Psychiatry Research: Neuroimaging 234 (2015) 239–251

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Head circumference and brain size in autism spectrum disorder: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 19 August 2015
Accepted 25 August 2015
Available online 28 September 2015

Keywords:
Autistic disorder
Head circumference
Macrocephaly
Brain volume
Structural brain imaging
Meta-analysis

ABSTRACT

Macrocephaly and brain overgrowth have been associated with autism spectrum disorder. We performed a systematic review and meta-analysis to provide an overall estimate of effect size and statistical significance for both head circumference and total brain volume in autism. Our literature search strategy identified 261 and 391 records, respectively; 27 studies defining percentages of macrocephalic patients and 44 structural brain imaging studies providing total brain volumes for patients and controls were included in our meta-analyses. Head circumference was significantly larger in autistic compared to control individuals, with 822/5225 (15.7%) autistic individuals displaying macrocephaly. Structural brain imaging studies measuring brain volume estimated effect size. The effect size is higher in low functioning autistics compared to high functioning and ASD individuals. Brain overgrowth was recorded in 142/1558 (9.1%) autistic patients. Finally, we found a significant interaction between age and total brain volume, resulting in larger head circumference and brain size during early childhood. Our results provide conclusive effect sizes and prevalence rates for macrocephaly and brain overgrowth in autism, confirm the variation of abnormal brain growth with age, and support the inclusion of this endophenotype in multi-biomarker diagnostic panels for clinical use.

1. Introduction

Autism spectrum disorder (ASD) represents a heterogeneous group of neurodevelopmental conditions characterized by social and communication deficits, accompanied by repetitive and stereotyped behaviors, insistence on sameness and sensory issues, with onset generally prior to three years of age (American Psychiatric Association, 2013). Despite many advances in our understanding of the neurobiological and developmental processes underlying ASD, our knowledge remains limited and its translational impact into the clinics is still insufficient (State and Levitt, 2011; Chugani, 2012; Freitas et al., 2012). Furthermore, autistic subjects vary widely in clinical features, developmental trajectory, degree of severity and treatment response. This complexity is raising an intensive search to identify biological markers and specific endophenotypes able to aid clinicians in reaching earlier diagnoses and in predicting clinical prognosis as well as treatment response (Walsh et al., 2011). A biomarker can be defined as a biological variable associated with the disease of interest across and within individuals, measurable directly in a given patient or in his/her biomaterials using sensitive and reliable quantitative procedures. The concept of endophenotype goes one step beyond and has specific relevance in autism research. This term, introduced by Gottesman and Shields (1973), designates a heritable, familial, and trait-dependent biomarker, an internal construct that "cannot be observed from the outside with unaided eyes", but can fill the gap between clinical symptoms and the underlying genes (Gottesman and Gould, 2003).

Macrocephaly (i.e., cranial circumference >97th percentile) represents one of the endophenotypes most consistently encountered in a subgroup encompassing 14%–34% of autistic patients (Courchesne et al., 2001; Aylward et al., 2002; Dementieva et al., 2005; Dissanayake et al., 2006; Sacco et al., 2007, 2010). It is also familial and heritable, with first-degree relatives of macrocephalic probands displaying significantly larger head sizes compared to first-degree relatives of normo- or microcephalic autistic individuals (Sacco et al., 2007, 2010). Our understanding of the link between autistic disorder and macrocephaly is still very limited. Neonates later developing autism and macrocephaly apparently display normal head circumferences at birth (Dissanayake et al., 2006; Sacco et al., 2007). Head growth rates begin accelerating during the first year of life, continue approximately until 4 years of age, and then slow down undergoing a premature arrest; no significant difference in head circumference is thus

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http://dx.doi.org/10.1016/j.pscychresns.2015.08.016
0925-4927/

present between patients and controls at adolescence (Courchesne et al., 2001), at least in most cases. Neuroimaging studies have shown several years ago that enlarged brain volumes as responsible for macrocephaly in autism (Woodhouse et al., 1996; Lainhart et al., 1997). However, some studies describe a generalized enlargement of frontal, temporal and parietal lobes, involving both gray and white matter (Sparks et al., 2002); others find overgrowth mainly limited to the frontal lobes and to cortical gray matter, accompanied by an enlargement of the superficial white matter immediately adjacent to the gray matter (Redcay and Courchesne, 2005); still others report increased brain volume due to excessive cerebral white matter only (Hazlett et al., 2005). Altogether, despite significant heterogeneity, these findings have generally been interpreted as reflecting increased neurite sprouting and/or reduced pruning, resulting in a local overabundance of neuropil (Carper et al., 2002; Herbert et al., 2003). This phenomenon would seemingly result in cortical surface area overgrowth (Hazlett et al., 2011) directly yielding macrocephaly, although the neocortex in ASD actually displays complex and region-specific increases in surface area and cortical thickness (Ecker et al., 2010; Hazlett et al., 2011). Neurobiological mechanisms hypothesized to possibly underlie excessive neural growth in autism include several growth factors, hormones, and neurotransmitters, but direct experimental evidence is generally lacking.

Descriptions of the clinical correlates of head circumference in autism are also inconsistent. Some studies have reported higher levels of functioning (Aylward et al., 2002; Courchesne and Pierce, 2005; McCaffery and Deutsch, 2005; Sacco et al., 2007) among macrocephalic patients and have found that children with relatively larger head circumference have higher non-verbal abilities. Conversely, other studies have described no correlation between cranial circumference and specific abilities or cognitive functions (Gillberg and de Souza, 2002; Deutsch and Joseph, 2003). Moreover, larger brain volumes are not unique to ASD and have been reported in a subgroup of children with developmental language disorder (Hardan et al., 2007), as well as in multiple dysmorphic and metabolic syndromes, including Weaver, Sotos, Macrocephaly Capillary Malformations, Phosphatase and Tensin Homolog (PTEN)-related disorders (Tsatsanis et al., 2003).

In light of current interest in the creation of multi-biomarker panels for ASD, we undertook a systematic review of all studies assessing head circumference and total brain volume in autism. We then defined the cumulative percentage of ASD patients with macrocephaly and with enhanced total brain volume according to structural MRI, and perform a series of meta-analyses providing an overall estimate of the effect size and statistical significance for the association between macrocephaly and brain overgrowth with autism.

2. Method

2.1. Literature search

Publications suitable for inclusion in the present study were found applying a strategy similar to the one we recently used to systematically review and meta-analyze publications addressing another well-known ASD biomarker, elevated serotonin blood levels (Gabriele et al., 2014): an initial search protocol was defined *a priori*, then followed by reiterative modifications aimed at progressively maximizing search efficiency by yielding increased numbers of pertinent studies. Our research involved the PUBMED, Scopus, Google Scholar databases and is updated to November, 2014. Once original publications were collected, bibliographies were manually searched for additional eligible references. The search strategy was supplemented using a cited reference search and by inspecting the reference lists of included articles. Final search terms for head circumference were as follows:

(autism OR autistic OR pervasive developmental disorders OR asperger) AND (head circumference OR cranial circumference OR macrocephaly OR head size OR megalencephaly).

Search term list for structural MRI was as follows:

(autism OR autistic disorder OR pervasive developmental disorders OR asperger) AND (volumetric magnetic resonance imaging OR brain volume).

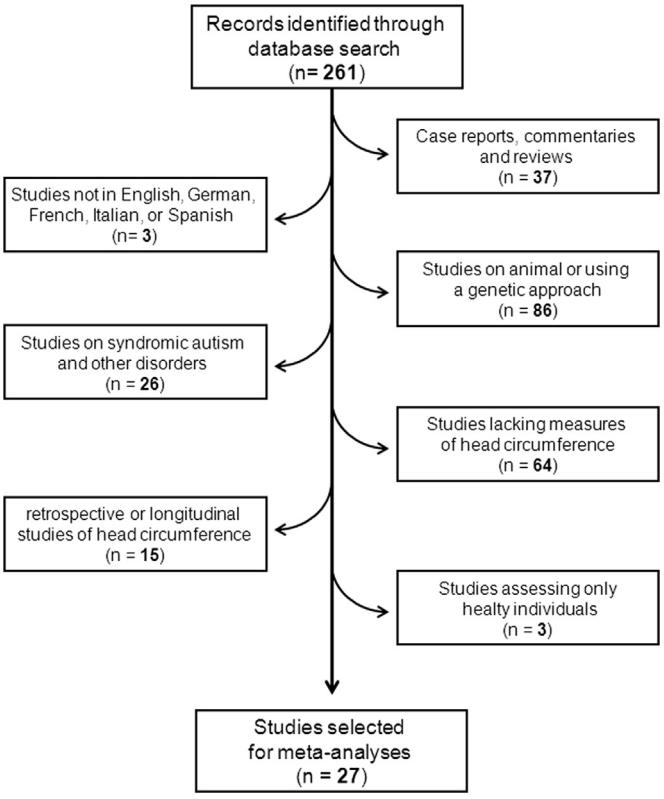

Fig. 1. Study flow chart for head circumference studies. Abbreviations: ASD=Autism Spectrum Disorder; HC=head circumference.

