Cerebellar volume in autism: Meta-analysis and analysis of the ABIDE cohort

Nicolas Traut[1,2], Anita Beggiato[1,3], Thomas Bourgeron[1], Richard Delorme[1,3], Laure Rondi-Reig[2], Anne-Lise Paradis[2], Roberto Toro[1]

[1] Unité de Génétique Humaine et Fonctions Cognitives, Département de Neuroscience, Institut Pasteur, Paris, France,
[2] Sorbonne Universités, UPMC, CNRS, Inserm, IBPS, Neuroscience Paris Seine, France,
[3] Département de Psychiatry de l'Enfant et de l'Adolescent, Hôpital Robert Debré, APHP, Paris, France

Keywords: Cerebellum, Autism, Meta-analysis, Computational Neuroanatomy, Neuroimaging

Abstract

Cerebellar volume abnormalities have been often suggested as a possible endophenotype for autism spectrum disorder (ASD). We aimed at objectifying this possible alteration by performing a systematic meta-analysis of the literature, and an analysis of the Autism Brain Imaging Data Exchange (ABIDE) cohort. Our meta-analysis sought to determine a combined effect size of ASD diagnosis on different measures of the cerebellar anatomy, as well as the effect of possible factors of variability across studies. We then analysed the cerebellar volume of 328 patients and 353 controls from the ABIDE project. The meta-analysis of the literature suggested a weak but significant association between ASD diagnosis and increased cerebellar volume ($p=0.049$, uncorrected), but the analysis of ABIDE did not show any relationship. The studies in the literature were generally underpowered, however, the number of statistically significant findings was larger than expected. Although we could not provide a conclusive explanation for this excess of significant findings, our analyses would suggest publication bias as a possible reason. Finally, age, sex and IQ were important sources of cerebellar volume variability, however, independent of autism diagnosis.

Introduction

Autism spectrum disorders (ASD) affect 1% of the population and are characterised by impairments in social interactions, and the variety of interests. Through the years, many reports have suggested that cerebellar abnormalities may be implicated in the onset of Autism spectrum disorders (ASD) (review in Wang, Kloth, and Badura 2014). The cerebellum is a heavily folded region of the rhombencephalon, with a number of neurons comparable to those of the neocortex. It is characterised by a highly regular arrangement of neurons and connections, supposed to support massive parallel computing capabilities in particular through long term synaptic plasticity (D'Angelo 2014; Dean et al. 2010). The cerebellum has been traditionally involved in the performance of precise motor behaviour, and patients with ASD also present varying degrees of dyspraxia (Dziuk et al. 2007; Åhsgren et al. 2005). There is also growing evidence for an involvement of the cerebellum in cognitive and affective functions, which could be impaired in autism (Leiner, Leiner, and Dow 1993; Manni and Petrosini 2004; Rondi-Reig et al. 2014; Schmahmann and Sherman 1998).

The first case report of abnormal cerebellar anatomy in autism was published in 1980 (Williams et al. 1980), and described a reduced count of Purkinje cells in the cerebellar vermis of a patient with ASD. In 1987, Courchesne et al. were the first to find a cerebellar abnormality in a patient with ASD using in vivo magnetic resonance imaging (Eric Courchesne et al. 1987). Since then, various studies comparing the volumes and areas of cerebellum sub-regions between patients with ASD and controls with typical development have described significant differences. These studies pointed at the cerebellar volume as an interesting endophenotype for ASD: the volume of the cerebellum and its different subregions being relatively easy to measure from standard T1-weighted magnetic resonance imaging data. However, whereas many articles report statistically significant differences, many others fail to detect such differences. These discrepancies could be due to many factors, for example, to the high heterogeneity in the etiology of ASD, to differences in the inclusion criteria across studies, or to differences in the eventual comorbidities affecting patients in different groups. The discrepancies could also reveal methodological bias, such as differences in MRI sequences, segmentation protocols, or statistical analyses. Finally, they could also result from chance when small sample sizes lead to noisy estimations of mean volumes.

Here, our aim was thus to objectify the alterations of cerebellar volumes in ASD. In the first part of this article we describe our systematic meta-analysis of the literature to examine the differences across previous reports and to determine a combined effect size. In the second part, we describe our analysis of cerebellar volume in the ABIDE cohort (Di Martino et al. 2014), and study the consistency of these results with those from the meta-analysis. Finally, we describe our analyses of the impact of distinct sources of variability such as sex, age at inclusion or IQ on the volume differences between patients with ASD and controls.

Materials and methods

1. Meta-analysis of the literature

Collection and selection of articles. We queried PubMed on October 12, 2016 for all the articles that met the search criteria "cerebell* AND autis*". When one of these results was a systematic review or a meta-analysis on the differences of volumes and surfaces between individuals with ASD and controls on several brain regions including the cerebellum, we added all their cited references.
The selection of articles was made in two steps. First, we screened all the titles and abstracts to eliminate the articles that did not meet the following inclusion criteria: we kept articles written in English with the title or abstract indicating that the size of a brain region was measured in individuals with ASD and we removed items like books, invalid references, reviews, meta-analyses or other studies where the cerebellum was excluded from analysis, as well as studies focused in functional activity, molecules, or with measurements made with technologies other than magnetic resonance imaging.

Second, we recovered the selected articles in their full versions, and included those with available volumetric or area MRI measurements (mean and standard deviation) on at least one region of the cerebellum for both individuals with ASD and healthy controls. Each selected region had to be measured in at least five articles to be included. We tried to avoid the overlap of subjects between studies, favouring articles with more complete information and larger cohorts. We kept the articles regardless of whether individuals with autism exhibited neurological disorders such as epilepsy or followed a pharmacological treatment.

Data abstraction. For each selected article we collected means and standard deviations of cerebellar region volumes or areas in order to calculate Cohen's d effect size. When there were more than one ASD or healthy control group, we reconstructed the mean ($\bar{x}$) and standard deviations (s) of the merged group from the means ($\bar{x}_i$), standard deviations (s_i) and numbers of subjects (n_i) of the subgroups:

$$\bar{x} = \frac{\sum n_i \, \bar{x}_i}{n},$$

$$s = \sqrt{\frac{\sum (n_i - 1) \; s_i{}^2 + n_i \, (\bar{x} - \bar{x}_i)^2}{n-1}}.$$

We also collected mean age and Intelligence Quotient (IQ) for analysing their impact on volume or area differences using meta-regression. When such means were not reported, we approximated them from mid-ranges or textual descriptions.

