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Review

Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies

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Abstract

Background. – Structural brain abnormalities have been described in autism but studies are often small and contradictory. We aimed to identify which brain regions can reliably be regarded as different in autism compared to healthy controls.

Method. – A systematic search was conducted for magnetic resonance imaging studies of regional brain size in autism. Data were extracted and combined using random effects meta-analysis. The modifying effects of age and IQ were investigated using meta-regression.

Results. – The total brain, cerebral hemispheres, cerebellum and caudate nucleus were increased in volume, whereas the corpus callosum area was reduced. There was evidence for a modifying effect of age and IQ on the cerebellar vermal lobules VI–VII and for age on the amygdala.

Conclusions. – Autism may result from abnormalities in specific brain regions and a global lack of integration due to brain enlargement. Inconsistencies in the literature partly relate to differences in the age and IQ of study populations. Some regions may show abnormal growth trajectories.

Keywords: Autism; MRI; Meta-analysis

1. Introduction

Autism is a clinically defined syndrome characterised by significantly impaired social interactions, communication deficits and a restricted, repetitive pattern of interests and activities—the ''autistic triad'' [1]. While early writers proposed that autism was caused by a lack of maternal responsiveness [2] it is now widely regarded as neurodevelopmental in origin. The underlying aetiopathological mechanisms remain essentially unknown but the advent of magnetic resonance imaging has enabled the detailed in vivo examination of the brain in people with autism. A wide variety of brain regions have been reported to be structurally abnormal but there is often disagreement between studies.

It is possible that the current lack of consensus reflects the generally low power of studies and differences between study populations which confound results. For example, a reduction in the cross-sectional area of cerebellar vermal lobules VI–VII was one of the first structural abnormalities reported to be associated with autism [3]; but while this finding has been replicated by some studies [4] others have failed to find such an association [5,6]. Vermal hypoplasia has also been identified in other neurodevelopmental syndromes [7] leading some authors to suggest that it is a non-specific effect of IQ rather than related to autistic features per se [8]. More recently interest has focused on the total brain volume in autism; again however some studies find an enlargement [9]

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while others find no difference in size [10]. Other studies have reported that these differences are dependent on age, with younger autistic subjects showing an enlargement that is not seen in their older counterparts [11,12]. However the exact age at which this distinction can be seen varies between studies and brain enlargement has also been reported in adult autistic populations [13]. A similar relationship with age has also been proposed for the amygdala [14] which, despite being found to be functionally abnormal in autism [15], has been variously reported as enlarged [9], reduced [16] or no different in size [17] relative to controls. Results for the hippocampus are equally inconsistent although no age related changes have been shown [9,17,18].

Several reviewers have drawn together this rather disparate literature qualitatively [19,20] but this does not permit firm conclusions to be made. Quantitative rather than qualitative review methods may therefore be required to establish if there is a characteristic neuroanatomy of autism. A recent meta-analysis addressed whether brain enlargement in autism is age dependent but was limited only to this specific question [21]. The current study applies the methodology of systematic review and meta-analysis to the wider structural MRI literature in autism. We sought to determine what reliable conclusions can be reached about the nature and extent of structural MRI abnormalities of the brain in autism. We included an analysis of the effects of age, IQ and gender as potential confounders of the findings of the meta-analysis.

2. Methods

2.1. Literature search

Two authors (ACS and RP) searched Medline, EMBASE and PsychINFO for all English language studies published between January 1984 and November 2006 that reported structural MRI data in people with autism and unaffected controls. Search terms included ‘autism’, ‘Asperger’s syndrome’, ‘pervasive developmental disorder’ and related terms combined using the AND operator with ‘magnetic resonance imaging.’ Both free-text and expanded medical subject headings were used. The search strategy was supplemented using a cited reference search and by inspecting the reference lists of included articles.

2.2. Criteria for inclusion

Two authors (ACS and RP) independently assessed all abstracts for inclusion, and retrieved articles in full text where appropriate. Full text articles were then inspected independently by the same authors, according to study inclusion criteria. Any disagreements at either stage were resolved by discussion amongst the authors.

Primary research studies were considered for inclusion if they were published as a peer-reviewed article in English and compared a sample of formally diagnosed autistic subjects with a group of healthy controls. Only studies reporting structural MRI data where means and standard deviations were available (or could be extracted) for each group were included.

2.3. Data abstraction

Three authors (MDS, ACS and SG) extracted data from all included studies and one author (ACS) checked all the extracted data. Characteristics of the autistic and control groups which possibly confounded any observed difference (including mean/median age, gender distribution and IQ) were also recorded.

The majority of included studies provided full-scale IQ results from the Wechsler Adult Intelligence Scale (WAIS) or Wechsler Intelligence Scale for Children (WISC) as appropriate to the age of the subjects. When verbal and performance IQ results were provided separately, full-scale IQ results were derived according to standard protocols (WAIS manual).

Data were utilised when volume or area results were available for a region of interest from three or more studies. Where both volume and area data were available, only volumes were considered. Area and volume data were never combined in the same analysis. Additionally, where a study reported raw and adjusted values, the unadjusted values were utilised. When there was evidence of repeat publication, only the study with the most data for each specific region of interest was chosen. When a study gave means by age and IQ stratified subgroups these were combined to give a pooled mean and standard deviation for use in the main meta-analysis. However, to fully investigate the effects of age and IQ on the results, the values for each subgroup were also recorded separately for use in the meta-regression.

