total corpus callosum areas	8
	10.9 ± 4.0 years old (4.7–16.6)	10.9 ± 2.9 years old (5.3–14.6)	IR not reported		
	IQ < 70	IQ: supposed normal	Area measurements; no covariates		
Hardan et al. [33]	22 male ADI	22 male healthy controls	1.5 T 3 mm thick	Reduced anterior callosal sub-region areas	10.5
	22.4 ± 10.1 years old (12.2–51.8)	22.4 ± 10.0 years old (12.9–52.2)	IR ≥ 0.91	No abnormalities in total, middle, and posterior callosal areas	
	IQ: 100.4 ± 14.7 (83–136)	IQ: 100.5 ± 14.2 (72–131)	Area measurements; total brain covariated		

IQ: intelligence quotient; IR: inter-rater reliability; ADI: Autism Diagnostic Interview.

abnormal neural network sustaining stereotyped behaviors in autism.

It is stimulating to note that it has recently been shown that male people with high-functioning autism and with high brain volumes have significantly smaller thalamic volumes compared to age-, gender-, IQ-, and brain volume-matched normal controls [71].

3.6. Corpus callosum

Abnormally reduced anterior (genu and rostrum), middle (body), and posterior (isthmus and splenium) callosal sub-regions have consistently been reported in juvenile and adult male individuals with autism, either mentally or non-mentally retarded, even after covarying for gender and total brain measures [19,33,48,56]. Additionally, several studies described abnormalities in total corpus callosum areas in autism [19,48], but some did not [20,27,33] (Table 4).

4. Discussion

The MRI studies reviewed here suggest the existence of morphometric abnormalities in several brain structures in autism, even though some findings have often been controversial (Table 5). Nonetheless, MRI remains the gold-standard technique to identify structural brain alterations in patients with neuropsychiatric disorders, such as autism, in order to provide a neuroanatomic model of pathophysiology and, ultimately, contribute to developing effective therapeutic interventions.

Increased total brain, parieto-temporal lobe, and cerebellar hemisphere volumes in individuals with autism have been replicated by several well-designed MRI reports with satisfactory methodology, although there are still some inconsistencies among MRI studies exploring cerebellar hemisphere size (Table 5). Hypothetically, abnormalities of these structures might be relevant in underlying certain impaired abilities in autism, such as altered responses to emotional clues,

Table 5
Summary of MRI findings in autism

Structures	Decreased size, *N* studies (measurements)	Increased size, *N* studies (measurements)	Negative findings, *N* studies (measurements)
Cerebellar vermis			
Total vermis			3 (areas and volumes)
Lobules I–V	1 (areas)		10 (areas)
Lobules VI–VII	5 (areas) (same group)	2 (areas) (same group)	11 (areas)
Lobules VIII–X	2 (areas)	1 (gray matter density)	7 (areas)
Cerebellar hemispheres	2 (areas)	3 (volumes)	3 (1 areas, 2 volumes)
Total brainstem	2 (areas)		1 (areas and volumes)
Pons	3 (areas)		8 (areas)
Midbrain	4 (areas) (same group)		4 (areas)
Medulla	4 (areas) (same group)		2 (areas)
Total brain		7 (areas and volumes)	5 (areas and volumes)
Cortical lobes			
Frontal		1 (volumes)	2 (volumes)
Temporal		3 (volumes)	
Parietal		2 (volumes)	1 (qualitative signs)
Occipital	1 (volumes)	1 (volumes)	
Planum temporale	1 (volumes)		
Ventricular system			
Lateral ventricles		2 (areas and volumes)	2 (volumes)
Third ventricles		1 (volumes)	
Fourth ventricles		2 (areas) (same group)	7 (areas and volumes)
Hippocampus	2 (areas and volumes)		5 (areas and volumes)
Amygdala	1 (volumes)	3 (volumes)	1 (volumes)
Basal ganglia			
Caudate		1 (volumes)	2 (areas and volumes)
Putamen	1 (areas)		1 (volumes)
Globus pallidus			1 (volumes)
Thalamus	1 (volumes)		1 (areas)
Corpus callosum			
Total	2 (areas)		3 (areas)
Anterior sub-regions	2 (areas)		2 (areas)
Middle body	2 (areas)		2 (areas)
Posterior sub-regions	3 (areas)		1 (areas)