2.2. Study selection criteria

For head circumference a total of 261 studies were initially identified through the methodology outlined above (Fig. 1). The following exclusion criteria were then applied: (1) case reports, commentaries and reviews; (2) studies not in English, German, French, Italian, or Spanish; (3) studies on animal models or studies using a genetic approach; (4) reports on known syndromic forms of autism, Rett syndrome or specific diagnoses other than idiopathic ASD; (5) publications lacking measures of head circumference, including clinical, neurocognitive, biochemical, brain imaging and post-mortem studies; (6) retrospective or longitudinal studies of head circumference trajectory providing multiple data points per each individual; (7) reporting head circumference measurements of healthy individuals only.

At the end of this process, 27 studies were selected, each assessing patients with idiopathic autism (i.e., DSM-IV diagnoses of either Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder Not Otherwise Specified, PDD-NOS), measuring head circumference in autistic patients and providing the percentage of macrocephalic individuals (Bolton et al., 1994; Bailey et al., 1995; Woodhouse et al., 1996; Davidovitch et al., 1996; Stevenson et al., 1997; Lainhart et al., 1997; Skjeldal et al., 1998; Fombonne et al., 1999; Ghaziuddin et al., 1999; Fidler et al., 2000;

Table 1
Summary of 27 studies systematically reviewed and selected for meta-analysis of head circumference in autistic patients.

Reference	Ethnicity	Sample size autistics	Mean age ± SD or age range or median age (yrs)	% Males	Diagnosis	% Patients with macrocephaly[a]
Bolton et al. (1994)	UK	27	2–16	63.0	Autism	37.0 (10/27)
Bailey et al. (1995)	UK	21	2–16	100	Autism	42.0 (9/21)
Woodhouse et al. (1996)	UK	37	2–16	N/A	PDD-NOS	29.7 (11/37)
Davidovitch et al. (1996)	CA	148	4.0	83.1	Autism	18.2 (27/148)
Stevenson et al. (1997)	CA	100	2–21	83.3	Autism	24.0 (24/100)
Lainhart et al. (1997)	CA	91	3–38	77.0	Autism	14.3 (13/91)
Skjeldal et al. (1998)	Norvegian	25	4–17	56.0	Autism	12.0 (3/25)
Fombonne et al. (1999)	French	126	7.9 ± 3.6	67.5	Autism	16.7 (21/126)
Ghaziuddin et al. (1999)	CA	20	10.9 ± 3.9	100	PDD-NOS	20 (4/20)
Fidler et al. (2000)	CA	41	13.6 ± 8.9	80.5	Autism	12.2 (5/141)
Miles et al. (2000)	American (mixed)	137	9.4 ± 8.1	83.8	Autism	23.4 (32/137)
Gillberg and de Souza (2002)	Swedish					
(a)		50	1–13	90.0	Autism	9.0 (4/42)
(b)		50	1.6–16	90.0	AS	20.9 (9/43)
Deutsch and Joseph (2003)	CA	63	7.4 ± 2.3	86.0	Autism	14.0 (9/63)
Torrey et al. (2004)	American (mixed)	15	3.0	73.0	Autism	13.3 (2/15)
Dementieva et al. (2005)	CA	251	8.1 ± 4.4	72.9	Autism	18.7 (47/251)
Lainhart et al. (2006)	CA	338	10.8 ± 7.5	83.7	ASD	17.3 (36/208)
Sacco et al. (2007)	Italian	241	3-16	85.1	ASD	31.1 (75/241)
Van Daalen et al. (2007)	Dutch	53	4 ± 0.8	83.0	ASD	11.3 (6/53)
Webb et al. (2007)	CA	28	3–4	100.0	ASD	21.4 (6/28)
Miles et al. (2008)	American (mixed)	172	8.1 ± 7.1	84.2	ASD	17.4 (30/172)
Davidovitch et al. (2011)	Israeli	317	2.5 ± 1	85.2	ASD	4.4 (14/317)
Chawarska et al. (2011)	CA	98	2.0 ± 0.6	100.0	ASD	21.4 (21/98)
Ververi et al. (2012)	Greek	222	1.5 ± 9	76.6	ASD	21.2 (47/222)
Froehlich et al. (2013)	CA	255	4–18	85.5	ASD	21.2 (54/255)
Chaste et al. (2013)	CA	1889	8.9 ± 3.5	86.9	ASD	14.7 (277/1889)
Grandgeorge et al. (2013)	French	422	7.6 ± 2.0	80.3	ASD	5.7 (24/422)
Cederlund et al. (2014)	Swedish	33	3.0	84.8	ASD	3.0 (1/33)

Abbreviations: PDD-NOS=pervasive developmental disorder – not otherwise specified, ASD=autism spectrum disorder, AS=Asperger syndrome; N/A=not available, yrs=age range expressed in years; CA=Caucasian-American.

[a] Macrocephaly defined a head circumference above the 97th percentile.

Miles et al., 2000; Gillberg and de Souza, 2002; Deutsch and Joseph, 2003; Torrey et al., 2004; Dementieva et al., 2005; Lainhart et al., 2006; Sacco et al., 2007; Van Daalen et al., 2007; Webb et al., 2007; Miles et al., 2008; Chawarska et al., 2011; Davidovitch et al., 2011; Ververi et al., 2012; Chaste et al., 2013; Froehlich et al., 2013; Grandgeorge et al., 2013; Cederlund et al., 2014). For each selected study, macrocephaly was defined as a head circumference above the 97th percentile. Data extracted from the original publications are summarized in Table 1.

For the structural MRI literature, a total of 391 articles were initially identified applying the strategy summarized above (Fig. 2). The following exclusion criteria were then applied: (1) case reports, commentaries and reviews; (2) studies not in English, German, French, Italian, or Spanish; (3) studies on animal models or studies using a genetic approach; (4) reports on syndromic autism, Rett syndrome or specific diagnoses other than idiopathic ASD; (5) publications lacking measures of total brain volume, including clinical, neurobehavioral, biochemical and post-mortem studies; (6) publications reporting only volumetric data for specific or isolated brain regions or limited to gray or white matter. When both total brain volume or area were provided, only the former was considered; (7) studies reporting intracranial volume (ICV) and not total brain volume (TBV), whereby ICV also includes cerebrospinal fluid (CSF); (8) studies employing other electrophysiological or neuroimaging techniques, including Diffusion Tensor Imaging, functional magnetic resonance imaging, proton magnetic resonance spectroscopy, Voxel Based Morphometry, Positron Emission Tomography, Single Photon Emission Tomography, and EEG brain mapping, or providing physical or neuroanatomical parameters other than TBV, including cortical thickness and cortical surface; (9) studies providing longitudinal data of total brain volume; (10) reporting data only from healthy individuals or from patients only; (11) reporting data of identical or overlapping previously-published data sets; (12) reporting data not provided by the Authors as mean ± SD.

At the end of this process, 44 studies were selected, each assessing patients with idiopathic autism (i.e., DSM-IV diagnoses of either Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder Not Otherwise Specified, PDD-NOS) and controls (Piven et al., 1995; Aylward et al., 1999; Haznedar et al., 2000; Hardan et al., 2000; Courchesne et al., 2001; Pierce and Courchesne, 2001; Aylward et al., 2002; Carper et al., 2002; McAlonan et al., 2002; Rojas et al., 2002; Sparks et al., 2002; Hardan et al., 2003; Herbert et al., 2003; Tsatsanis et al., 2003; Akshoomoff et al., 2004; Kates et al., 2004; Palmen et al., 2004; Schumann et al., 2004; Palmen et al., 2005; Vidal et al., 2006; Bloss and Courchesne, 2007; Girgis et al., 2007; Mostofsky et al., 2007; Tate et al., 2007; Cleavinger et al., 2008; Hardan et al., 2008; Freitag et al., 2009; Hallahan et al., 2009; Hardan et al., 2009; Scott et al., 2009; Bigler et al., 2010; Griebling et al., 2010; Jou et al., 2010a, 2010b; Schumann et al., 2010; Tamura et al., 2010; Tepest et al., 2010; Cheung et al., 2011; Hong et al., 2011; Calderoni et al., 2012; Greimel et al., 2013; Nordahl et al., 2013; Stamova et al., 2013; Say et al., 2014). Only studies reporting structural MRI data, specifically TBV expressed as cc or ml where means and standard deviations were available or could be obtained were included. Data extracted from the original publications are summarized in Table 2.