When the volume data were provided for two separate regions, we estimated the mean and the standard deviation of the combined region using the following formulae:

$$\overline{\mathrm{x} + \mathrm{y}} = \bar{\mathrm{x}} + \bar{\mathrm{y}},$$
$$s_{x+y} = \sqrt{s_x{}^2 + s_y{}^2 + 2 \cdot \rho \cdot s_x \cdot s_y},$$

where ρ is the assumed correlation coefficient between the two regions. If the two regions in question were two areas of different types, we assumed $\rho = 0.5$.

Meta-analysis. We conducted two meta-analyses. The first one compared mean cerebellar volume between ASD patients and controls. Effect sizes were computed a standardised mean differences (Cohen's d) using Hedges' g as estimator (Hedges 1981). The second meta-analysis compared the variability of cerebellar volumes between patients and controls by computing the log-variance ratio (Traut 2017). We combined effect sizes using a random effects model. In such a model, if the variability between the estimated effects is larger than expected from sample variance alone, studies are considered heterogeneous, i.e., there is also variability between the true effects (Borenstein et al. 2009, pt. 3). The between-study variance τ^2 was estimated using the restricted maximum likelihood (REML) method from which we computed the proportion of variance imputable to heterogeneity (I^2). To assess the impact of age and IQ on the effect size and thus identify possible sources of heterogeneity, we also conducted a meta-regression with average age and average IQ of patients with ASD as fixed effects (Borenstein et al. 2009, chap. 20). After the meta-regression, we could estimate an effect size for each study, removing the linear contribution of age and IQ.

We evaluated publication bias and p-hacking in several ways. First, we calculated the rate of studies showing a statistically significant difference between ASD and controls. We compared this rate to the average statistical power obtained by assuming that the actual effect is equal to the effect estimated after the meta-regression for each study. Second, we evaluated the symmetry of the funnel plot (Light and Pillemer 1984) using Egger's test. Egger's test relies on the assumption that studies with larger samples are less subject to publication bias than studies with smaller samples and that significant results would tend to report larger effect sizes (Egger et al. 1997). Finally, we plotted the p-curve which shows the distribution of significant p-values. We evaluated p-curves for the inferred power – the most likely statistical power of the studies to get the observed p-curve (Simonsohn, Nelson, and Simmons 2014).

The computations were performed using R (https://www.r-project.org) and the packages meta and metafor along with the online p-curve app 4.0 (http://www.p-curve.com/app4/). We report statistical significance for an alpha level of 0.05. P-values are not corrected for multiple comparisons.

2. Analysis of ABIDE

We analysed the MRI data made available by the ABIDE (Autism Brain Imaging Data Exchange) project, which includes 539 brain MRI of individuals with ASD and 573 brain MRI of controls. Cerebellum volumes were automatically segmented using FreeSurfer 5.1. We developed