2.4. Data synthesis

Statistical analyses were conducted by one author (AM) using STATA SE version 8 (STATA Corp, College Station, TX). Hedge’s unbiased estimator of standardised effect size [22], and its variance, was calculated from each study using the pooled means and standard deviations such that each study contributed only one data point per region of interest to the meta-analysis. Standardised effects sizes were then combined using random-effects meta-analysis using techniques based on the method of maximum likelihood [23]. Publication bias was assessed using Egger’s test. The size of between-study heterogeneity was estimated using the I^2 statistic (a measure of the proportion of variance in summary effect size due to heterogeneity) and its statistical significance calculated using Cohen’s Q [24]. Where I^2 exceeded 50% and for the total brain volume, the modifying effects of age, gender and IQ were investigated using meta-regression. Only studies for which these data were available were included in the meta-regression and when studies provided data in age or IQ defined subgroups these were considered as separate data points in the appropriate meta-regression. A regression model was fitted to the data with the mean age and IQ and the gender ratio of the autistic subjects fitted as fixed effects [22]. The study was modelled as

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a random effect and the model estimated using residual maximum likelihood (REML). Where significant relationships were found their nature was investigated graphically by fitting the ordinary least squares line to the data points. The meta-regression was also repeated using the pooled mean values to ensure that the results were not related to one study contributing a disproportionate number of data points to the analysis.

3. Results

The literature search of the three databases yielded 738 articles of which 136 were retrieved in full text format. Fig. 1 summarises the study flow and reasons for exclusion.

Forty-six publications were included in the final analysis and provided information regarding 20 regions of interest from over 800 individuals with autism and a similar number of controls. The exact number could not be calculated as overlapping groups of subjects provided data for different brain regions in different publications. Table 1 lists the key demographic and diagnostic information for each study report. Publications with overlapping populations are indicated and results stratified by age or IQ are recorded in italics under the pooled means and standard deviations of the parent study.

Standardised effect sizes (denoted by ES in the text), and their 95% confidence intervals, for the 20 regions of interest are presented in Table 2 along with estimates of heterogeneity. Statistically significant effects were obtained for 9 regions of interest. In order of effect size, areas of the midbrain (ES −0.77), vermal lobules VIII-X (ES −0.43), the corpus callosum (ES −0.28) and vermal lobules VI–VII (ES −0.27) were significantly smaller in autistic subjects compared to controls. In contrast, cerebellar (ES 0.72), cerebral hemisphere (ES 0.62) intracranial (ICV, ES 0.51), caudate (ES 0.41) and total brain (TBV, ES 0.32) volumes were significantly increased in autistic subjects compared to controls. Substantial overlaps in the confidence intervals (see Table 2) indicated that there were no significant differences in the magnitude of the effect sizes between regions.

Statistically significant heterogeneity was seen for 9 of the 18 regions examined including several for which no differences between autistic subjects and controls were found. Significant relationships were found between the effect size for the cerebellar vermal lobules VI–VII and the mean age (20 data points, $z = 2.3$, $p = 0.02$) and IQ (6 data points, $z = 2.7$, $p < 0.01$) of the autistic subjects. Graphical representation of these relationships indicated that as subject age and IQ increase the observed reductions in vermal lobules VI–VII become less apparent (Figs. 2–4). In addition significant relationships were found between age and effect size for the left and right amygdalae (7 data points, $z = -2.7$, $p = 0.04$ and 7 data points, $z = -2.5$, $p = 0.01$ respectively). The graphs for both demonstrate that as age increases amygdala volume in autistic subjects decreases relative to controls (Fig. 5). There was also a significant relationship between the proportion of autistic subjects who were male and the size difference of vermal lobules I–V (8 data points, $z = 2.8$, $p < 0.01$). Studies with proportionally less males were more likely to show a reduction in this area than those with more males (Fig. 6). There were no significant relationships with age and IQ for any of the other regions including for age and total brain volume (21 data points, $z = -1.2$, $p = 0.22$) (Fig. 7). In line with a previous meta-analysis [21] we also fitted a 2nd order regression line to the age-total brain volume data which was also non-significant. There were no significant changes to these relationships when the pooled mean values were used. Although a variety of diagnostic methods were employed between studies these were not found to significantly contribute to the heterogeneity of the results.