N: number.

information processing, social and higher cognitive functions. Although it is still conflicting whether frontal lobes are anatomically abnormal in autism, considerable evidences from several controlled functional reports support their involvement in the pathophysiology and cognitive impairment of autism [30,42,72]. Several controlled MRI studies with autistic patients reported negative findings for size abnormalities in cerebellar vermis, brainstem, basal ganglia, and 4th ventricle, suggesting that these structures are anatomically preserved (Table 5). However, the absence of volumetric abnormalities does not exclude the existence of functional impairments sustaining a possible role in the pathophysiology of the illness.

Other structures such as the hippocampus, amygdala, and corpus callosum have recently been suggested to be structurally abnormal in patients with autism, and possibly implicated in the pathophysiology of this disorder. Specifically, the available literature in autism suggests that corpus callosum may be reduced and amygdala, although less clearly, may be increased, whereas findings on hippocampus are still conflicting (Table 5). Hippocampus and amygdala are involved in social learning, cognitive functions, and emotional processing in humans [2,17] and might play a role in social behavior and social intelligence deficits in patients with autism. Furthermore, corpus callosum size reduction may diminish inter-hemispheric connectivity and may be involved in pathophysiology of the cognitive impairments and clinical features of autism.

A disturbed neural network probably involving the temporo-parietal cortex, limbic system, cerebellum, prefrontal cortex, and corpus callosum appears to be involved in pathophysiology of autism. The brain changes could possibly result from abnormalities in brain development, subsequent to disturbance of brain growth in early life, and could

anatomically underlie the cognitive and social impairments of subjects with autism [11]. This abnormal development might be characterized by increased rate of brain growth from early infancy (2- to 3-year-old) through preschool period (particularly in frontal, temporal and parietal lobes, and cerebellum), followed by an abnormally slow cerebral and cerebellar volume increase during late childhood, puberty and adolescence [4,6,9,12,46]. Several developmental processes may be contributing to brain abnormalities in autism, including increased neurogenesis and/or myelination, and decreased neuronal elimination. These developmental abnormalities could be the result of gene mutations, inappropriate levels of neurotrophines, and environmental factors which, together or independently, are affecting brain development and leading to pathological states.

The rate scores of the check-list (see the last column of the tables) show that the quality of MRI investigations has steadily improved over recent years. Similar check-lists should be considered by future overview of neuroimaging findings in psychiatric disorders to rate the completeness of MRI studies. In particular, although all items were scored 1 if satisfied, it is important to note that some of them are critical in improving the quality of a MRI study, such as sample size, controlling for confounding variables, and reproducibility of the methodology. Several MRI studies suffered from considerable methodological limitations, limiting the generalization of their findings. Thus, future structural MRI reports should attempt to overcome the sample and design limitations of earlier investigations. First, longitudinal MRI studies will be essential to examine abnormal brain development, and crucial to a better understanding of the developmental neurobiology of autism. Second, rigorous matching should occur between autistic patients and normal controls on several variables including age, gender, social-economic status (SES), and IQ, while taking into account confounding factors such as total brain sizes. Finally, novel technologies such as voxel-based morphometry, magnetization-transfer imaging, and diffusion tensor MR imaging will be necessary for investigating the relative contributions of each tissue compartment to changes in brain structures and for clarifying whether putative callosal reduction is due to decreased myelination or loss of cortical projections. The application of these innovative methodologies would allow the mapping of the neural networks involved in the pathophysiology of autism and would potentially help the characterization of biological sub-groups, and facilitate the creation of diagnostic categories based on specific brain mechanisms.