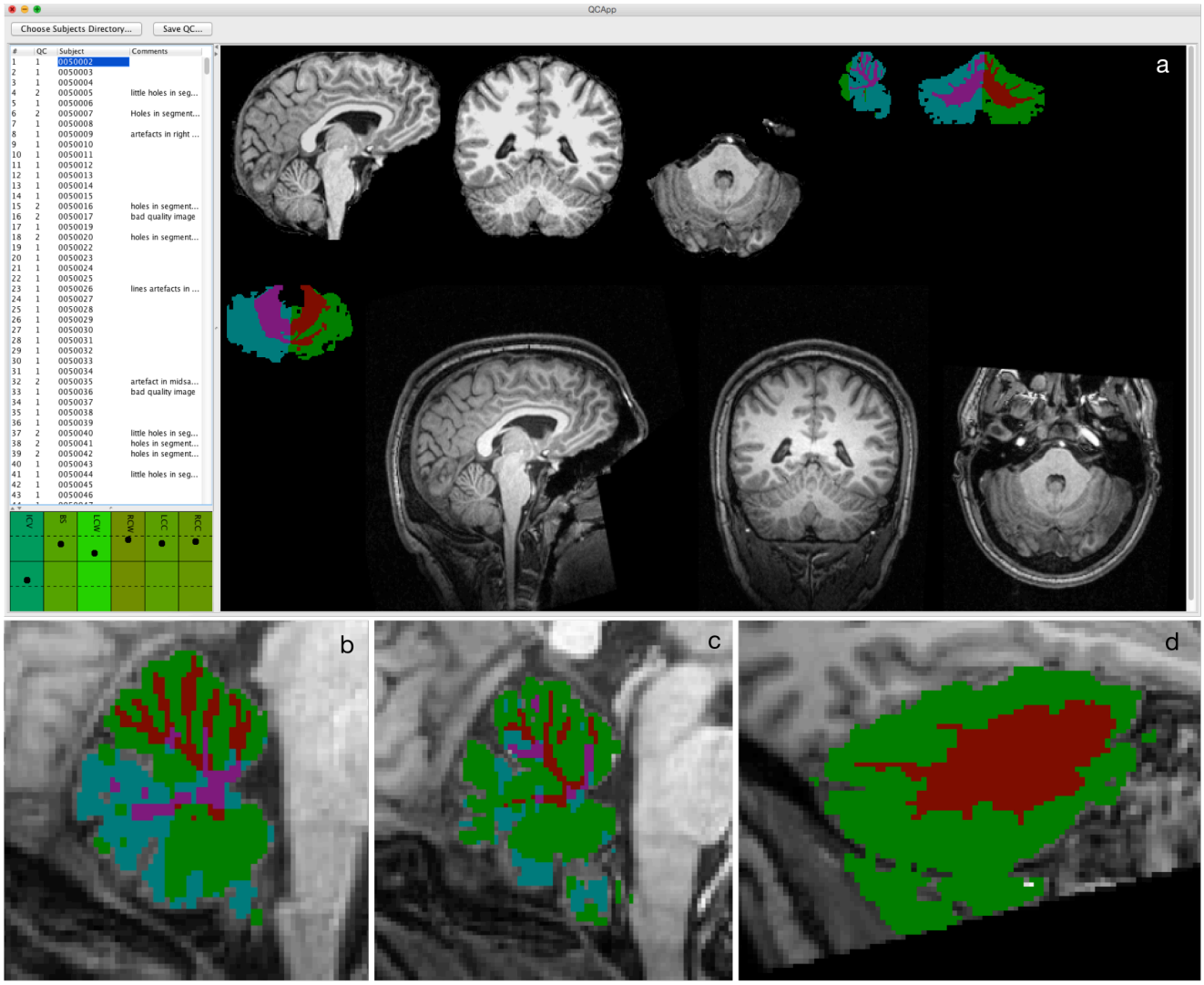

Figure 1. Quality control of the cerebellum automatic segmentation. **a.** Quality control tool: for each subject we evaluated the quality of the segmentation and the raw data in three different planes. The graph at the bottom left shows the value of the total intracranial volume, brain volume, and the left and right, white and grey cerebellar volumes and their deviation from the overall mean. **b.** A segmentation evaluated as correct; **c.** A segmentation with an excess of unlabelled regions. **d.** A segmentation with major labelling errors.

a tool for FreeSurfer segmentations to visually check the quality of the segmentation for each subject (Figure 1, https://github.com/r03ert0/QCApp-Cb). We kept only the subjects for whom the segmentation quality was clearly good.

Some MRIs with minor segmentation errors could have been manually corrected, however, because of their number we chose to exclude them from the present analyses. Our quality control focused on the cerebellum, but we combined its results with our previous quality control of the whole brain (Lefebvre et al. 2015) and conserved only the subjects that passed both.

Following our previous results showing the nonlinear variation of brain anatomy relative to brain volume (Toro et al. 2008; Toro et al. 2009; Lefebvre et al. 2015), we studied the allometric scaling of cerebellar volume. The division of regional volume measurements by total brain volume ("normalisation") is often used to control for differences in brain volume between groups. This strategy would only be appropriate if the volume of the cerebellum scaled proportionally to total brain volume. We assessed the scaling factor of the cerebellum with total brain volume by regressing the logarithms of total brain volume (BV) and the volume of the cerebellum (Cb):

$$log[Cb] = a \cdot log[BV] + b,$$

where a is the scaling factor.

We evaluated the effect of diagnosis and other factors on whole cerebellum volume, cerebellar white matter volume and cerebellar grey matter volume with two linear models. The first model included group, age, IQ, scanning site, sex and brain volume as fixed effects; the second model included

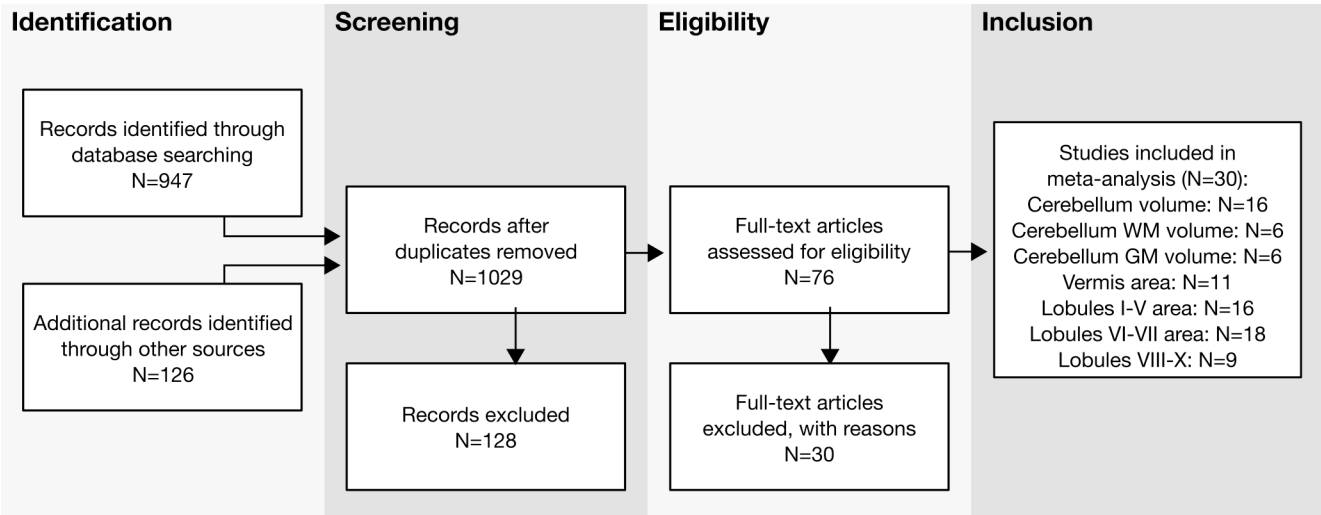

Figure 2. PRISMA workflow for identification and selection of studies (Moher et al. 2009).

in addition the interactions of group with age, IQ, scanning site, sex and brain volume.

Because these statistical models are not the same as those used in the meta-analysis of the literature, we also analysed the ABIDE data using the same meta-analytical approach as for the literature. In the meta-analysis of ABIDE the volume estimations of each site were combined using a random effects model, where each estimation is weighted by the inverse of the estimation's variance. At each site we eliminated the minimal number of subjects that would ensure that the age and sex matching were respected, as in the meta-analysis of the literature. We did this iteratively, eliminating one subject after another, until the p-values on the differences of age mean, age variance and sex ratio were each above 0.2. We used JMP Pro 12.1.0 for fitting linear models and R version 3.3.1 for the meta-analysis approach.

Results

1. Meta-analysis of the literature

Selection of articles. The PubMed queries ("cerebell* AND autis*") returned 947 items that were combined with the 124 references cited by a systematic review (Brambilla et al. 2003) and a meta-analysis on cerebellum in ASD (Stanfield et al. 2008). We also added two studies (Langen et al. 2009; Evans et al. 2014) that we found by other means. After removing duplicates, we obtained a total of 1029 articles. We screened the titles and abstracts of these items with our relevance criteria and recovered the full text of 76 articles. Our final analyses were based on 30 articles covering seven different regions of interest (see Figure 2 for the PRISMA workflow). The three most reported measures were whole cerebellum volume (1050 subjects in total), vermal lobules VI-VII areas (965 subjects in total) and vermal lobules I-V areas (861 subjects in total) (see Table 1 for a description of the selected articles).