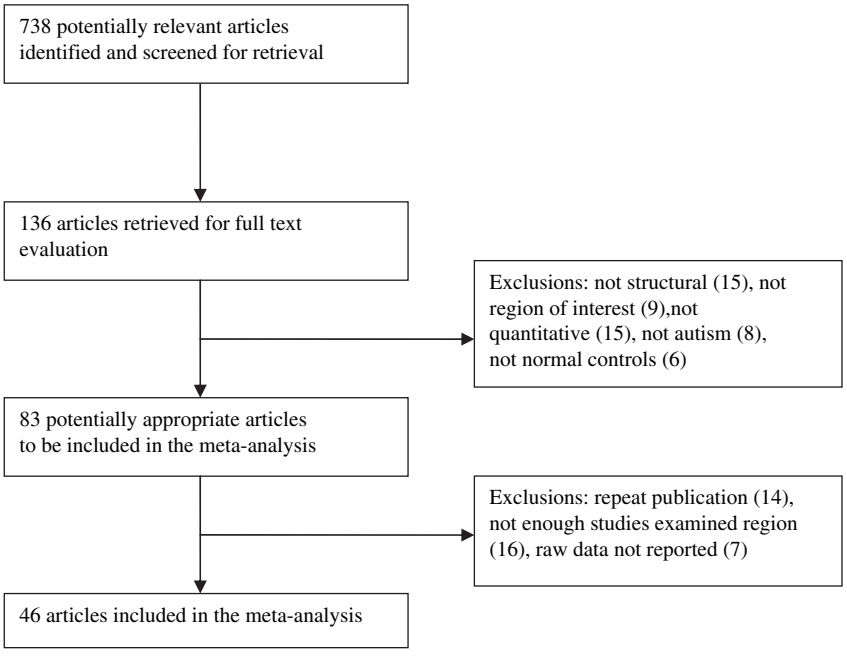

Fig. 1. Study flow and reasons for exclusion.

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Table 1
Demographic characteristics of included study populations

Study (year)	Diagnostic instruments	Autistic subjects			Control subjects			Regions used
		N (M:F)	Mean/ median age	Mean IQ	*N*	Mean/ median age	Mean IQ	
Akshoomoff (2004) [25]*	DSM-IV, CARS, ADI, ADOS	42 (42:0)	3.8	67	15 (15:0)	3.6	111	cbr, cbl, I–V, VI–VII
		30	*3.8*	*57*	*15*	*3.6*	*111*	
		12	*3.8*	*86*	*15*	*3.6*	*111*	
Aylward (2002) [12]	ADI, ADOS	67 (58:9)	18.8	102.7	83 (76:7)	18.9	107	tbv
		23	*10*	–	*28*	*10*	–	
		20	*15*	–	*27*	*15*	–	
		24	*32*	–	*28*	*32*	–	
Carper (2000) [26]	DSM-IV, CARS, ADI, ADOS	42 (42:0)	5.4	79.5	29 (29:0)	6	114	VI–VII
Carper (2002) [27]*	DSM-IV, CARS, ADI, ADOS	38 (38:0)	5.7	–	39 (39:0)	6.5	–	tbv
		12	*3.5*	–	*8*	*3.4*	–	
		19	*5.7*	–	*17*	*5.7*	–	
		7	*9.4*	–	*14*	*9.3*	–	
Cieseilski (1997) [28]	DSM-III-R	9 (5:4)	16.8	–	10 (7:3)	16.6	–	I–V, VI–VII, pons
Courchesne (1994) [29]	DSM-III	50 (41:9)	–	–	53 (43:10)	18.8	–	I–V, VI–VII
Egaas (1995) [30]	DSM-III-R, CARS, ADI, ADOS	51 (45:6)	15.5	–	51 (45:6)	15.5	–	cc
Elia (2000) [31]	DSM-IV, CARS	22 (22:0)	10.9	–	11 (11:0)	10.9	–	cc, mb, pons, vermis, VI–VII
Gaffney (1987) [32]†	DSM-III	13 (10:3)	11.3	84.9	35 (21:14)	12	–	cc
Gaffney (1988) [33]†	DSM-III	13 (10:3)	11.3	84.9	35 (21:14)	12	–	med, mb, pons
Garber (1989) [34]‡	DSM-III	15 (11:4)	11.6	–	15 (11:4)	–	–	4V
Garber (1992) [35]‡	DSM-III	12 (9:3)	27.2	–	12 (8:4)	26.4	–	4V, pons, vermis, I–V, VI–VII
Girgis (2006) [36]	ADI, ADOS	11 (11:0)	10.6	93.1	18 (18:0)	10.4	115.4	tbv
Hardan (2000) [37]**	ADI, ADOS	22 (22:0)	22.4	100.4	22 (22:0)	22.4	100.5	cc
Hardan (2001) [38]**	ADI, ADOS	16 (16:0)	22.2	102.8	19 (19:0)	22.2	101.2	icv, cbr
Hardan (2001) [5]**	ADI, ADOS	22 (22:0)	22.4	100.4	22 (22:0)	22.4	100.5	cbl, vermis, I–V, VI–VII, VIII–X, 4V, med, mb, pons
Hardan (2003) [39]††	ADI, ADOS	40 (38:2)	19.3	103.1	41 (39:2)	18.6	104.2	tbv, caudate
Hardan (2004) [40]	ADI, ADOS	30 (30:0)	21.8	101.8	32 (32:0)	21.7	105.3	tbv
		12	*12.7*	*104.9*	*13*	*12.8*	*110.2*	
		18	*27.8*	*99.7*	*19*	*27.7*	*102*	
Hardan (2006) [41]	ADI, ADOS	17 (17:0)	10.5	90.7	14 (14:0)	10.7	110.9	tbv
Hardan (2006) [83]††	ADI, ADOS	40 (38:2)	19.3	103.1	41 (39:2)	18.6	104.2	thalamus
Hashimoto (1995) [4]	DSM-III-R, CLAC	102 (76:26)	6.1	–	112 (65:47)	7.2	–	vermis, I–V, VI–VII, VIII–X, 4V, med, mb, pons
		11	*1*		*25*	*1*		
		42	*3*		*20*	*3*		
		10	*5*		*7*	*5*		
		11	*7*		*12*	***7***		
		3	*9*		***8***	*9*		
		8	*11*		*156*	*11*		
		8	*13*		*12*	*13*		
		4	*15*		*9*	*15*		
		5	*18*		*4*	*18*		
Hazlett (2006) [42]‡‡	DSM-III-R, ADI	23 (23:0)	19.1	89.9	15 (15:0)	21.6	102.3	cbr
Haznedar (2000) [17]***	DSM-IV, ADI	10 (–:–)	–	–	17 (15:2)	28.8	–	tbv, amy, hc
Haznedar (2006) [43]***	DSM-IV, ADI	10 (–:–)	–	–	17 (15:2)	28.8	–	thalamus
Herbert (2003) [44]	DSM-III-R, WADIC	17 (17:0)	–	>80	15 (15:0)	–	>80	tbv, caudate, cbl
Holttum (1992) [45]	DSM-III-R, ADI, ADOS	18 (18:0)	20.2	94.5	18 (18:0)	20.2	95.2	I–V, VI–VII, VIII–X
Howard (2000) [18]	DSM-IV	10 (10:0)	23.8	99	10 (10:0)	24.2	102	icv, cbr, amy, hc
Hsu (1991) [46]	–	34 (27:7)	18.9	82.6	44 (40:4)	19.8	113	mb, pons
Kates (2004) [10]	ABC, ADI-R, ADOS	8 (–:–)	7.6	69.6	16 (14:2)	8.3	123.6	tbv
Kaufmann (2003) [7]	DSM-IV, ADI, ADOS	10 (10:0)	6.9	66.1	21 (21:0)	8.3	120.8	I–V, VI–VII, VIII–X
Kleiman (1992) [6]	DSM-III-R	10 (8:2)	6.6	–	17 (–:–)	–	–	pons, I–V, VI–VII
Levitt (1999) [47]	DSM-IV, ADI	8 (–:–)	12.5	83.3	21 (–:–)	12	114.9	VIII–X
Lotspeich (2004) [48]	ADI, ADOS	31 (31:0)	11.9	–	21 (21:0)	12.5	–	cbr
McAlonan (2005) [49]	ADI-R	17 (16:1)	12	101	17 (16:1)	11	114	tbv