2.3. Data synthesis and statistical analyses

The Comprehensive Meta Analysis Program (Biostat, Version 2.0, 2005) was used for meta-analyses. Between-study heterogeneity was first assessed using the χ^2 goodness-of-fit test and the

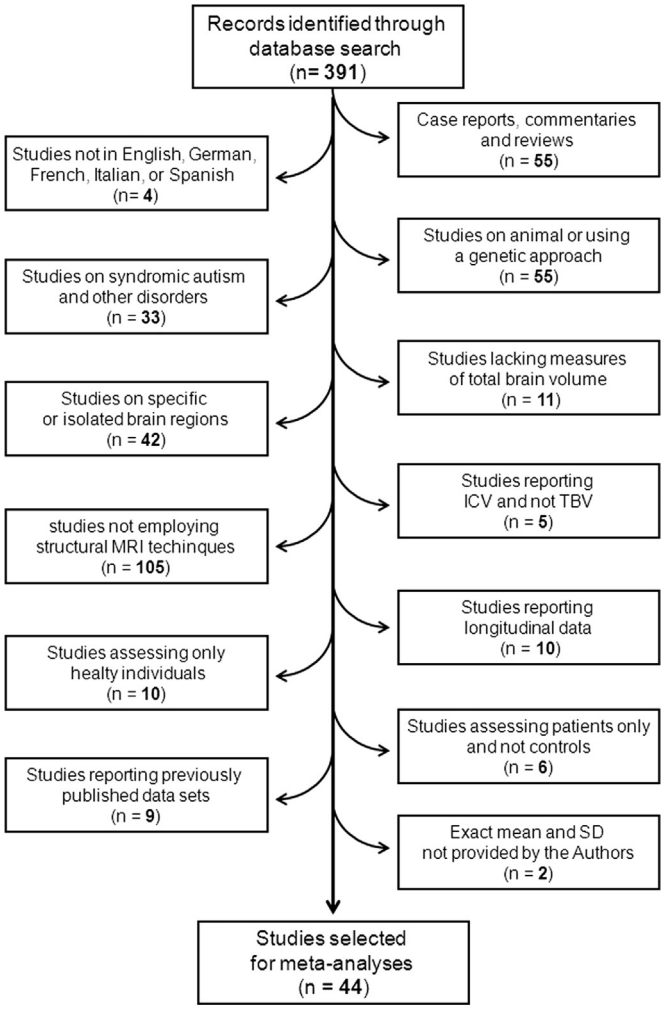

Fig. 2. Study flow chart for structural brain imaging studies reporting total brain volume. Abbreviations: ASD=Autism Spectrum Disorder; ICV=intracranial volume MRI=magnetic resonance imaging; TBV=total brain volume.

I^2 statistic (a measure of the proportion of variance in summary effect size due to heterogeneity), whereby statistical significance was calculated using Cohen's Q. Data were then analyzed using either a fixed effects model or a more conservative random effects model, depending on the absence or presence of significant between-study heterogeneity, respectively. The fixed effect model is based on the assumption that the true effect is shared by all studies. It follows that the combined effect is the estimation of a common effect size. On the contrary, the random effects model allows the true effect to vary from study to study. Publications selected for meta-analysis are assumed to be a random sample of the relevant distribution of effects, and the combined effect estimates the mean effect of this distribution. When heterogeneity is small, both models yield essentially identical results. In either case, effect sizes were combined using the inverse variance method, to generate a pooled effect size and 95% confidence intervals (CI). Publication bias was estimated by the method of Egger et al. (1997), which uses a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of odds ratios (O. R.). Statistical significance for the intercept was determined applying the *T* test.

The percentage of autistic subjects with brain overgrowth was calculated for each separate study, as follows: (a) the upper limit of the normal distribution of total brain volume was defined in each control sample as +2S.D. from mean control values; (b) the mean value of total brain volume in autistic subjects was then transformed into a z-score based on the control sample distribution; (c) the proportion of autistic individuals with total brain volume above the upper limit of the control distribution was estimated, and (d) expressed as percentage of the total number of autistic patients in each sample.

Where I^2 exceeded 50% for the total brain volume, the modifying effects of age as covariate or possible confounding factor on log odds ratios were investigated using meta-regression. Meta-regression differs from simple regression in two ways: (a) larger studies have more influence than smaller studies, since studies are weighted by the precision of their respective effect estimate; it is best to allow for residual heterogeneity among outcome variables, not modeled by the potential effect modifier. The regression coefficient obtained from a meta-regression analysis describes how the outcome variable changes with a unit increase in the explanatory variable. A meta-regression model was fitted to the data with the mean age of autistic patients set as fixed effects. This model was estimated using mixed effect regression, with two different computational options: method of moments and unrestricted maximum likelihood.

3. Results

3.1. Study characteristics

The Literature search yielded a total of 261 and 391 valid records for head circumference and for TBV, respectively. Applying our exclusion criteria, 28 studies were selected for review and meta-analysis of head circumference (Fig. 1). These 28 papers, listed in Table 1, were published between 1994 and 2014; 15 studies were conducted in the United States, 12 were from Europe, and 1 from Israel. Autistic sample sizes varied widely, ranging from 15 to 1889 individuals. Similarly, the age of autistic patients varied broadly, ranging from pre-puberal to adults. Regarding diagnostic status, most studies included patients with "typical" autistic disorder ($n=13$), 12 studies recruited individuals with autism spectrum disorder (ASD), 2 studies also included patients with pervasive developmental disorder, not otherwise specified (PPD-NOS), and 1 study comprised patients with Asperger's syndrome (Table 1). For total brain volume (TBV), applying our exclusion criteria, 44 studies published between 1995 and 2014 were selected for review and meta-analysis (Fig. 2): 33 were conducted in the USA, 8 in Europe, and 3 in Asia. The main features and outcome of these studies are summarized in Table 2. Sample sizes varied widely, ranging from 6 to 121. Clinical subgroups ranged from high functioning patients (i.e., IQ $\geq$ 70) with clinical diagnoses of ASD, Asperger syndrome or PDD-NOS, to unspecified autism samples (presumably compliant high functioning patients) to low functioning ASD patients (i.e., IQ < 70). Also age of cases and control individuals varied widely, spanning from pre-puberty to adulthood.

3.2. Studies measuring head circumference

Meta-analysis was performed applying a fixed effect model, since no significant between-study heterogeneity was detected (*Q*-value=23.69; 27 df; *P*-value=0.647; I^2=0%). A highly significant effect size for head circumference in autism was detected [O. R.=6.74; 95%CI (5.24–8.67); *Z*-value=14.869; $P=5.20*10^{-50}$] (Fig. 3). A total of 822/5225 (15.7%) autistic individuals were macrocephalic, as compared to 3% of population controls by definition (*T*-test=9.066; 27 df; *P*-value=$1.11*10^{-9}$). Egger's regression test indicated no publication bias for this meta-analysis [Intercept= −1.69; 95%CI (−4.31 to 0.92); *P*-value=0.19] (Suppl. Fig. S1).

Table 2
Summary of 44 studies systematically reviewed and selected for meta-analysis of total brain volume (TBV) measured by MRI in autistic patients vs controls.