Mean effect size. Significant mean effects were found for 3 out of the 7 regions studied (whole cerebellum: p=0.049, white matter: p=0.011 and Lobules VI-VII: p=0.022, See Table 2). Compared with controls, individuals with ASD displayed larger cerebellar white matter volume (Cohen's d=0.31, 95% CI: [0.07, 0.55]) and smaller areas for vermal VI-VII lobules (Cohen's d=-0.24, 95% CI: [-0.44, -0.03]). The effect of diagnosis on whole cerebellar volume was barely statistically significant (Cohen's d=0.23, 95% CI: [0.00, 0.45], see forest plot in Figure 4).

Heterogeneity and meta-regression. A statistically significant heterogeneity was found for 4 out of the 7 regions under study: cerebellum volume (p = 0.0001), vermal lobules I to V area (p = 0.0049), vermal lobules VI to VII area (p = 0.0081) and vermal lobules VIII to X areas (p = 0.019). Despite this high heterogeneity, our meta-regression did not show a significant impact of the age nor the IQ on total cerebellar volume. Age of individuals with ASD correlated reduced volume of cerebellar white matter (p = 0.025) and increased volume of cerebellar grey matter (p = 0.24) compared with controls. However, the number of studies included in the meta-regression may be insufficient to obtain reliable results. The IQ of individuals with ASD correlated with increased volume of the cerebellar white matter (p=0.0176) and increased area of vermal lobules I-V (p=0.019). Age and IQ did not seem to be the only factors producing heterogeneity: after the meta-regression, residual heterogeneity was still statistically significant for cerebellum volume (p=0.0020), vermal lobules VI-VII area (p=0.039) and vermal lobules VIII-X area (p=0.013). Table 2 shows the results of the random effects models and meta-regressions for the cerebellum regions and Figure 5 shows the observed effect sizes versus the expected effect from the meta-regression on whole cerebellum volume.

In Figure 5, each study is represented by a circle positioned according to the mean age and the mean IQ of the ASD group. The surface of each circle is inversely proportional to estimated error variance (Thompson and Higgins 2002), and

Table 1. Studies included in the meta-analysis

Study	N_{ASD} (F)	N_{Ctrl} (F)	Age_{ASD}	Age_{Ctrl}	IQ_{ASD}	IQ_{Ctrl}	Regions of interest
Hodge et al. 2010	22 (0)	11 (0)	9.4 ± 2.0	10.4 ± 2.7	87 ± 22	114 ± 11	Cbl, WM, GM, Vermis, I-V, VI-VII, VIII-X
Scott et al. 2009	48 (0)	14 (0)	12.4 ± 3.1	12.5 ± 3.1	79 ± 23	113 ± 12	Cbl, Vermis, I-V, VI-VII, VIII-X
Hallahan et al. 2009	114 (18)	60 (7)	31.9 ± 10.1	32.0 ± 9.0	97 ± 18	114 ± 12	Cbl
Webb et al. 2009	45 (7)	26 (8)	3.9 ± 0.3	3.9 ± 0.5	59 ± 21	115 ± 15[b]	Cbl, Vermis, I-V, VI-VII, VIII-X
Langen et al. 2009	99 (8)	89 (7)	12.9 ± 4.5	12.4 ± 4.8	108 ± 14	110 ± 13	Cbl
Lahuis et al. 2008	21 (0)	21 (0)	11.1 ± 2.2	10.4 ± 1.8	107 ± 14	103 ± 15	Cbl
Cleavinger et al. 2008	28 (0)	16 (0)	13.9 ± 5.3	13.9 ± 5.4	99 ± 18	102 ± 14	Cbl, WM, GM, Vermis, I-V, VI-VII, VIII-X
atani et al. 2008	15 (0)	16 (0)	31.0 ± 9.0	35.0 ± 11.0	109 ± 17	120 ± 21	Cbl
Bloss and Courchesne 2007	9 (9)	14 (14)	3.7 ± 0.9	3.8 ± 1.1	83 ± 18	119 ± 13	Cbl, WM, GM
Hazlett et al. 2005	51 (5)	14 (4)	2.7 ± 0.3	2.4 ± 0.4	54 ± 9	108 ± 19	Cbl, WM, GM
Palmen et al. 2004	21 (2)	21 (1)	20.1 ± 3.1	20.3 ± 2.2	115 ± 19	113 ± 10	Cbl
Kates et al. 2004	9 (1)	16 (2)	7.6 ± 2.4	8.3 ± 2.4	70 ± 19	124 ± 10	Cbl, WM, GM
Akshoomoff et al. 2004	52 (0)	15 (0)	3.8 ± 0.8	3.6 ± 1.1	82 ± 24	108 ± 18a	I-V, VI-VII
Herbert et al. 2003	17 (0)	15 (0)	9.0a ± 1.4[a]	9.0[a] ± 1.4[a]	100 ± 15[c]	115 ± 15[b]	Cbl
Kaufmann et al. 2003	10 (0)	22 (0)	6.9 ± 2.4	8.3 ± 1.9	66 ± 14	121 ± 9	Vermis, I-V, VI-VII, VIII-X
Pierce and Courchesne 2001	14 (2)	14 (4)	3.8 ± 1.1	4.4 ± 1.2	84 ± 24	110 ± 12	I-V, VI-VII
Courchesne et al. 2001	60 (0)	52 (0)	6.2 ± 3.5	8.1 ± 3.5	79 ± 26	115[a] ± 15[a]	Cbl, WM, GM
Hardan et al. 2001	22 (0)*	22 (0)*	22.4 ± 10.1	22.4 ± 10.0	100 ± 15	100 ± 14	Vermis, I-V, VI-VII, VIII-X, Cbl
Elia et al. 2000	22 (0)	11 (0)	10.9 ± 4.0	10.9 ± 2.9	55 ± 10[e]	115 ± 15b	Vermis, VI-VII
Carper and Courchesne 2000	42 (0)	29 (0)	5.4 ± 1.7	6.0 ± 1.8	80 ± 22	114 ± 12	VI-VII
Levitt et al. 1999	8 (-)	21 (-)	12.5 ± 2.2	12.0 ± 2.8	83 ± 12	115 ± 11	VIII-X
Piven et al. 1997	35 (9)	36 (16)	18.0 ± 4.5	20.2 ± 3.8	91 ± 20	102 ± 13	Cbl
Ciesielski et al. 1997	9 (4)	10 (3)	16.8 ± 5.2[a]	16.6 ± 5.4[a]	93[a] ± 13[a]	119[a] ± 10[a]	I-V, VI-VII
Hashimoto et al. 1995	96 (24)	112 (47)	6.4 ± 4.9	7.2 ± 5.2	60 ± 25	99 ± 18	Vermis, I-V, VI-VII, VIII-X
Courchesne et al. 1994	50 (9)	53 (10)	16.5 ± 11.6[a]	18.8 ± 10.4[a]	81[a] ± 31[a]	115 ± 15[b]	I-V, VI-VII
Piven et al. 1992	15 (0)	15 (0)	27.7 ± 10.7	28.8 ± 5.6	92 ± 23	130 ± 0	I-V, VI-VII
Holttum et al. 1992	18 (0)	18 (0)	20.2 ± 8.1	20.2 ± 8.3	94 ± 12	95 ± 12	Vermis, I-V, VI-VII, VIII-X
Garber and Ritvo 1992	12 (3)	12 (4)	27.2 ± 5.3	26.4 ± 3.6	95 ± 15[d]	115 ± 15[b]	Vermis, I-V, VI-VII
Kleiman, Neff, and Rosman 1992	13 (3)	17 (8)	7.7 ± 5.7	7.0 ± 4.3[a]	52 ± 17	115 ± 15[b]	I-V, VI-VII
Ritvo et al. 1988	15 (4)	15 (4)	11.6 ± 4.1	11.6 ± 4.1	75 ± 15	115 ± 15[b]	Vermis, I-V, VI-VII