(*continued on next page*)

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Table 1 (*continued*)

Study (year)	Diagnostic instruments	Autistic subjects			Control subjects			Regions used
		N (M:F)	Mean/ median age	Mean IQ	*N*	Mean/ median age	Mean IQ	
Pierce (2001) [50]	DSM-IV, CARS, ADI, ADOS	6 (6:0)	29.5	83.7	8 (8:0)	28.3	–	amy
Piven (1992) [51]	DSM-III-R, ADI	15 (15:0)	27.7	92.5	30 (30:0)	29.6	115	pons, I–V, VI–VII
Piven (1995) [13]‡‡	DSM-III-R, ADI	22 (22:0)	18.4	90.8	20 (20:0)	21.6	103.4	tbv
Piven (1996) [52]‡‡	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20.2	102.1	icv
Piven (1998) [53]‡‡	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20.2	102.1	hc
Rojas (2004) [54]	DSM-IV, ADI, ADOS	15 (13:2)	30.3	97.5	17 (8:9)	43.6	121.8	tbv, amy, hc
Schumann (2004) [14]	ADI-R, ADOS	39 (39:0)	12.9	74.8	22 (22:0)	13.1	115	cbr, amy, hc
		19	*10*	–	*11*	*10*	–	
		20	*15.5*	–	*11*	*15.5*	–	
Sears (1999) [55]‡‡	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20.2	102.1	caudate
Sparks (2002) [9]	DSM-IV, ADI, ADOS	29 (26:3)	3.9	–	26 (18:8)	4	–	tbv, cbr, cbl, hc, amy
Townsend (1999) [56]	DSM-III-R, CARS, ADI, ADOS	15 (–:–)	27	79	43 (–:–)	36.3	116	icv, tbv
Tsatsanis (2003) [57]	DSM-IV, ADI, ADOS	12 (12:0)	21	106.4	12 (12:0)	18.1	108.8	tbv, thalamus
Vidal (2006) [58]	DSM-IV, ADI, ADOS	24 (24:0)	10	95.9	26 (26:0)	11	104.8	tbv, cc

–, no data available; DSM, Diagnostic and Statistical Manual; III, third edition; IIIR, third edition revised; IV, fourth edition; ADI, Autism Diagnostic Inventory; ADOS, Autism Diagnostic Observational Schedule; CARS, Childhood Autism Rating Scale; WADIC, Wing Autistic Disorder Interview; CLAC, Checklist for the Autistic Child; icv, intracranial volume; tbv, total brain volume; cbr, cerebral hemispheres; cbl, cerebellum; amy, amygdala; hc, hippocampus; cc, corpus callosum; med, medulla; mb, midbrain; 4V, 4th ventricle. *, **, ***, †, ††, ‡, ‡‡, studies with overlapping subject groups. Age and IQ stratified results, when given, are entered under the pooled means for each study in italics.