In conclusion, despite a growing number of quantitative MRI studies, few robust findings have been observed. Structural abnormalities involving total brain volume, the cerebellum and, recently, corpus callosum have been consistently replicated. The available evidence suggests the existence of a disturbed neural network involving cortical and subcortical areas, including temporo-parietal cortex, limbic system, cerebellar, and prefrontal regions. In order to overcome design limitations of the previous morphometric neuroimaging reports, future quantitative MRI studies should focus on identifying possible morphological brain markers by including homogenous groups of well characterized individuals with autism and healthy controls, matched for age, gender, SES, and IQ and should longitudinally investigating those groups. Novel MR techniques will also be instrumental to further clarify the neural networks sustaining the pathophysiology of autism.

Acknowledgements

This work was partly supported by grants from the Biological Psychiatry Unit, Fatebenefratelli—Brescia (Ministry of Health) and the Italian Society for Neuroimaging in Psychiatry (SINIP, ‘F. Tenconi’ Award) to Dr. Brambilla. Dr. Soares was supported by NIMH MH 01736 and the Veterans Administration.

References

[1] F. Abell, M. Krams, J. Ashburner, R. Passingham, K. Friston, R. Frackowiak, F. Happe, C. Frith, U. Frith, The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans, Neuroreport 10 (1999) 1647–1651.
[2] R. Adolphs, S. Baron-Cohen, D. Tranel, Impaired recognition of social emotions following amygdala damage, J. Cogn. Neurosci. 14 (2002) 1264–1274.
[3] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC, 1994.
[4] E.H. Aylward, N.J. Minshew, K. Field, B.F. Sparks, N. Singh, Effects of age on brain volume and head circumference in autism, Neurology 59 (2002) 175–183.
[5] E.H. Aylward, N.J. Minshew, G. Goldstein, N.A. Honeycutt, A.M. Augustine, K.O. Yates, P.E. Barta, G.D. Pearlson, MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults, Neurology 53 (1999) 2145–2150.
[6] A. Bailey, P. Luthert, P. Bolton, A. Le Couteur, M. Rutter, B. Harding, Autism and megalencephaly, Lancet 341 (1993) 1225–1226.
[7] P. Bolton, H. Macdonald, A. Pickles, P. Rios, S. Goode, M. Crowson, A. Bailey, M. Rutter, A case-control family history study of autism, J. Child Psychol. Psychiatry 35 (1994) 877–900.
[8] R.A. Carper, E. Courchesne, Inverse correlation between frontal lobe and cerebellum sizes in children with autism, Brain 123 (Pt 4) (2000) 836–844.
[9] R.A. Carper, P. Moses, Z.D. Tigue, E. Courchesne, Cerebral lobes in autism: early hyperplasia and abnormal age effects, Neuroimage 16 (2002) 1038–1051.
[10] K.T. Ciesielski, R.J. Harris, B.L. Hart, H.F. Pabst, Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood, Neuropsychologia 35 (1997) 643–655.
[11] E. Courchesne, Abnormal early brain development in autism, Mol. Psychiatry 7 (Suppl. 2) (2002) S21–S23.
[12] E. Courchesne, C.M. Karns, H.R. Davis, R. Ziccardi, R.A. Carper, Z.D. Tigue, H.J. Chisum, P. Moses, K. Pierce, C. Lord, A.J. Lincoln, S. Pizzo, L. Schreibman, R.H. Haas, N.A. Akshoomoff, R.Y. Courchesne, Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study, Neurology 57 (2001) 245–254.
[13] E. Courchesne, G.A. Press, R. Yeung-Courchesne, Parietal lobe abnormalities detected with MR in patients with infantile autism, AJR Am. J. Roentgenol. 160 (1993) 387–393.