Volumes: Cbl, cerebellum; WM, cerebellum white matter; GM, cerebellum grey matter
Mid-sagittal areas: whole vermis and its lobules numbered (I-V, anterior; VI-VII, superior-posterior; VIII-X, inferior-posterior).
ASD, autism spectrum disorders; Ctrl, normal controls; F, female. Age and IQ data: mean ± SD
a Mean and/or standard deviation extrapolated from minimum and maximum
b IQ for normal control group supposed to be 115 ± 15
c IQ for high functioning autism group supposed to be 100 ± 15
d IQ for medium to high functioning autism group supposed to be 95 ± 15
e IQ for low functioning autism group supposed to be 55 ± 10
* Cerebellar volume was estimated for only 16 ASD and 19 control subjects in Hardan et al. 2001

the grey level corresponds to the observed effect size (SMD, Standardised Mean Difference): light grey means a larger cerebellum volume on average for the ASD group compared to the control group, dark grey means a smaller volume. The background colour gradient represents the effect size (of ASD versus control difference) predicted by the meta-regression. The colours of the circles were not well ordered, and they were often far from the background colour, reflecting that age and IQ of ASD alone were not good predictors of mean cerebellar volume difference between ASD and controls.

Statistical power. Despite a small mean effect size estimated at Cohen's d=0.23 for the whole cerebellum volume, 44% of the studies reported a significant result. If the actual effect size were fixed at this value, the mean statistical power for all the studies would be only 14%, that is, only 14% chances of detecting such a small effect size. The heterogeneity in age and IQ across studies appeared to limit the statistical power: mean achieved statistical power increased to 20% when taking into account the variations induced by age and IQ estimated by the meta-regression (the value is, however, still much lower than the observed 44% rate of detection which agrees with the fact that much of the heterogeneity was not explained).

Publication bias and p-hacking. Egger's test reported a statistically significant funnel plot asymmetry only for the whole vermis area (p=0.002). None of the remaining regions presented a significant funnel plot asymmetry (Figure 6).

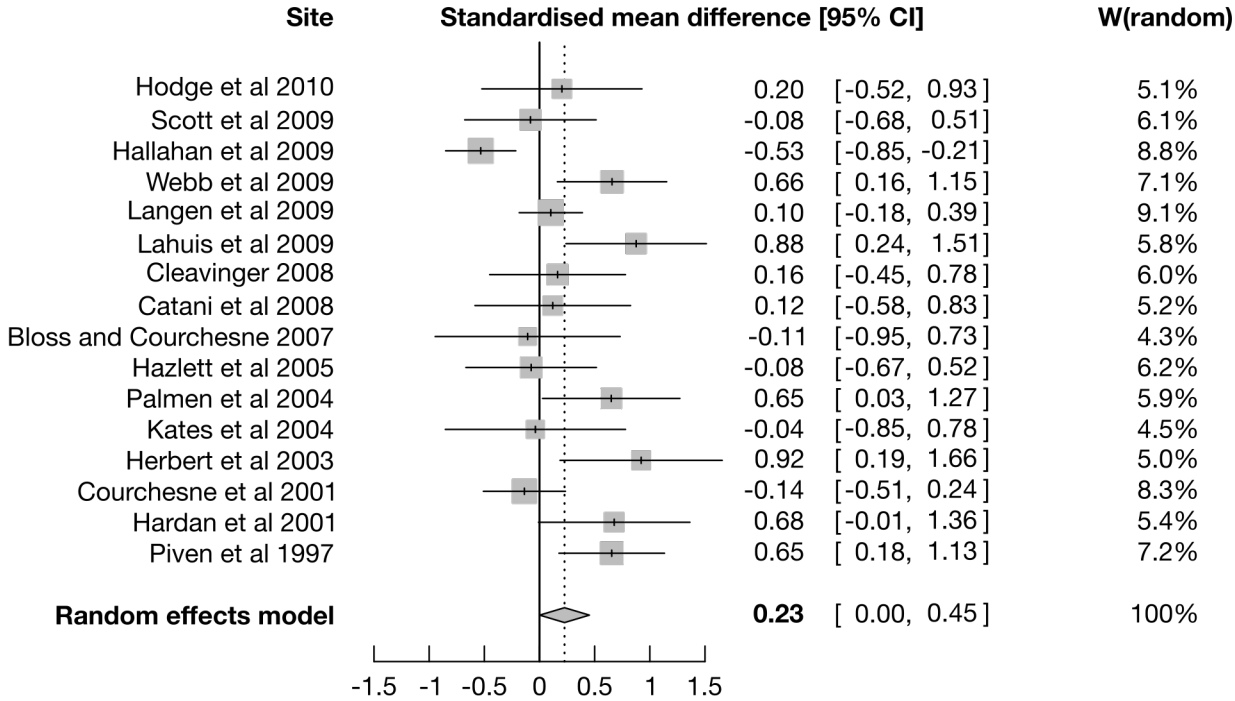

Figure 4. Forest plot for the cerebellum volume. For each study, the grey square is centred on the estimated standardised mean difference (SMD), the black segment illustrates the confidence interval (95%-CI), and the surface of the square is proportional to the number of subjects in the study. SMD is positive when the cerebellum volume is greater in ASD. W(random) represents the weight given to each study for the combination of effect sizes.