Evidence of publication bias was found only for the total vermal area (Egger test $p < 0.01$). Graphical investigation of this result suggests that larger studies found smaller vermal areas in subjects with autism compared to controls whereas smaller studies found the opposite result. However, the small number of studies of this region ($n = 4$) makes interpretation difficult.

4. Discussion

4.1. Methodological considerations

The research reports use a variety of methods on which to base a diagnosis of autism primarily DSM criteria (III, III-R and IV), the Autism Diagnostic Interview – Revised (ADI-R)

Table 2
Effect sizes and estimates of heterogeneity and publication bias for the 20 regions of interest

Anatomical region	Number of studies[a]	Standardised effect size (95% CI)	Heterogeneity I^2 (%)	Heterogeneity χ^2, *p*-value	Publication bias *p*-value
Volumes					
TBV	16 (21)	0.32 (0.16, 0.49)[a]	22.0	19.23, 0.21	0.43
ICV	4	0.51 (0.20, 0.81)[a]	0.0	1.23, 0.75	0.39
Cerebrum	7 (8)	0.62 (0.39, 0.86)[a]	0.0	5.36, 0.50	0.79
Cerebellum	4	0.72 (0.40, 1.03)[a]	0.0	0.88, 0.83	0.25
Thalamus L	3	−0.05 (−0.39, 0.30)	0.0	1.60, 0.45	0.95
Thalamus R	3	−0.04 (−0.38, 0.31)	0.0	1.57, 0.46	0.95
Amygdala L	6 (7)	0.15 (−0.46, 0.76)	75.8	20.68, <0.01	0.31
Amygdala R	6 (7)	0.28 (−0.32, 0.88)	74.9	19.94, <0.01	0.16
Hippocampus L	6	0.41 (−0.11, 0.93)	74.5	19.64, <0.01	0.78
Hippocampus R	6	0.29 (−0.27, 0.86)	78.8	23.57, <0.01	0.72
Caudate	3	0.41 (0.12, 0.71)[a]	0.0	1.58, 0.46	0.62
4V	3	0.22 (−0.28, 0.72)	28.4	2.79, 0.25	0.70
Areas					
I to V	9 (17)	0.10 (−0.28, 0.49)	71.5	28.11, <0.01	0.46
VI to VII	12 (20)	−0.27 (−0.51, −0.03)[a]	52.0	22.94, 0.02	0.38
VIII to X	5 (13)	−0.43 (−0.80, −0.06)[a]	49.5	7.92, 0.10	0.76
Total vermis	4 (12)	−0.22 (−0.51, 0.07)	20.6	3.78, 0.29	<0.01
Medulla	3 (11)	−0.99 (−2.17, 0.18)	92.8	27.96, <0.01	0.62
Midbrain	5 (13)	−0.77 (−1.52, −0.02)[a]	90.2	40.88, <0.01	0.52
Corpus callosum	5	−0.28 (−0.52, −0.03)[a]	0.0	0.43, 0.98	0.21
Pons	9 (17)	−0.53 (−1.19, 0.13)	90.6	84.94, <0.01	0.42

Significant at $p < 0.05$.
[a] Numbers in brackets represent the total number of data points used in the age meta-regression.

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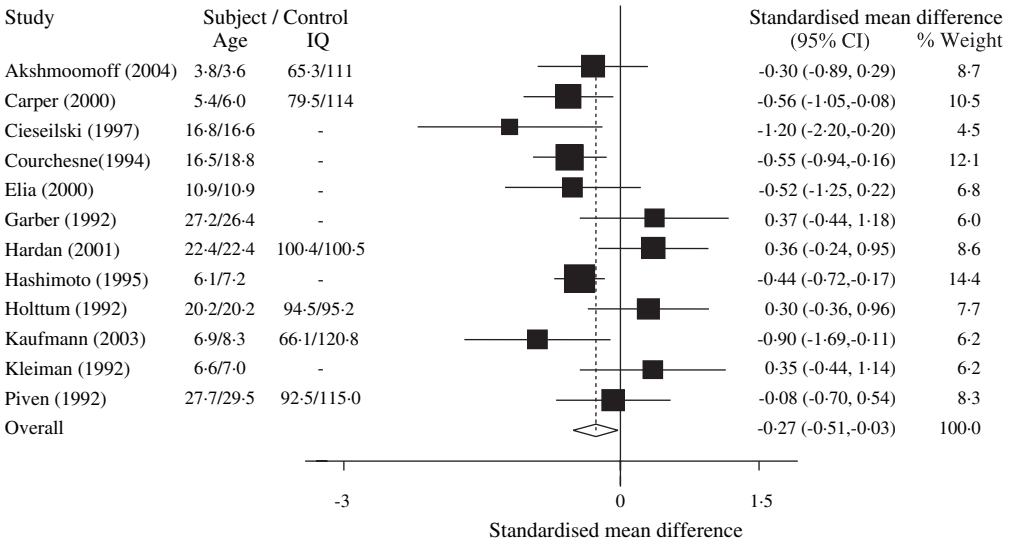

Fig. 2. Forest plot for vermal lobules VI–VII, showing the mean/median age and IQ of the subject and control groups.