Reference	Ethnicity	Sample size *autistics* *controls*	Mean age ± SD or age range or median age (yrs) *autistics* *controls*	Diagnosis	% Males *autistics* *controls*	Mean total brain volume[a] ± SD		Estimated % of patients with brain overgrowth
						Autistics	Controls	
Piven et al. (1995)	CA	22 20	18.4 ± 4.5 21.6 ± 3.5	Autism	100 100	1537.0 ± 148.8	1437.0 ± 97.3	26.4
Aylward et al. (1999)	CA	14 14	20.5 ± 1.8 20.3 ± 1.7	Autism	100 100	1363.1 ± 128.3	1331.6 ± 120.2	5.3
Haznedar et al. (2000)	CA	17 17	27.7 ± 11.3 28.8 ± 9.4	ASD	88.2 88.2	1304.0 ± 178.0	1314.0 ± 122.0	7.8
Hardan et al. (2000)	CA	16 19	22.2 ± 10.1 22.2 ± 9.4	Autism	100 100	1377.5 ± 210.3	1313.0 ± 109.5	23.3
Courchesne et al. (2001)	CA							
(a)		30 12	3.0 3.0	Autism	100 100	1298.0 ± 88.3	1179.0 ± 83.1	29.8
(b)		15 14	6.0 6.0	Autism	100 100	1347.0 ± 101.2	1361.5 ± 126.5	0.4
(c)		10 14	9.0 9.0	Autism	100 100	1342.6 ± 123.7	1361.5 ± 105.4	3.1
Pierce and Courchesne (2001)	CA	14 14	3.8 ± 1.1 4.4 ± 1.2	Autism	85.7 71.4	1239.9 ± 89.2	1214.8 ± 151.7	37.8
Aylward et al. (2002)	CA							
(a)		23 28	10.0 10.0	Autism	82.6 89.3	1335.4 ± 136.4	1293.2 ± 91.5	15.2
(b)		20 27	15.0 15.0	Autism	95.0 96.3	1341.1 ± 116.6	1328.2 ± 121.6	2.4
(c)		24 28	32.0 32.0	Autism	83.3 89.3	1273.3 ± 165.2	1269.3 ± 125.6	6.8
Carper et al. (2002)	CA							
(a)		12 8	3.4 ± 0.4 4.4 ± 1.2	Autism	100 100	1318.6 ± 81.5	1158.0 ± 77.4	52.8
(b)		19 17	3.8 ± 1.1 4.4 ± 1.2	Autism	100 100	1313.4 ± 114.0	1342.6 ± 125.4	0.7
(c)		7 14	3.8 ± 1.1 4.4 ± 1.2	Autism	100 100	1306.5 ± 107.5	1351.8 ± 100.7	1.1
Sparks et al. (2002)	CA	45 26	4.0 ± 0.5 4.0 ± 0.5	ASD	84.4 69.2	1191.9 ± 94.7	1085.9 ± 109.2	11.9
Rojas et al. (2002)	CA	15 15	29.9 ± 9.1 30.4 ± 9.3	Autism	86.7 86.7	1237.6 ± 127.8	1335.9 ± 30.7	10.6
McAlonan et al. (2002)	UK	21 24	32.1 ± 10.0 33.0 ± 7.0	AS	90.5 91.7	1084.0 ± 127.0	1105.0 ± 118.0	2.2
Herbert et al. (2003)	CA	17 15	9.0 9.0	Autism	100 100	1454.0 ± 137.0	1367.4 ± 106.2	18.1
Tsatsanis et al. (2003)	CA	12 12	21.0 ± 10.0 18.1 ± 6.3	Autism HF	100 100	1440.0 ± 63.8	1426.8 ± 39.2	15.4
Hardan et al. (2003)	CA	40 41	19.3 ± 9.9 18.6 ± 8.6	Autism	95.0 95.1	1350.5 ± 134.8	1315.1 ± 123.7	5.8
Kates et al. (2004)	CA	9 16	8.4 ± 2.6 8.3 ± 2.4	Autism	100 100	1310.9 ± 146.5	1361.5 ± 103.3	4.0
Palmen et al. (2004)	Dutch	21 21	20.1 ± 3.1 20.3 ± 2.2	Autism HF	90.5 95.2	1393.9 ± 105.9	1333.3 ± 86.6	14.5
Akshoomoff et al. (2004)	CA							
(a)		30 15	6.2 ± 1.1 3.6 ± 1.1	Autism LF	100 100	1280.5 ± 100.2	1188.5 ± 92.8	17.6
(b)		12 15	6.1 ± 1.0 3.6 ± 1.1	Autism HF	100 100	1283.6 ± 125.3	1188.5 ± 92.8	23.6
(c)		10 15	6.3 ± 0.8 3.6 ± 1.1	PDD-NOS	100 100	1272.5 ± 79.6	1188.5 ± 92.8	10.2
Schumann et al. (2004)	CA							
(a)		18 22	13.1 ± ± 3.0 13.1 ± 3.1	Autism LF	100 100	1224.0 ± 158.0	1190.8 ± 77.0	22.4
(b)		21 22	12.7 ± 3.5 13.1 ± 3.1	Autism HF	100 100	1214.0 ± 97.0	1190.8 ± 77.0	9.0
(c)		24 22	13.0 ± 2.9 13.1 ± 3.1	AS	100 100	1204.0 ± 103.0	1190.8 ± 77.0	8.7
Palmen et al. (2005)	Dutch	21 21	11.1 ± 2.2 10.4 ± 1.8	Autism HF	100 100	1422.8 ± 92.6	1357.9 ± 70.0	20.9
Vidal et al. (2006)	CA	24 26	10.0 ± 3.3 11.0 ± 2.5	Autism	100 100	1581.9 ± 132.1	1569.0 ± 97.0	8.5
Mostofsky et al. (2007)	CA	20 36	10.3 ± 1.7 10.5 ± 1.3	Autism	85.0 72.2	1341.3 ± 96.9	1352.2 ± 107.0	1.0
Girgis et al. (2007)	CA	11 18	10.6 ± 1.3 10.4 ± 1.2	Autism	100 100	1357.0 ± 125.0	1336.0 ± 97.0	8.4
Bloss et al. (2007)	CA							
(a)		9	3.7 ± 0.9	Autism	0 (all females)	1189.9 ± 68.4	1115.1 ± 63.6	22.4

Table 2 (*continued*)

Reference	Ethnicity	Sample size *autistics* *controls*	Mean age ± SD or age range or median age (yrs) *autistics* *controls*	Diagnosis	% Males *autistics* *controls*	Mean total brain volume[a] ± SD		Estimated % of patients with brain overgrowth
						Autistics	Controls	
		14	3.8 ± 1.1		0 (all females)			
(b)		27	3.7 ± 0.8	Autism	100	1288.1 ± 95.4	1195.5 ± 113.1	8.1
		13	3.6 ± 1.2		100			
Tate et al. (2007)	CA	34	14.7 ± 5.9	Autism	100	929.4 ± 113.9	959.4 ± 142.6	0.3
		26	13.6 ± 4.7		100			
Hardan et al. (2008)	CA	12	16.4 ± 8.0	AS	100	1321.7 ± 84.1	1310.5 ± 121.4	0.3
		12	17.3 ± 7.2		100			
Cleavinger et al. (2008)	CA	28	13.9 ± 5.4	Autism	100	1349.3 ± 109.7	1324.8 ± 80.7	10.8
		16	13.9 ± 5.4		100			
Hardan et al. (2009)	CA	22	10.7 ± 1.4	Autism	100	1360.0 ± 114.4	1339.0 ± 101.1	5.7
		23	10.5 ± 1.4		100			
Hallahan et al. (2009)	CA							
(a)		114	32.0 ± 11.0	ASD	84.2	1422.4 ± 149.2	1429.7 ± 128.9	3.8
		60	32.0 ± 9.0		88.3			
(b)		80	33.0 ± 11.0	AS	88.7	1436.4 ± 139.9	1429.7 ± 128.9	3.7
		60	32.0 ± 9.0		88.3			
(c)		28	29.0 ± 7.0	Autism	75.0	1397.5 ± 169.5	1429.7 ± 128.9	4.4
		60	32.0 ± 9.0		88.3			
(d)		6	30.0 ± 9.0	PDD-NOS	66.7	1375.8 ± 176.0	1429.7 ± 128.9	3.8
		60	32.0 ± 9.0		88.3			
Freitag et al. (2009)	German	15	17.5 ± 3.5	Autism LF	86.7	1253.5 ± 85.4	1227.7 ± 150.6	0.1
		15	18.6 ± 1.1		86.7			
Scott et al. (2009)	CA	48	7.5–18.5	ASD	100	1195.0 ± 201.0	1190.0 ± 78.0	22.7
		14	7.5–18.5		100			
Tamura et al. (2010)	Japanese							
(a)		12	13.1 ± 4.3	Autism	83.3	1376.0 ± 113.0	1496.0 ± 181.0	0
		16	11.5 ± 4.2		62.5			
(b)		15	13.3 ± 2.8	AS	80.0	1477.0 ± 141.0	1496.0 ± 181.0	0.3
		16	11.5 ± 4.2		62.5			
(c)		11	12.0 ± 4.5	PDD-NOS	90.9	1478.0 ± 199.0	1496.0 ± 181.0	2.9
		16	11.5 ± 4.2		62.5			
Jou et al. (2010a, b)	CA	18	13.5 ± 3.4	Autism HF	100	1326.0 ± 120.0	1300.0 ± 135.0	2.1
		19	13.7 ± 3.0		100			
Schumann et al. (2010)	CA	41	2.5 ± 1.0	Autism	78.0	984.0 ± 76.0	920.0 ± 85.0	8.2
		44	2.5 ± 1.0		72.7			
Jou et al. (2010a, b)	CA							
(a)		6	12.3 ± 2.4	Autism	100	1433.0 ± 172.0	1366.0 ± 120.0	15.9
		8	13.0 ± 2.5		100			
(b)		9	13.4 ± 2.7	AS	100	1289.1 ± 101.0	1366.0 ± 120.0	0.1
		8	13.0 ± 2.5		100			
Bigler (2010)	CA	42	14.4 ± 6.1	Autism	100	1402.4 ± 137.8	1364.3 ± 144.6	3.4
		59	13.4 ± 5.4		100			
Griebling et al. (2010)	CA	33	8–45	Autism HF	93.9	1315.0 ± 124.5	1349.8 ± 136.5	0.7
		37	8–45		94.6			
Tepest et al. (2010)	German	29	33.2 ± 9.5	Autism HF	62.1	1129.0 ± 125.0	1136.0 ± 125.0	2.0
		29	33.0 ± 9.1		62.1			
Cheung et al. (2011)	Hong Kong	36	11.0	ASD	83.3	1450.0 ± 105.0	1440.0 ± 108.0	2.5
		55	11.0		85.4			
Hong et al. (2011)	Chinese Han	18	8.7 ± 2.2	Autism HF	100	1481.0 ± 72.0	1498.0 ± 76.0	1.0
		16	9.8 ± 1.9		100			
Calderoni et al. (2012)	Italian	38	4.5 ± 1.5	ASD	0 (all females)	1283.0 ± 100.0	1220.0 ± 140.0	1.5
		38	4.5 ± 1.5		0 (all females)			
Stamova et al. (2013)	CA	30	2.9 ± 0.4	ASD	100	1049.7 ± 87.4	994.8 ± 65.0	19.8
		20	3.0 ± 0.3		100			
Greimel et al., 2013	German	47	21.4 ± 10.1	Autism HF	100	1344.0 ± 123.9	1402.9 ± 128.6	0.5
		51	18.3 ± 7.5		100			
Nordahl et al. (2013)	CA	121	3.0 ± 0.5	ASD	100	1038.0 ± 79.8	994.7 ± 74.9	9.2
		50	3.0 ± 0.5		100			
Say et al. (2014)	Turkish	15	11.6 ± 3.8	AS	100	1188.0 ± 166.2	1208.72 ± 99.32	9.3
		15	11.6 ± 3.8		100			