Our analyses of the p-curves were not conclusive on the presence of p-hacking. In 5 out of the 7 regions there were only 2 or 3 p-values <0.05, which resulted in very imprecise estimations with wide confidence intervals. Total cerebellum and lobules VI-VII had each 7 p-values <0.05, which still produced unreliable estimations. P-curve analyses suggested low statistical power for both regions (Cerebellum: 22%, 95% CI [5%, 67%] and Lobules VI-VII: 38%, 95% CI [6%, 78%]). The statistical powers inferred from the p-curves were not incompatible with the respective rates of significant studies, but a gain, confidence intervals were very wide.

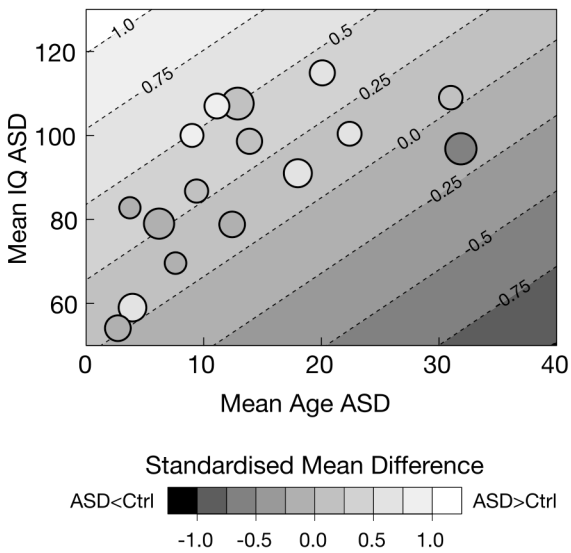

Figure 5. Meta-regression on standardised mean difference for the whole cerebellum volume.

Table 3 summarises the results for the different publication bias and p-hacking analyses. Figure 7 shows the observed p-curve for the total cerebellar volume.

Mean achieved powers are based on the effect sizes estimated by the meta-regression (taking into account the impacts of average age and IQ of ASD groups)

Meta-analysis of variability (log-variance ratio). A barely statistically significant (uncorrected) effect was found for vermal lobules VIII-X areas, suggesting larger volume variations for the ASD groups (p=0.049). No significant effect was found for any other regions. Heterogeneity was statistically significant only for the whole cerebellar volume (p = 0.0052, uncorrected). As for the meta-analysis of mean differences, taking into account age and IQ in the meta-regression did not significantly reduce the heterogeneity (see Table 4).

2. Analysis of the ABIDE data

From the original 1112 subjects, 328 patients (61% of the evaluated subjects) and 353 controls (62% of the evaluated subjects) were retained for further analysis after quality control (see Table 6 for a description of selected subjects by ABIDE site). Among the excluded subjects, 411 subjects did not pass the quality control step and 20 subjects were excluded because of unavailable FIQ (Full-scale Intelligence Quotient).

Allometry. The scaling between cerebellar volume and brain volume was not isometric (i.e., the volume of the cerebellum

Table 2. Standardised mean difference: combination of effect sizes

		Random Effects model			Meta-regression		
Region	**Number of studies**	**Effect size (Cohen's d)**	**p-value**	**Heterogeneity (I^2)**	**Age impact ($year^{-1}$)**	**IQ impact (IQ^{-1})**	**Residual heterogeneity (I^2)**
Cerebellum	16	0.23 (0.00, 0.45)	0.049	66% (42%, 80%)	-0.026 (-0.057, 0.005)	0.014 (-0.002, 0.030)	57% p=0.002
Cerebellum WM	6	0.31 (0.07, 0.55)	0.011	19% (0%, 64%)	-0.153 (-0.287, -0.019)	0.042 (0.007, 0.077)	0% p=0.943
Cerebellum GM	6	-0.22 (-0.47, 0.03)	0.085	16% (0%, 79%)	0.152 (0.020, 0.284)	-0.033 (-0.067, 0.002)	0% p=0.837
Whole vermis	11	-0.09 (-0.30, 0.13)	0.416	21% (0%, 60%)	0.011 (-0.039, 0.062)	0.009 (-0.010, 0.029)	0% p=0.657
Lobules I-V	16	0.00 (-0.22, 0.23)	0.971	54% (20%, 74%)	-0.019 (-0.054, 0.016)	0.020 (0.003, 0.038)	29% p=0.061
Lobules VI-VII	18	-0.24 (-0.44, -0.03)	0.022	50% (14%, 71%)	0.009 (-0.024, 0.041)	0.010 (-0.006, 0.026)	36% p=0.039
Lobules VIII-X	9	-0.20 (-0.50, 0.10)	0.192	56% (8%, 79%)	-0.043 (-0.167, 0.080)	0.008 (-0.038, 0.055)	65% p=0.013

Values in parentheses represent 95% confidence intervals; WM white matter; GM: grey matter.