[14] E. Courchesne, O. Saitoh, R. Yeung-Courchesne, G.A. Press, A.J. Lincoln, R.H. Haas, L. Schreibman, Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: identification of hypoplastic and hyperplastic subgroups with MR imaging, AJR Am. J. Roentgenol. 162 (1994) 123–130.
[15] E. Courchesne, J. Townsend, O. Saitoh, The brain in infantile autism: posterior fossa structures are abnormal, Neurology 44 (1994) 214–223.
[16] E. Courchesne, R. Yeung-Courchesne, G.A. Press, J.R. Hesselink, T.L. Jernigan, Hypoplasia of cerebellar vermal lobules VI and VII in autism, N. Engl. J. Med. 318 (1988) 1349–1354.
[17] H. Critchley, E. Daly, M. Phillips, M. Brammer, E. Bullmore, S. Williams, T. Van Amelsvoort, D. Robertson, A. David, D. Murphy, Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study, Hum. Brain Mapp. 9 (2000) 93–105.
[18] M. Davidovitch, B. Patterson, P. Gartside, Head circumference measurements in children with autism, J. Child Neurol. 11 (1996) 389–393.
[19] B. Egaas, E. Courchesne, O. Saitoh, Reduced size of corpus callosum in autism, Arch. Neurol. 52 (1995) 794–801.
[20] M. Elia, R. Ferri, S.A. Musumeci, S. Panerai, M. Bottitta, C. Scuderi, Clinical correlates of brain morphometric features of subjects with low-functioning autistic disorder, J. Child Neurol. 15 (2000) 504–508.
[21] S. Eliez, A.L. Reiss, MRI neuroimaging of childhood psychiatric disorders: a selective review, J. Child Psychol. Psychiatry 41 (2000) 679–694.
[22] D.J. Fidler, J.N. Bailey, S.L. Smalley, Macrocephaly in autism and other pervasive developmental disorders, Dev. Med. Child Neurol. 42 (2000) 737–740.
[23] E. Fombonne, B. Roge, J. Claverie, S. Courty, J. Fremolle, Microcephaly and macrocephaly in autism, J. Autism Dev. Disord. 29 (1999) 113–119.
[24] G.R. Gaffney, S. Kuperman, L.Y. Tsai, S. Minchin, Morphological evidence for brainstem involvement in infantile autism, Biol. Psychiatry 24 (1988) 578–586.
[25] G.R. Gaffney, S. Kuperman, L.Y. Tsai, S. Minchin, Forebrain structure in infantile autism, J. Am. Acad. Child Adolesc. Psychiatry 28 (1989) 534–537.
[26] G.R. Gaffney, S. Kuperman, L.Y. Tsai, S. Minchin, K.M. Hassanein, Midsagittal magnetic resonance imaging of autism, Br. J. Psychiatry 151 (1987) 831–833.
[27] G.R. Gaffney, L.Y. Tsai, S. Kuperman, S. Minchin, Cerebellar structure in autism, Am. J. Dis. Child 141 (1987) 1330–1332.
[28] H.J. Garber, E.R. Ritvo, Magnetic resonance imaging of the posterior fossa in autistic adults, Am. J. Psychiatry 149 (1992) 245–247.
[29] H.J. Garber, E.R. Ritvo, L.C. Chiu, V.J. Griswold, A. Kashanian, B.J. Freeman, W.H. Oldendorf, A magnetic resonance imaging study of autism: normal fourth ventricle size and absence of pathology, Am. J. Psychiatry 146 (1989) 532–534.
[30] M.S. George, D.C. Costa, K. Kouris, H.A. Ring, P.J. Ell, Cerebral blood flow abnormalities in adults with infantile autism, J. Nerv. Ment. Dis. 180 (1992) 413–417.
[31] C. Gillberg, L. de Souza, Head circumference in autism, Asperger syndrome, and ADHD: a comparative study, Dev. Med. Child Neurol. 44 (2002) 296–300.
[32] A.Y. Hardan, N.J. Minshew, K. Harenski, M.S. Keshavan, Posterior fossa magnetic resonance imaging in autism, J. Am. Acad. Child Adolesc. Psychiatry 40 (2001) 666–672.
[33] A.Y. Hardan, N.J. Minshew, M.S. Keshavan, Corpus callosum size in autism, Neurology 55 (2000) 1033–1036.
[34] A.Y. Hardan, N.J. Minshew, M. Mallikarjuhn, M.S. Keshavan, Brain volume in autism, J. Child Neurol. 16 (2001) 421–424.