[59] and the Autism Diagnostic Observational Schedule (ADOS) [60]). It is important to note that it is not clear whether these methods identify the same groups of patients. DSM III-R criteria, in particular, have been criticised as being too broad and less reliable than those of DSM-III [61] and DSM-IV [62]. While the ADOS and the ADI have been shown to have a reasonable level of diagnostic agreement [63], this finding is by no means consistent [64,65]. Interestingly however we did not find that the choice of diagnostic method had any clear impact on the MRI findings for each region. This may reflect the tendency of many researchers to use a combination of the methods to reach a diagnosis of autism (Table 1). Given the possible lack of agreement between diagnostic methods such an approach may be advisable if one wishes to identify a tightly defined group of autistic individuals but it is important to be aware that such a group is likely to represent the more severe end of the autistic spectrum.

Many studies considered only subjects with IQs of greater than 70 which, given that around 70% of individuals with autism have IQs lower than this [66], means that the available literature is not representative of the general clinical population. Studies which considered high IQ autism tended to contain groups which were well matched for IQ however in those which examined lower functioning individuals the control groups were often of higher IQ than the cases. The issue of controlling for IQ in autism research is a thorny one and disagreements exist about whether the use of an IQ matched control group is appropriate. There are many who argue that low IQ is part of the autistic syndrome, and is indicative of a severely affected individual, hence to use an IQ matched control group will obscure differences which relate to the syndrome itself [67]. Furthermore, defining an appropriate IQ matched control group is difficult due to the heterogeneous aetiology

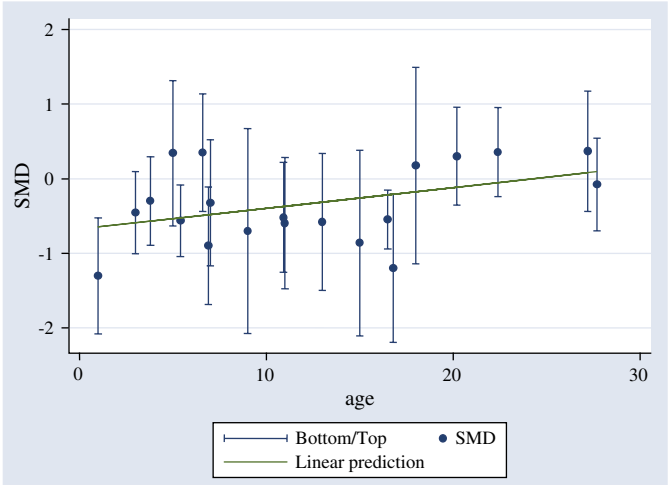

Fig. 3. Graph of standardised mean difference (SMD) versus mean age of the autistic groups for vermal lobules VI–VII. When studies provided data in age stratified subgroups these are shown separately.

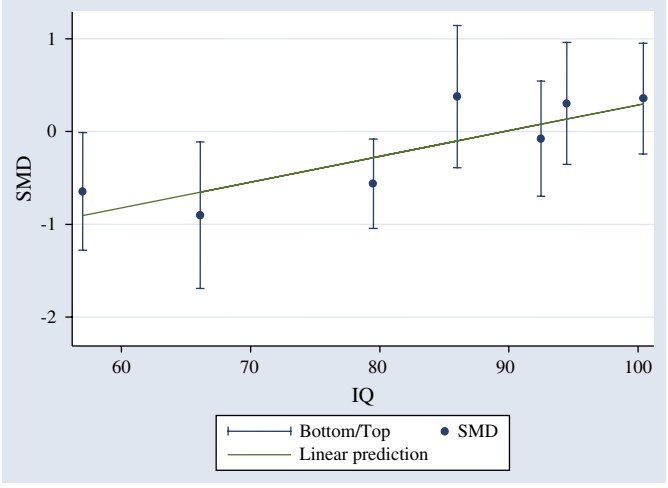

Fig. 4. Graph of standardised mean difference (SMD) versus mean IQ of the autistic groups for vermal lobules VI–VII. Only studies reporting IQ results are included and when studies providing data by IQ stratified subgroups are shown separately.

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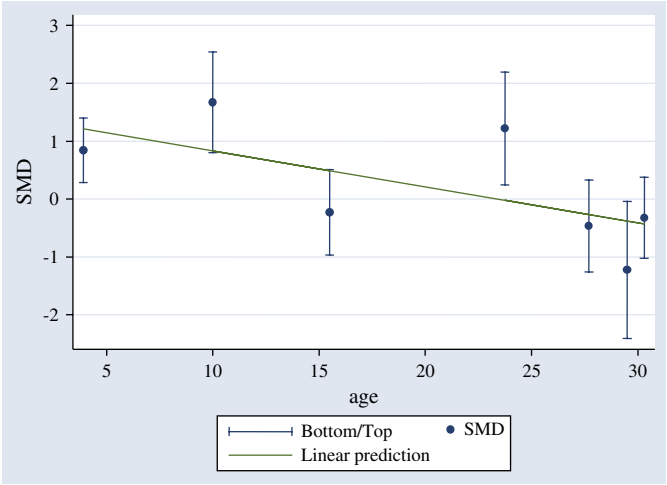

Fig. 5. Graph of standardised mean difference (SMD) versus mean age of the autistic groups for left amygdala.