Abbreviations; PDD-NOS=pervasive developmental disorder – not otherwise specified, ASD=autism spectrum disorder, AS= Asperger syndrome; HF=high functioning; LF=low functioning; N/A=not available, yrs=age range expressed in years; CA=Caucasian-American.

[a] Total brain volume expressed in cc or ml.

3.3. Studies measuring total brain volume using structural MRI

To evaluate the standardized effect size of TBV in autism, four meta-analyses were performed. We first performed a meta-analysis, using all 44 selected studies, yielding a significant effect size of TBV in autism [fixed effect model: O.R.=1.93; 95%CI (1.68–2.20); *Z*-value=9.557; *P*-value=$1.21*10^{-21}$] (Fig. 4). This meta-analysis did not reveal significant between-study heterogeneity (*Q*-value=73.77; 60 df; *P*-value=0.109; I^2=19%). Egger's regression test provided evidence of publication bias [Intercept 1.25; 95% CI (0.29–2.21)]; *P*-value=0.011] and the funnel plot revealed the presence of three outlier studies (Courchesne et al., 2001; Carper et al., 2002; Bloss and Courchesne, 2007) (Table 2 and Suppl. Fig. S2). As there was not evidence of significant degree of heterogeneity, we decided to include these studies in the analysis. Meta-regression, based on the fixed effects method, detected a significant interaction between age and brain volume measure [Intercept=1.14; 95%CI (0.89–1.39); *P*-value=$7.63*10^{-6}$] (Suppl. Fig. S3), confirming that macrocephaly is especially evident during early childhood and brain growth progressively slows down with age (Courchesne et al., 2001). Overall, brain overgrowth (i.e., brain size > +2 S.D. compared to controls in each study) was estimated to be present in 142/1558 of autistic patients (9.1%).

In order to take account the possible effect of intellectual disability and diagnostic status on log odds of brain volume, we performed additional meta-analyses on selected studies grouped for diagnostic status of patients recruited: high functioning patients (HF), including subjects with Asperger's Syndrome, low functioning patients (LF), including PDD-NOS, and patients with a diagnosis of ASD (Autism Spectrum Disorder). A higher effect size was found in studies involving LF autistics [fixed and random effect model: O.R.=2.11; 95%CI (1.74–2.11); *Z*-value=7.643; *P*-value=$2.11*10^{-14}$] (Fig. 5), compared to HF patients [fixed and random effect model: O.R.=1.65; 95%CI (1.28–2.12); *Z*-value=3.884; *P*-value=$1.03*10^{-4}$) (Fig. 6), and to ASD subjects [fixed and random effect model: O.R.=1.91; 95%CI (1.44–2.53); *Z*-value=4.493; *P*-value=$7.03*10^{-6}$) (Fig. 7). Finally, brain overgrowth was detected in 9.2% of LF autistics compared to 8.1% of HF and to 7.3% of ASD. These results partially explain the significant difference between percentages of macrocephaly (15.7%) and brain overgrowth (9.1%) revealed by our meta-analyses as well as brain imaging studies enrolled mainly high functioning autistic patients.

4. Discussion

We performed a systematic review of studies measuring head circumference and TBV in autistic and control samples. Data from selected studies were then meta-analyzed, yielding results expressed as (a) global mean odds ratios and (b) overall percentage of ASD patients displaying macrocephaly and excessive TBV. The procedure employed here to systematically detect published papers on head circumference and total brain volume in autism, measured by structural MRI, was broad-based and thorough. Our strict selection criteria requiring that data from both cases and controls of comparable age and gender be reported in the same paper, reduced to a large extent the number of studies eligible for meta-analysis, as is always the case when this approach is employed in Literature surveys.

Our results reliably confirm the consistent association of

Study name	O.R.	Low limit	Up limit	Z-Value	P-value
Bolton, 1994	18.99	4.73	76.19	4.15	3.28×10^{-5}
Bailey, 1995	23.41	5.55	98.73	4.29	1.75×10^{-5}
Woodhouse, 1996	13.66	3.55	52.59	3.80	1.44×10^{-4}
Davidovitch, 1996	7.19	2.12	24.43	3.16	0.002
Stevenson, 1997	10.21	2.96	35.19	3.68	2.32×10^{-4}
Lainhart, 1997	5.40	1.48	19.60	2.56	0.010
Skjeldal, 1998	4.41	0.83	23.33	1.75	0.081
Fombonne, 1999	6.48	1.87	22.41	2.95	0.003
Ghaziuddin, 1999	8.08	1.65	39.54	2.58	0.010
Fidler, 2000	4.49	1.02	19.77	1.99	0.047
Miles, 2000	9.88	2.93	33.29	3.69	2.20×10^{-6}
Gillberg, 2002a	3.20	0.67	15.23	1.46	0.144
Gillberg, 2002b	8.54	2.18	33.42	3.08	0.002
Deutsch & Joseph, 2003	5.26	1.36	20.33	2.41	0.016
Fuller Torrey, 2004	4.96	0.76	32.56	1.67	0.095
Dementieva, 2005	7.58	2.30	24.97	3.33	0.001
Lainhart, 2006	6.76	2.07	22.08	3.17	0.002
Sacco, 2006	14.59	4.48	47.54	4.45	8.62×10^{-6}
Van Daalen, 2007	4.12	0.99	17.20	1.94	0.052
Webb, 2007	8.80	2.04	37.96	2.92	0.004
Miles, 2008	6.62	1.96	22.34	3.05	0.002
Davidovitch, 2011	1.49	0.42	5.29	0.61	0.539
Chawarska, 2011	8.59	2.35	31.44	3.25	0.001
Ververi, 2012	8.70	2.64	28.68	3.55	3.80×10^{-4}
Froehlich, 2013	8.59	2.62	28.19	3.55	3.86×10^{-4}
Chaste, 2013	5.57	1.75	17.70	2.91	0.004
Grandgeorge, 2013	1.95	0.58	6.62	1.08	0.282
Cederlund, 2014	1.00	0.10	10.04	0.00	1.000
	6.74	5.24	8.67	14.87	5.20×10^{-50}