[35] T. Hashimoto, K. Murakawa, M. Miyazaki, M. Tayama, Y. Kuroda, Magnetic resonance imaging of the brain structures in the posterior fossa in retarded autistic children, Acta Paediatr. 81 (1992) 1030–1034.
[36] T. Hashimoto, M. Tayama, M. Miyazaki, K. Murakawa, Y. Kuroda, Brainstem and cerebellar vermis involvement in autistic children, J. Child Neurol. 8 (1993) 149–153.
[37] T. Hashimoto, M. Tayama, M. Miyazaki, K. Murakawa, S. Shimakawa, Y. Yoneda, Y. Kuroda, Brainstem involvement in high functioning autistic children, Acta. Neurol. Scand. 88 (1993) 123–128.
[38] T. Hashimoto, M. Tayama, K. Murakawa, T. Yoshimoto, M. Miyazaki, M. Harada, Y. Kuroda, Development of the brainstem and cerebellum in autistic patients, J. Autism Dev. Disord. 25 (1995) 1–18.
[39] M.M. Haznedar, M.S. Buchsbaum, T.C. Wei, P.R. Hof, C. Cartwright, C.A. Bienstock, E. Hollander, Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging, Am. J. Psychiatry 157 (2000) 1994–2001.
[40] R.L. Hendren, I. De Backer, G.J. Pandina, Review of neuroimaging studies of child and adolescent psychiatric disorders from the past 10 years, J. Am. Acad. Child Adolesc. Psychiatry 39 (2000) 815–828.
[41] J.R. Holttum, N.J. Minshew, R.S. Sanders, N.E. Phillips, Magnetic resonance imaging of the posterior fossa in autism, Biol. Psychiatry 32 (1992) 1091–1101.
[42] B. Horwitz, J.M. Rumsey, C.L. Grady, S.I. Rapoport, The cerebral metabolic landscape in autism. Intercorrelations of regional glucose utilization, Arch. Neurol. 45 (1988) 749–755.
[43] M.A. Howard, P.E. Cowell, J. Boucher, P. Broks, A. Mayes, A. Farrant, N. Roberts, Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism, Neuroreport 11 (2000) 2931–2935.
[44] M. Hsu, R. Yeung-Courchesne, E. Courchesne, G.A. Press, Absence of magnetic resonance imaging evidence of pontine abnormality in infantile autism, Arch. Neurol. 48 (1991) 1160–1163.
[45] M.D. Kleiman, S. Neff, N.P. Rosman, The brain in infantile autism: are posterior fossa structures abnormal? Neurology 42 (1992) 753–760.
[46] J.E. Lainhart, J. Piven, M. Wzorek, R. Landa, S.L. Santangelo, H. Coon, S.E. Folstein, Macrocephaly in children and adults with autism, J. Am. Acad. Child Adolesc. Psychiatry 36 (1997) 282–290.
[47] J.G. Levitt, R. Blanton, L. Capetillo-Cunliffe, D. Guthrie, A. Toga, J.T. McCracken, Cerebellar vermis lobules VIII–X in autism, Prog. Neuropsychopharmacol. Biol. Psychiatry 23 (1999) 625–633.
[48] F. Manes, J. Piven, D. Vrancic, V. Nanclares, C. Plebst, S.E. Starkstein, An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals, J. Neuropsychiatry Clin. Neurosci. 11 (1999) 470–474.
[49] J.H. Miles, L.L. Hadden, T.N. Takahashi, R.E. Hillman, Head circumference is an independent clinical finding associated with autism, Am. J. Med. Genet. 95 (2000) 339–350.
[50] N.J. Minshew, J.B. Payton, New perspectives in autism, Part I. The clinical spectrum of autism, Curr. Probl. Pediatr. 18 (1988) 561–610.
[51] N.J. Minshew, J.B. Payton, New perspectives in autism, Part II. The differential diagnosis and neurobiology of autism, Curr. Probl. Pediatr. 18 (1988) 613–694.
[52] J.W. Murakami, E. Courchesne, G.A. Press, R. Yeung-Courchesne, J.R. Hesselink, Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism, Arch. Neurol. 46 (1989) 689–694.
[53] M.A. Nowell, D.B. Hackney, A.S. Muraki, M. Coleman, Varied MR appearance of autism: fifty-three pediatric patients having the full autistic syndrome, Magn. Reson. Imaging 8 (1990) 811–816.
[54] J. Piven, S. Arndt, J. Bailey, N. Andreasen, Regional brain enlargement in autism: a magnetic resonance imaging study, J. Am. Acad. Child Adolesc. Psychiatry 35 (1996) 530–536.