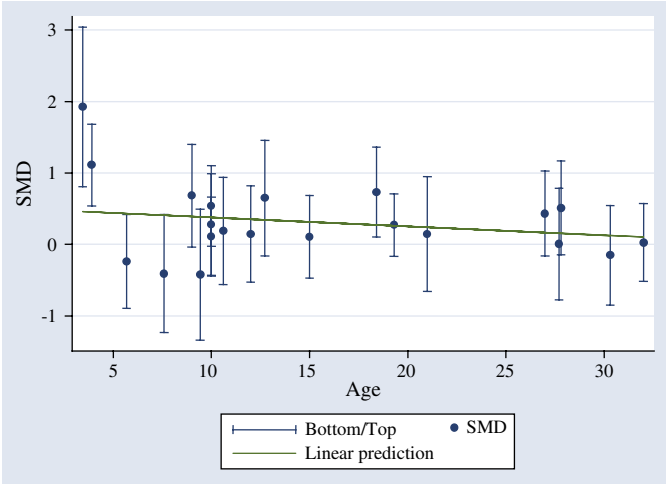

Fig. 7. Graph of standardised mean difference (SMD) versus mean age of autistic groups for total brain volume. When studies provided data in age stratified subgroups these are entered separately.

of low IQ and the subsequent lack of a standard neuroanatomy of learning disability, although some researchers have attempted to address this issue [68]. The contrary argument is that by not taking into account IQ one risks false positive findings that are related to general cognitive impairment rather than to autistic features [69]. There is no definitive answer to this problem although the use of two control groups, one IQ-matched and the other consisting of typically developing individuals, may prove to optimally aid the interpretation of results.

Although all autistic individuals will show impairment in the three domains which make up the autistic triad the severity of impairment seen in each of these domains may vary markedly between individuals who all meet diagnostic criteria for autism. In addition, as discussed above, individuals with autism show a wide range of global intellectual abilities. While most studies provided information regarding IQ, meaning that we were able to take it into account in the meta-regression, the majority of studies do not provide detailed information regarding the severity of impairment in each domain of the autistic triad. It is possible therefore that we have combined groups of individuals who, despite all having a diagnosis of autism, in fact display widely differing clinical features. As such this may mask significant differences between groups and account for some of the unexplained neuroanatomical heterogeneity that we identified. Similarly it has been suggested that there may exist, within the autistic population, two groups with distinct neuroanatomical features [29]. Unfortunately it is not possible to confirm or refute this suggestion within the context of this meta-analysis without individual subject data from each study.

It is important to note that any meta-regression is inherently limited in its power to detect significant effects by the number of studies which provide sufficient relevant data. For example, the meta-regression for the hippocampus contained only 6 separate data points and it is possible that we did not detect significant age or IQ effects due to a lack of power. In addition, we employed full scale IQ in the meta-regression and it could be argued that the use of performance IQ or certain subtests of the WAIS not thought to be impaired in autism may have been more appropriate. However, there are disagreements between studies on whether or not there is a characteristic pattern of WAIS subtest impairment in autism [70,71] and it is not necessarily clear that islets of preserved, or possibly even enhanced, ability give a more accurate estimate of intellectual ability in autism than full scale IQ.

Several papers were excluded from the meta-analysis as they did not present raw data and others were excluded as they combined autistic individuals with those suffering from other pervasive developmental disorders. In addition 15 studies were excluded as they concerned regions for which less than 3 publications were available. Clearly there are likely to be parts of the brain which are structurally abnormal in autism beyond those reported in the meta-analysis which with replication will become apparent in time.

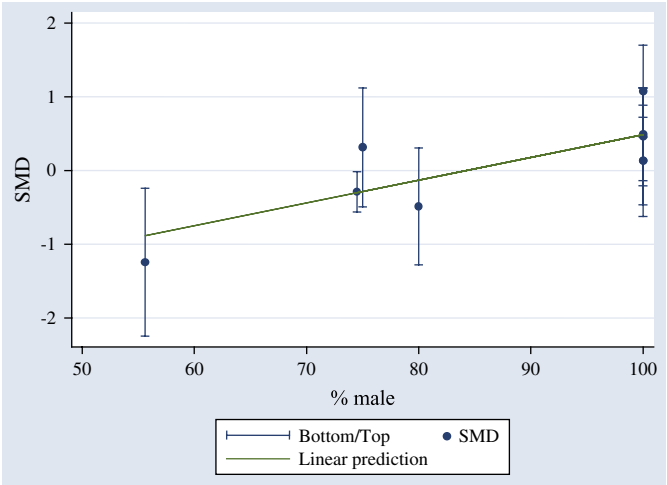

Fig. 6. Graph of standardised mean difference (SMD) versus the percentage of the autistic subjects who were male for cerebellar lobules I–V.

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4.2. Main findings and clinical implications

We found consistent evidence for an increase of the total brain volume, the cerebral hemispheres and the cerebellum in autism. In addition, an increase in the volume of the caudate nucleus was seen whereas the corpus callosum was reduced in size. Reductions in the size of the midbrain and the cerebellar vermal lobules VI–VII and VIII–X were also found although with significant heterogeneity. For vermal lobules VI–VII this heterogeneity was related to the age and IQ of the study population. While no difference in size was found for the amygdala a significant effect of age on the data was apparent. Similarly there was an effect of gender on the result for vermal lobules I to V although no overall difference in size was observed.