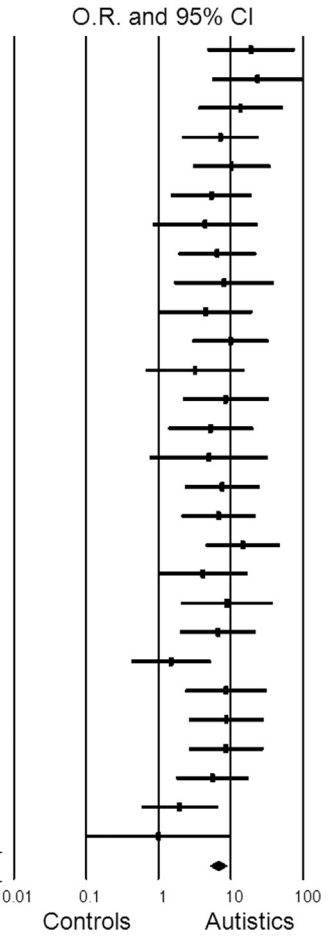

Fig. 3. Odds Ratio (O.R.) from random effects and fixed effect meta-analysis of selected studies reporting macrocephaly rates measured in autistic patients.

Study name	O.R.	Low limit	Up limit	Z-Value	p-Value
Piven, 1995	4.173	1.334	13.047	2.456	0.014
Aylward, 1999	1.583	0.411	6.102	0.668	0.504
Haznedar, 2000	1.126	0.333	3.813	0.191	0.849
Hardan, 2000	2.048	0.606	6.921	1.153	0.249
Courchesne, 2001a	11.986	3.185	45.111	3.673	2.40×10^{-4}
Courchesne, 2001b	1.259	0.336	4.725	0.342	0.733
Courchesne, 2001c	1.354	0.310	5.913	0.402	0.687
Pierce & Courchesne, 2001	1.442	0.375	5.545	0.532	0.595
Aylward, 2002a	1.959	0.714	5.371	1.306	0.192
Aylward, 2002b	1.216	0.426	3.474	0.366	0.715
Aylward, 2002c	1.051	0.391	2.826	0.099	0.921
Carper, 2002a	38.259	5.298	276.257	3.613	3.03×10^{-4}
Carper, 2002b	1.558	0.473	5.127	0.729	0.466
Carper, 2002c	2.222	0.421	11.726	0.941	0.347
Sparks, 2002	6.813	2.686	17.283	4.040	5.34×10^{-5}
Rojas, 2002	6.810	1.703	27.230	2.713	0.007
McAlonan, 2002	1.366	0.471	3.958	0.574	0.566
Herbert, 2003	3.564	0.974	13.043	1.920	0.055
Tsatsanis, 2003	1.572	0.366	6.747	0.608	0.543
Hardan, 2003	1.643	0.743	3.634	1.226	0.220
Kates, 2004	2.147	0.481	9.588	1.001	0.317
Palmen, 2004	3.115	1.013	9.583	1.982	0.047
Akshoomoff, 2004a	5.503	1.694	17.875	2.837	0.005
Akshoomoff, 2004b	4.917	1.164	20.769	2.166	0.030
Akshoomoff, 2004c	5.663	1.228	26.120	2.223	0.026
Schumann, 2004a	1.650	0.530	5.136	0.865	0.387
Schumann, 2004b	1.619	0.545	4.812	0.867	0.386
Schumann, 2004c	1.299	0.454	3.715	0.488	0.626
Palmen, 2005	4.196	1.343	13.109	2.467	0.014
Vidal, 2006	1.225	0.448	3.354	0.395	0.693
Mostofsky, 2007	1.210	0.449	3.264	0.377	0.706
Girgis, 2007	1.422	0.364	5.559	0.506	0.613
Bloss, 2007a	7.943	1.552	40.647	2.488	0.013
Bloss, 2007b	5.247	1.497	18.384	2.591	0.010
Tate, 2007	1.535	0.606	3.887	0.903	0.366
Hardan, 2008	1.215	0.284	5.191	0.263	0.793
Cleavinger, 2008	1.557	0.509	4.763	0.777	0.437
Hardan, 2009	1.424	0.492	4.121	0.652	0.515
Hallahan, 2009a	1.097	0.622	1.935	0.321	0.748
Hallahan, 2009b	1.094	0.596	2.008	0.290	0.772
Hallahan, 2009c	1.505	0.666	3.403	0.982	0.326
Hallahan, 2009d	2.084	0.452	9.596	0.942	0.346
Freitag, 2009	1.466	0.399	5.387	0.576	0.565
Scott, 2009	1.051	0.357	3.095	0.091	0.928
Tamura, 2010a	4.040	0.990	16.480	1.946	0.052
Tamura, 2010b	1.236	0.344	4.438	0.324	0.746
Tamura, 2010c	1.189	0.295	4.790	0.244	0.807
Jou, 2010	1.446	0.448	4.669	0.616	0.538
Schumann, 2010	4.208	1.888	9.377	3.514	4.41×10^{-5}
Jou, 2010a	2.326	0.333	16.270	0.851	0.395
Jou, 2010b	3.543	0.598	20.985	1.394	0.163
Bigler, 2010	1.628	0.792	3.347	1.325	0.185
Griebling, 2010	1.619	0.689	3.807	1.105	0.269
Tepest, 2010	1.107	0.435	2.816	0.213	0.831
Cheung, 2011	1.185	0.553	2.540	0.436	0.663
Hong, 2011	1.518	0.446	5.169	0.667	0.505
Calderoni, 2012	2.558	1.116	5.862	2.220	0.026
Stamova, 2013	3.511	1.222	10.086	2.332	0.020
Greimel, 2013	2.319	1.119	4.804	2.263	0.024
Nordahl, 2013	2.723	1.484	4.996	3.234	0.001
Nur Say, 2014	1.315	0.358	4.826	0.413	0.679
	1.926	1.684	2.203	9.557	1.21×10^{-21}

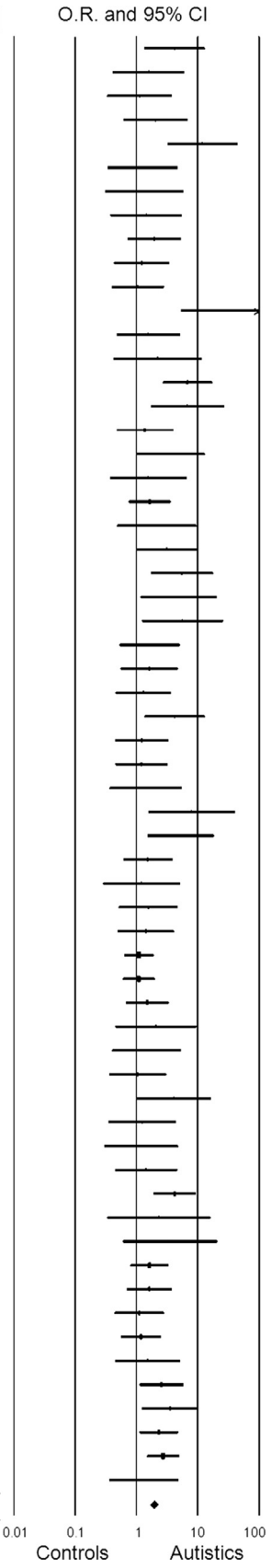

Fig. 4. Odds Ratio (O.R.) from random effects and fixed effect meta-analysis of selected studies reporting total brain volume measured by structural MRI.

macrocephaly (i.e. head circumference above the 97th percentile) with autism. The prevalence of macrocephaly in the autism spectrum disorder group was largely higher than the prevalence predicted in controls (15.7% vs 3%, respectively). The lack of significant between-study heterogeneity further strengthens the reliability of our overall effect size estimation, with a sizable cumulative O.R. of 6.74 (Fig. 3). This conclusively demonstrates that macrocephaly, although not autism-specific (Ghaziuddin et al., 1999), should indeed be considered in the definition of future biomarker panels applicable to ASD.