Table 4. Log-variance ratio: combination of effect sizes

		Random Effects model			Meta-regression		
Region	**Number of studies**	**Effect size**	**p-value**	**I^2 indicator of heterogeneity**	**Age impact ($year^{-1}$)**	**IQ impact (IQ^{-1})**	**I^2 indicator of residual heterogeneity**
Cerebellum	16	0.02 (-0.27, 0.31)	0.898	54% (19%, 74%)	0.018 (-0.021, 0.057)	-0.014 (-0.034, 0.006)	45% p = 0.033
Cerebellum WM	6	-0.20 (-0.56, 0.15)	0.259	0% (0%, 37%)	-0.039 (-0.235, 0.157)	0.014 (-0.037, 0.066)	0% p = 0.640
Cerebellum GM	6	0.08 (-0.43, 0.60)	0.749	44% (0%, 78%)	0.254 (0.058, 0.450)	-0.064 (-0.115, -0.012)	0% p = 0.530
Whole vermis	11	0.03 (-0.21, 0.28)	0.778	0% (0%, 39%)	-0.013 (-0.089, 0.063)	0.001 (-0.028, 0.031)	0% p = 0.621
Lobules I-V	15*	0.01 (-0.25, 0.26)	0.962	17% (0%, 54%)	0.014 (-0.039, 0.067)	0.001 (-0.024, 0.027)	26% p = 0.185
Lobules VI-VII	18	0.10 (-0.09, 0.29)	0.311	0% (0%, 49%)	0.040 (0.001, 0.079)	-0.008 (-0.026, 0.010)	0% p = 0.658
Lobules VIII-X	9	0.25 (0.00, 0.51)	0.049	0% (0%, 32%)	0.034 (-0.077, 0.145)	-0.009 (-0.048, 0.030)	0% p = 0.717

* An article (Ciesielski et al. 1997) had to be excluded from the meta-analysis on the log-variance ratio for lobules I-V because the standard deviation in

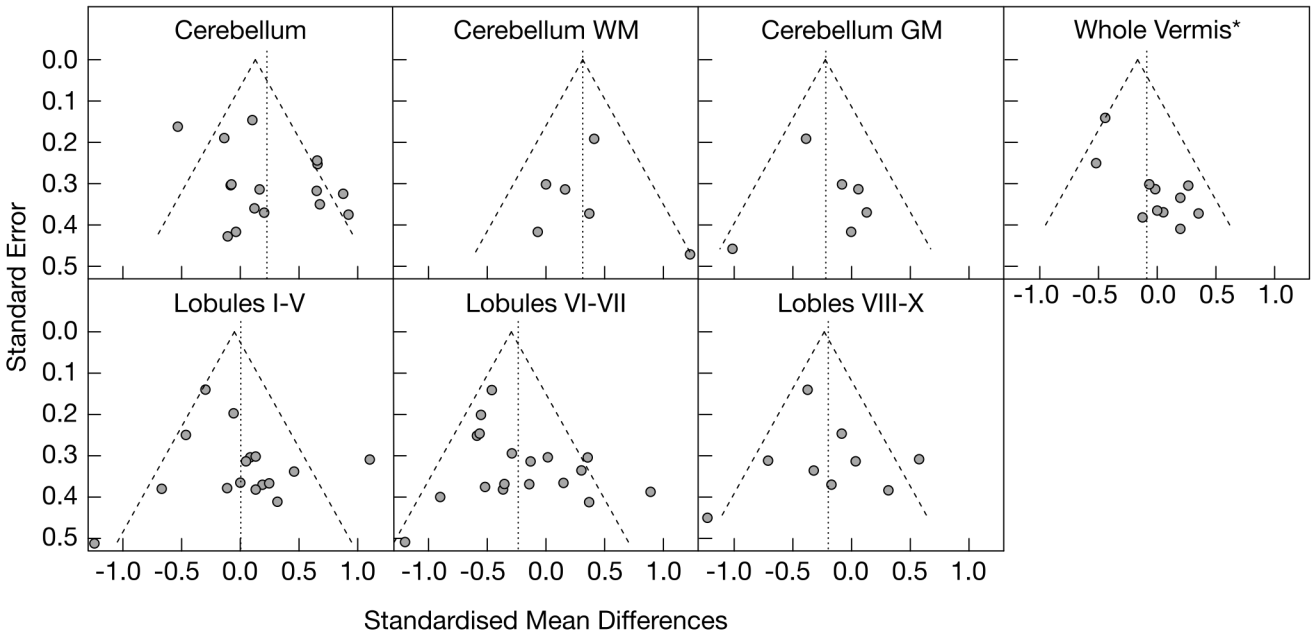

Figure 6. Funnel plot for the different regions WM: white matter; GM: grey matter; * statistically significant asymmetry of the funnel plot (p=0.002). The dotted line represents the meta-analytic effect size whereas the two dashed lines represent the boundaries of the 95% confidence interval for effect combined with the fixed effect model. Heterogeneity: I^2=65.9%, τ^2=0.1235, p=0.0001.

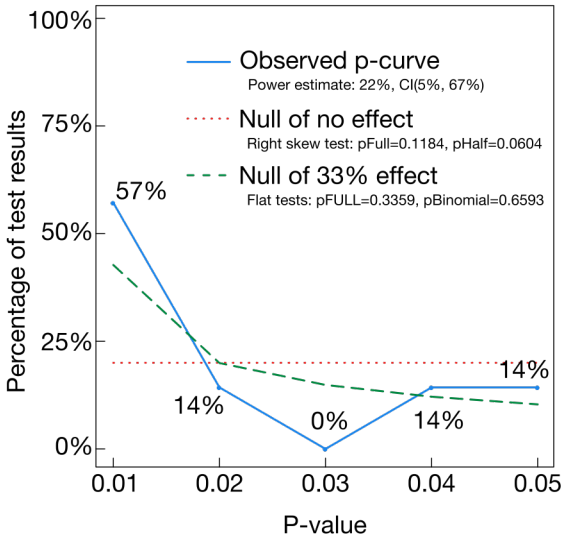

Figure 7. P-curve of studies with a significant result for the cerebellum volume. Null of: expected p-curve in case of. Note: The observed p-curve includes 7 studies with statistically significant results (p<.05). Among them, 5 had p<.025. There were 8 additional studies excluded from the p-curve analysis because their results did not pass significance (p>.05).

was not directly proportional to brain volume). The scaling factor was estimated at 0.518 (95% CI: 0.457, 0.578), statistically significantly smaller than 1 (which would be the case for isometry) (Figure 10). Our estimation shows that large brains have a proportionally smaller cerebellum. Because of this non-proportional relationship, the normalisation of cerebellar volumes by total brain volume should not be used to control for group differences. This validates our choice of using instead brain volume as covariate in our linear models.