The consistent finding of cerebral enlargement is in keeping with those post-mortem studies of autistic individuals which have reported megalencephaly, cortical thickening and an increase in cerebral neuronal density [72]. Increased numbers of smaller and less dense cortical minicolumns (vertical chains of cells extending through the cortical layers thought to be functional sub-units of cortex) have also been reported at post-mortem [73]. A larger less well organised cerebral cortex has been hypothesised to lead to inefficient connectivity and less integration of dispersed brain regions, a view supported by a variety of functional neuroimaging studies [74]. In addition the reduction in the size of the corpus callosum, the major interhemispheric white matter tract, and the enlargement of the cerebellum would likely affect the co-ordination of brain activity. Previously regarded as being solely involved in motor activities, it is now known that the cerebellum also connects to cortical regions involved in emotional and cognitive functions and it is thought to play a similar role in these domains as in the regulation of motor function [75,76]. A lack of integration and regulation of distributed brain functions could lead to deficits in complex processes which require the recruitment of a variety of brain regions, such as language and social behaviour [74].

An increase was also found in caudate volume, without evidence of heterogeneity. This finding was also recently reported in a study of individuals with autistic spectrum disorders in which the size of the caudate was found to correlate with the degree of restricted, repetitive behaviours [77]. Previous findings of enlarged caudate volume and abnormal perfusion of fronto-striatal-thalamic structures in obsessive compulsive disorder lend further, albeit indirect, support to this result [78]. It is therefore likely that caudate enlargement in autism is linked to an intrinsic abnormality of neuronal circuitry although it is possible that the use of antipsychotic medications, which have been associated with caudate enlargement [79], may be confounding the findings. Unfortunately, there was not enough information in the original reports to discern whether or not those with autism were receiving psychotropic medications, let alone to examine any potential dose relationship.

4.3. Effect of confounding variables

The midbrain and lobules VIII–X of the vermis were found to be reduced in size but with significant heterogeneity which was not explained by age or IQ. These findings should therefore be interpreted with great caution. Lobules VI–VII of the vermis were also reduced in size and the heterogeneity of this finding was at least partly accounted for by differences in the age and IQ of the study population. As can be seen in Fig. 2 the case and control groups for this region were generally well matched for age. The significant finding for age may therefore represent a change in the difference in vermal size between the groups as they grow older, i.e. there is a different growth trajectory for this region in autistic individuals as compared to controls which produces a normalisation of size with increasing age (Fig. 3). The largest single study of this region, which included 98 autistic individuals, found a similar relationship with age to that which we have identified [4]. While this study contributed 9 data points to the meta-regression the result remained significant even when these were pooled to give one mean value, showing our findings are not driven solely by this study. With respect to IQ, the lower the IQ of the autistic groups the less well matched they were to the control groups which tended to be of average IQ. Therefore the significant finding for IQ indicates that as the IQ *differences* between the groups lessen so do the volumetric differences (Fig. 4). Taken together these findings indicate that younger autistic individuals show real reductions in the size of vermal lobules VI–VII whereas those identified in older individuals may be an artefact of IQ differences between case and control groups.

Age was also found to have a significant effect on the results for the amygdala with younger autistic individuals showing enlargements which are not present in older groups. Functional imaging studies indicate that the amygdala is involved in social cognition, in particular empathy and ''theory of mind'' (the ability to attribute mental states to others) [80]. It has been shown that lesions in childhood are especially likely to lead to theory of mind impairments [81]. In addition, a larger amygdala volume in 3–4 year old autistic individuals has been found to predict worse social and communication skills several years later [82]. Deficits in these skills are characteristic of autism and the early structural abnormality of the amygdala which we report is likely to play a key role in the development of such impairments.

A significant effect for gender was seen for the cerebellar lobules I to V with studies which contain more female subjects tending to show reductions in this area compared to those which were predominantly male. This result must be treated with caution because few studies examined numerically large numbers of females. For example, the study which reported the largest reduction contained only 4 female subjects out of a total of 9 [28]. In addition, there was a greater proportion of females in the subject than in the control group (44% vs. 30%) which may have biased the result. However, it is possible that female autistic subjects may show different changes to brain structure than males and a large study of females with autism would be a useful addition to the literature.

We did not find a statistically significant relationship between age and effect size for total brain volume, a result which appears to contrast with that of a previous meta-analysis of

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MRI and head circumference studies by Redcay and Courchesne [21]. They found that brain volume enlargements are apparent in young children in the first 4 years of life but normalise following this period. The difference between the two meta-analyses is the inclusion of head circumference studies in infants under 2 years old as a proxy for brain volume in the Redcay and Courchesne report. It is possible that we did not find an age−brain volume relationship due to a lack of MRI studies in these very young autistic individuals. Certainly the two studies in our meta-analysis pertaining to subjects around 4 years old show markedly greater effect sizes when compared with those of older children and adults (Fig. 6). Prospective cohort studies will however be required to settle this issue [69].

5. Conclusion

On the basis of the existing literature, we can conclude that autism is associated with generalised enlargements of the cerebral hemispheres, the cerebellum and the caudate nucleus; with reductions in the size of the corpus callosum and possibly the midbrain and vermal lobules VI−VII and VIII−X. These can be related to the cardinal features of the disorder. In addition some regions have abnormal developmental trajectories which could point towards particular aetiopathological factors and timeframes for possible interventions.

6. Conflict of interest

Nil.

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