Head circumference can be considered as a strongly heritable trait and has been shown to be a reliable measure of brain volume in children less than 6 years of age. Despite to different growth trajectories through adulthood, cranial circumference remains a good predictor of brain volume after childhood. The presence of inconsistent results raised from previous studies could have been explained by specific confounding variables as genetic ancestry, age and height (Chaste et al., 2013). However, Raznahan et al., (2013) suggest as several cross-sectional reports, that used head circumference norms with known biases toward the over-identification of head circumference enlargement, could have overestimated the mean macrocephaly rate in ASD. No single norm can be valid for all humans in reference to body growth/size parameters, which are race- and ethnic-specific. For this reason, we have meta-analyzed percentiles as provided in each published study, assuming that raw data were transformed into percentiles using nation-specific norms. However, normative data from typically developing children may not be available in every nation and this poses the unavoidable limitation that some data sets may have been transformed into percentiles applying norms drawn from other ethnic groups. However, the consistency of macrocephaly rates in ASD across many studies performed in many different nations (Table 1) raises confidence in the reliability of the overall estimates provided by the present metanalysis.

Brain overgrowth and the resulting macrocephaly in autism can seemingly stem from several different mechanisms, which may contribute to a different extent in different patients. To this date, it is not entirely clear whether and to what extent neuronal or glial cell number, neuropil length and branching, synaptic contacts, extracellular matrix and fluids, and cell size each contribute to brain overgrowth in autism. Several genetic syndromes confer susceptibility to both autism and macrocephaly, such as

Study name	O.D.	Low limit	Up limit	Z-Value	p-Value
Piven, 1995	4.173	1.334	13.047	2.456	0.014
Aylward, 1999	1.583	0.411	6.102	0.668	0.504
Hardan, 2000	2.048	0.606	6.921	1.153	0.249
Courchesne, 2001a	11.986	3.185	45.111	3.673	2.40E-04
Courchesne, 2001b	1.259	0.336	4.725	0.342	0.733
Courchesne, 2001c	1.354	0.310	5.913	0.402	0.687
Pierce & Courchesne,2001	1.442	0.375	5.545	0.532	0.595
Aylward, 2002a	1.959	0.714	5.371	1.306	0.192
Aylward, 2002b	1.216	0.426	3.474	0.366	0.715
Aylward, 2002c	1.051	0.391	2.826	0.099	0.921
Carper, 2002a	38.259	5.298	276.257	3.613	3.03E-04
Carper, 2002b	1.558	0.473	5.127	0.729	0.466
Carper, 2002c	2.222	0.421	11.726	0.941	0.347
Rojas, 2002	6.810	1.703	27.230	2.713	0.007
Herbert, 2003	3.564	0.974	13.043	1.920	0.055
Hardan, 2003	1.643	0.743	3.634	1.226	0.220
Kates, 2004	2.147	0.481	9.588	1.001	0.317
Akshoomoff, 2004a	5.503	1.694	17.875	2.837	0.005
Akshoomoff, 2004c	5.663	1.228	26.120	2.223	0.026
Schumann, 2004a	1.650	0.530	5.136	0.865	0.387
Vidal, 2006	1.225	0.448	3.354	0.395	0.693
Mostofsky, 2007	1.210	0.449	3.264	0.377	0.706
Girgis, 2007	1.422	0.364	5.559	0.506	0.613
Bloss, 2007a	7.943	1.552	40.647	2.488	0.013
Bloss, 2007b	5.247	1.497	18.384	2.591	0.010
Tate, 2007	1.535	0.606	3.887	0.903	0.366
Cleavinger, 2008	1.557	0.509	4.763	0.777	0.437
Hardan, 2009	1.424	0.492	4.121	0.652	0.515
Hallahan, 2009c	1.505	0.666	3.403	0.982	0.326
Hallahan, 2009d	2.084	0.452	9.596	0.942	0.346
Freitag, 2009	1.466	0.399	5.387	0.576	0.565
Tamura, 2010a	4.040	0.990	16.480	1.946	0.052
Tamura, 2010c	1.189	0.295	4.790	0.244	0.807
Schumann, 2010	4.208	1.888	9.377	3.514	4.41E-04
Jou, 2010a	2.326	0.333	16.270	0.851	0.395
Bigler, 2010	1.628	0.792	3.347	1.325	0.185
	2.114	1.745	2.561	7.643	2.11E-14

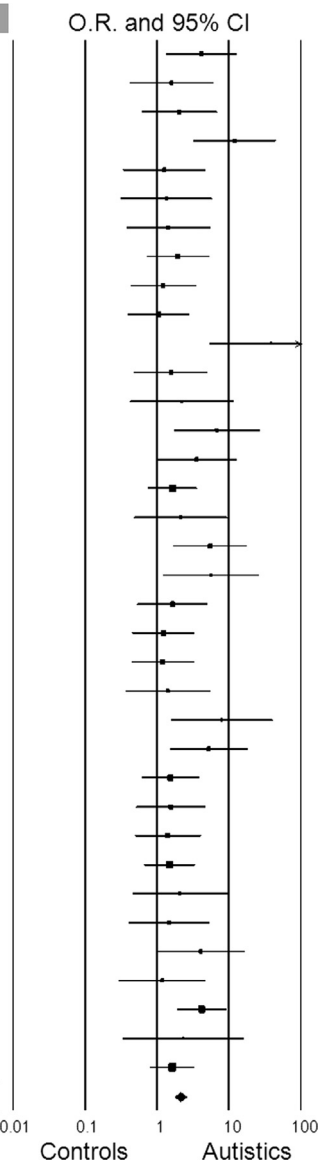

Fig. 5. Odds Ratio (O.R.) from random effects and fixed effect meta-analysis of selected studies reporting total brain volume involving only low functioning autistics.

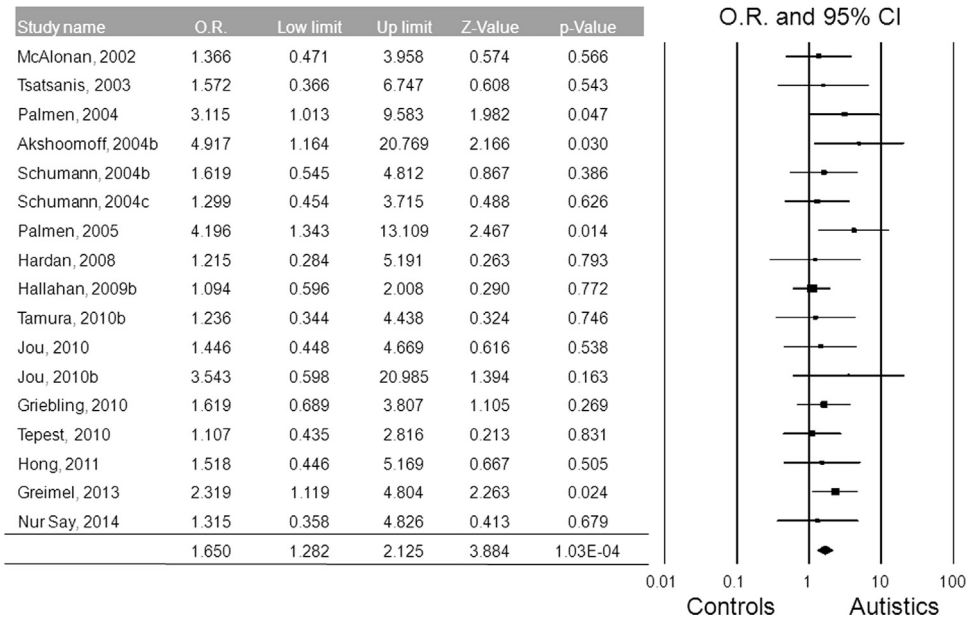

Fig. 6. Odds Ratio (O.R.) from random effects and fixed effect meta-analysis of selected studies reporting total brain volume involving only high functioning autistics.