[55] J. Piven, S. Arndt, J. Bailey, S. Havercamp, N.C. Andreasen, P. Palmer, An MRI study of brain size in autism, Am. J. Psychiatry 152 (1995) 1145–1149.
[56] J. Piven, J. Bailey, B.J. Ranson, S. Arndt, An MRI study of the corpus callosum in autism, Am. J. Psychiatry 154 (1997) 1051–1056.
[57] J. Piven, J. Bailey, B.J. Ranson, S. Arndt, No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals, J. Autism Dev. Disord. 28 (1998) 105–110.
[58] J. Piven, E. Nehme, J. Simon, P. Barta, G. Pearlson, S.E. Folstein, Magnetic resonance imaging in autism: measurement of the cerebellum, pons, and fourth ventricle, Biol. Psychiatry 31 (1992) 491–504.
[59] J. Piven, K. Saliba, J. Bailey, S. Arndt, An MRI study of autism: the cerebellum revisited, Neurology 49 (1997) 546–551.
[60] I. Rapin, Autism in search of a home in the brain, Neurology 52 (1999) 902–904.
[61] I. Rapin, R. Katzman, Neurobiology of autism, Ann. Neurol. 43 (1998) 7–14.
[62] E.R. Ritvo, H.J. Garber, Cerebellar hypoplasia and autism (letter), N. Engl. J. Med. 319 (1988) 1152.
[63] D.C. Rojas, S.D. Bawn, T.L. Benkers, M.L. Reite, S.J. Rogers, Smaller left hemisphere planum temporale in adults with autistic disorder, Neurosci. Lett. 328 (2002) 237–240.
[64] O. Saitoh, E. Courchesne, B. Egaas, A.J. Lincoln, L. Schreibman, Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities, Neurology 45 (1995) 317–324.
[65] O. Saitoh, C.M. Karns, E. Courchesne, Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentata in autism, Brain 124 (2001) 1317–1324.
[66] G.B. Schaefer, J.N. Thompson, J.B. Bodensteiner, J.M. McConnell, W.J. Kimberling, C.T. Gay, W.D. Dutton, D.C. Hutchings, S.B. Gray, Hypoplasia of the cerebellar vermis in neurogenetic syndromes, Ann. Neurol. 39 (1996) 382–385.
[67] L.L. Sears, C. Vest, S. Mohamed, J. Bailey, B.J. Ranson, J. Piven, An MRI study of the basal ganglia in autism, Prog. Neuropsychopharmacol. Biol. Psychiatry 23 (1999) 613–624.
[68] B.F. Sparks, S.D. Friedman, D.W. Shaw, E.H. Aylward, D. Echelard, A.A. Artru, K.R. Maravilla, J.N. Giedd, J. Munson, G. Dawson, S.R. Dager, Brain structural abnormalities in young children with autism spectrum disorder, Neurology 59 (2002) 184–192.
[69] M.C. Stevens, D.A. Fein, M. Dunn, D. Allen, L.H. Waterhouse, C. Feinstein, I. Rapin, Subgroups of children with autism by cluster analysis: a longitudinal examination, J. Am. Acad. Child Adolesc. Psychiatry 39 (2000) 346–352.
[70] S.M. Strakowski, M.P. DelBello, C. Adler, D.M. Cecil, K.W. Sax, Neuroimaging in bipolar disorder, Bipolar Disord. 2 (2000) 148–164.
[71] K.D. Tsatsanis, B.P. Rourke, A. Klin, F.R. Volkmar, D. Cicchetti, R.T. Schultz, Reduced thalamic volume in high-functioning individuals with autism, Biol. Psychiatry 53 (2003) 121–129.
[72] M. Zilbovicius, B. Garreau, Y. Samson, P. Remy, C. Barthelemy, A. Syrota, G. Lelord, Delayed maturation of the frontal cortex in childhood autism, Am. J. Psychiatry 152 (1995) 248–252.