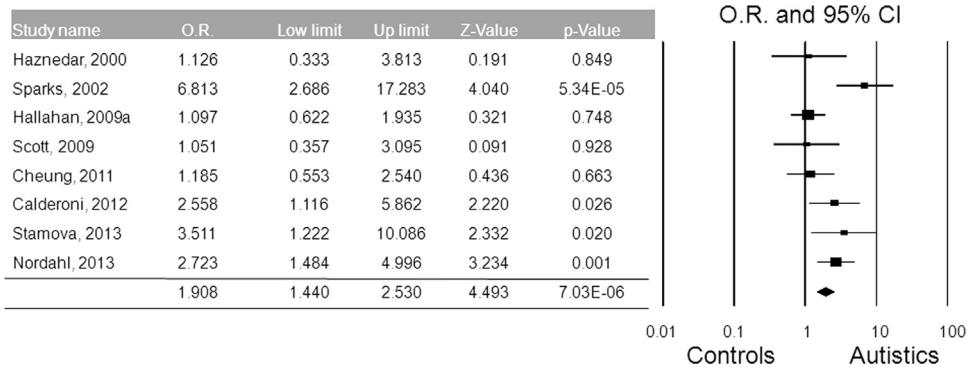

Fig. 7. Odds Ratio (O.R.) from random effects and fixed effect meta-analysis of selected studies reporting total brain volume involving only ASD individuals.

tuberous sclerosis, neurofibromatosis and phosphatase and tensin homolog (PTEN)-related syndromes. Specifically, the TSC1/TSC2, NF1 and PTEN genes act as negative effectors of the rapamycin-sensitive m-TOR raptor complex (mTORC1), a major regulator of protein translation and cell proliferation in mitotic cells (Buxbaum et al., 2007). Interestingly, in the majority of cases macrocephaly is part of a broader macrosomy, underscoring that overgrowth in many autistic children is not limited to the central nervous system (CNS), but is a systemic phenomenon (Sacco et al., 2007, 2010). Furthermore, at least in some children with autism, macrocephaly is familial (Carper et al., 2002), and even the early acceleration of head growth during the first year of life displays a familial tendency (Constantino et al., 2010). Surprisingly, the only articles reporting a macrocephaly rate much below average are the studies by Davidovitch et al. (2011) and Cederlund et al. (2014), conducted in Israeli and Swedish children with autism. From one hand, the small size of sample ($N=33$) in Cederlund et al. (2014) could have reduced the statistical power of this study; on the other hand, the results from Davidovitch et al. (2011), although based on a larger sample, were non replicated in a following study including Israeli autistic children characterized by syndromic features (Ben-Itzchak et al., 2013).

Also estimated prevalence of excessive TBV, a sign of brain overgrowth as measured by structural MRI, was found elevated with autism in our meta-analysis, although to a lesser extent compared to macrocephaly (9.1% vs 15.7%). The selection of high-functioning, compliant individuals for structural MRI studies may have significantly contributed to this difference. In fact, macrocephalic children tend more often to have lower functioning, as measured using the Vineland Adaptive Behavior Scales (Sacco et al., 2007, 2010). Hence the prevalence and extent of brain overgrowth may be underestimated by brain imaging studies, which require compliance to MRI scanning procedures. This experimental bias may also explain the wider age range characterizing MRI studies, in contrast to macrocephaly records (compare Tables 1 and 2). Hence, we have also analyzed the possible confounding effect of age on TBV, detecting a statistically significant relationship between age and effect size, in accordance with a previous meta-analysis (Redcay and Courchesne, 2005) also supporting brain enlargement as present primarily in young children with ASD. This important age effect also likely explains the small, yet detectable publication bias, identified by Eggar's statistics. Three studies of TBV, all coming from the same Center, display prominent differences in TBV between ASD and controls (Courchesne et al., 2001; Pierce and Courchesne, 2001; Carper et al., 2002). Interestingly, these studies were focused on very young ASD children and assessments at older ages from the same group yielded much less prominent differences (Courchesne et al., 2001). Finally, structural MRI studies, albeit proving that the macrocephaly in autistics is directly related to a larger brain volume (Woodhouse et al., 1996; Sparks et al., 2002), may not only provide biased prevalence estimates of brain overgrowth for the

reasons summarized above, but most importantly may hold much greater information content if region-specific analyses of cortical thickness and cortical surface are performed, rather than using TBV altogether (Hazlett et al., 2011; Philip et al., 2012; Ecker et al., 2013).

Several studies have found brain volume enlargement especially pronounced during early childhood in autistic individuals (Aylward et al., 2002; Sparks et al., 2002). This early overgrowth seemingly slows down in late childhood, although this has not been entirely confirmed by large longitudinal studies (Courchesne et al., 2003). The enlargement seems to occur in both gray and white matter, with some, but not all, studies suggesting that in early childhood there is a disproportionate contribution by white matter to this volumetric increase (Dementieva et al., 2005; Redcay and Courchesne, 2005). Although it was not possible to estimate the influence of age on head circumference, since young children and adults were combined into single patient and control samples in many published papers (Table 1), our results conclusively confirm the role of age as a covariate in brain overgrowth, meta-analyzing as many as 1558 cases and 1527 controls reported in all published brain imaging studies (Table 2). The consistent finding of cerebral enlargement is in keeping with post-mortem studies, reporting cortical thickening and increased neuronal density in megalencephalic autistic brains (Varga et al., 2009; Jou et al., 2010a, b). A larger less well organized cortex has been hypothesized to lead to less accurate connectivity and deficient integration of dispersed brain regions, a view supported by a variety of functional neuroimaging and electrophysiological studies (Constantino et al., 2010). In addition to larger TBV, many regional specificities have also been detected (Amaral et al., 2008). Abnormalities in cerebellar volume have been reported since 1988 (Courchesne et al., 1988); larger amygdala volume has been recorded in some, but not all studies (Aylward et al., 1999; Schumann et al., 2004), with meta-analyses again supporting age as a crucial factor, as enlargement is present only in young children with autism (Constantino et al., 2010; Jou et al., 2010a, b); decreased thickness of the corpus callosum, resulting in reduced interhemispheric connectivity (Vidal et al., 2006); increased volume of the caudate nucleus, correlated with the severity of stereotypic behaviors (Hollander et al., 2006); enlarged frontal (Hardan et al., 2009), temporal (Rojas et al., 2005; Jou et al., 2010a, b), and parietal lobes (Courchesne et al., 1993); abnormal thalamus (Hardan et al., 2008; Tamura et al., 2010) and brainstem (Rodier, 2002). In summary, on the basis of the existing literature, it is possible conclude that autism is associated with generalized enlargements of the cerebral hemispheres, the cerebellum and the caudate nucleus with, conversely, reductions in the size of the corpus callosum and possibly the midbrain and vermal lobules VI–VII and VIII–X. Additionally, some cerebral areas show abnormal developmental trajectories which could point towards specific time windows for possible interventions. New techniques, such as cortical thickness measurements and surface morphometry, have been directed to elucidate patterns of abnormal neurodevelopmental processes, as they evolve with age (Travers et al., 2012). Collectively, these results demonstrate that autism is associated with an atypically connected and often overgrown brain. These broad neurodevelopmental abnormalities are, however, dictated at the single patient level by very “personalized” genetic and epigenetic underpinnings, responsible for an extreme inter-individual heterogeneity in regional patterns of brain overgrowth and of developmental trajectories. Also differential alternative splicing in blood mRNA of ASD individuals, compared to typically developing children, could be related to variability in head size and brain volume. Stamova et al. (2013) demonstrate the presence of differential alternative splicing of 27 genes when they compare ASD with normal total brain volume and ASD with large total cerebral volume.

In conclusion, this systematic review and meta-analysis conclusively demonstrates that (a) 15.7% of ASD individuals displays abnormally enlarged head circumference, with an effect size of O. R.=6.74; (b) structural MRI studies seemingly underestimate the prevalence of macrocephaly at 9.1%, likely due to a patient selection bias; (c) age is a critical covariate, resulting in larger head circumference and brain size during early childhood. The identification of the mechanisms underlying macrocephaly in each single patient, through gene-network analysis and multi-level biomarker panels, will be extremely useful in paving the path to targeted pharmacological intervention, since inhibitors of mTOR, RAS and neuroinflammation, all potentially involved in this phenomenon, are currently under clinical trial (Ruggeri et al., 2014; Vorstman et al., 2014).

Contributors

RS collected the data and performed all statistical analyses; SG collected the data; AP conceived the study design and drafted the manuscript

Financial disclosure

The Authors have no conflict of interest, financial or otherwise, related directly or indirectly to the submitted work.

Acknowledgments

This work was supported by the Italian Ministry for University, Scientific Research and Technology (PRIN n.2006058195 and n.2008BACT54_002), the Italian Ministry of Health (RFPS-2007-5-640174, RF-2011-02350537, RF-2011-02350537 and CCM program 2012, progetto NIDA), the Fondazione Gaetano e Mafalda Luce (Milan, Italy), Autism Aid ONLUS (Naples, Italy), Autism Speaks (Princeton, NJ), the Autism Research Institute (San Diego, CA), and the European Union (Innovative Medicines Initiative Joint Undertaking, EU-AIMS, n. 115300).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2015.08.016.

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