Linear model. A very significant site effect was found for each volume, this effect was also different between patients and controls for the whole cerebellum volume and the cerebellum grey matter volume. The effect of diagnosis group for the total cerebellum volume was not significant (estimated at -0.59 cm^3, Cohen's d=-0.04, 95% CI: [-0.16, 0.09], in the first model – including group, age, IQ, scanning site, sex and brain volume as fixed effects; and at -1.22 cm^3, Cohen's d=-0.08, 95% CI: [-0.27, 0.11], in the second model – including in addition the interactions of group with age, IQ, sex, brain volume and scanning site). These estimations were more precise than in the meta-analysis of the literature, with narrower confidence intervals. Despite this, we did not find any significant difference between patients and controls. We did not find either any impact of age, sex, IQ or brain volume on cerebellar volume that would differ by diagnosis group. The analysis of cerebellar subregions (white and grey matter volumes) did not lead to a statistically significant group effect either. See Table 7 for the results of the linear model with group as main effect and Table 8 for the results model including the interaction of group with the other variables.

ABIDE meta-analysis. The results of the analyses using the meta-analytical approach agreed with those of the direct fit of linear models. Despite a smaller number of subjects than in the meta-analysis of the literature (Table 9), the confidence intervals for the combined mean differences were narrower. This was due to a smaller estimated between-study variance among ABIDE sites compared with that among articles in the literature. We did not find a statistically significant standard mean difference between patients and controls: d=0.06 (95 % CI: -0.12; 0.24) (Figure 11). In the meta-regression, no significant effect was found for age (p=0.888) nor IQ (p=0.726). Table 9 describes the characteristics of the subjects selected for the preservation of age and sex matching between patients and controls. Figure 11 shows the forest plot of ABIDE sites combined with the random effects model.
The meta-analytical approach did not show either any statistically significant difference in the variability of volume

Table 6. Demographics of ABIDE subjects for analysis

Site	Institution	N_{ASD} (F)*	N_{Ctrl} (F)*	Age_{ASD}	Age_{Ctrl}	IQ_{ASD}	IQ_{Ctrl}
Caltech	California Institute of Technology, USA	14/19 (3/4)	14/19 (4/4)	27.4±10.7	30.1±12.2	108±13	112±9
CMU	Carnegie Mellon University, USA	0/14 (0/3)	0/13 (0/3)	-	-	-	-
KKI	Kennedy Krieger Institute, USA	17/22 (3/4)	29/33 (9/9)	10.1±1.5	10.1±1.3	95±16	114±9
Leuven	University of Leuven, Belgium	29/29 (3/3)	32/35 (5/5)	17.8± 5.0	17.8±5.0	101±16	113±11
MaxMun	Ludwig Maximilian University Munich, Germany	14/24 (2/3)	18/33 (4/4)	23.8± 14.0	27.0±10.3	108±15	109±12
NYU	New York University Langone Medical Center, USA	29/79 (5/11)	53/105 (17/26)	13.3± 5.3	17.1±6.7	111±17	114±11
OHSU	Oregon Health and Science University, USA	11/13 (0/0)	15/15 (0/0)	11.1± 1.9	10.1±1.1	106±22	116±11
Olin	Olin, Institute of Living at Hartford Hospital, USA	15/20 (2/3)	16/16 (2/2)	16.5± 3.0	16.9±3.7	110±18	115±17
Pitt	University of Pittsburg, School of Medicine, USA	23/30 (3/4)	20/27 (4/4)	19.4± 7.9	17.4±5.1	110±15	110±10
SBL	Netherlands Institute for Neurosciences, Netherlands	0/15 (0/0)	0/15 (0/0)	-	-	-	-
SDSU	San Diego State University, USA	7/14 (1/1)	17/22 (5/6)	14.8±1.9	14.1±2.1	111±19	109±11
Stanford	Stanford University, USA	5/20 (2/4)	5/20 (2/4)	10.0±1.6	11.0±2.0	108±26	121±9
Trinity	Trinity Centre for Health Sciences, Ireland	22/24 (0/0)	23/25 (0/0)	17.7±3.4	17.2±3.8	109±16	112±12
UCLA	University of California, Los Angeles, USA	49/62 (6/7)	43/47 (6/6)	13.1±2.4	13.0±2.0	101±13	107±11
UM	University of Michigan, USA	16/68 (2/10)	6/77 (2/18)	13.5±2.5	16.9±1.1	107±20	114±5
USM	University of Utah, School of Medicine, USA	52/58 (0/0)	38/43 (0/0)	22.6±7.9	21.8±7.9	100±16	115±13
Yale	Yale Child Study Center, USA	25/28 (8/8)	24/28 (8/8)	13.0±3.0	12.8±2.8	94±21	106±18
	Total	328/539 (40/65)	353/573 (68/99)	16.8±7.5	16.8±7.4	104±17	112±12

ASD, autism spectrum disorders; Ctrl, controls; F, female. Age and IQ data: mean±SD
* Number of subjects retained / Number of subjects segmented (Number of female subjects retained / Number of female subjects segmented)

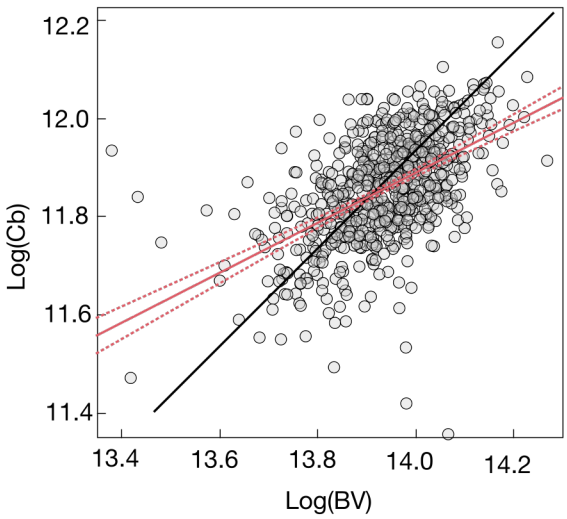

Figure 10. Log of cerebellar volume versus log of total brain volume.

measures between patients and controls (log-variance ratio=0.17, 95 % CI: -0.18; 0.52).

Discussion

Neuroanatomical diversity appears to capture a substantial proportion of the risk to ASD (Sabuncu et al. 2016). However, and even though several candidate neuroanatomical biomarkers have been proposed, it is not yet clear which are exactly the neuroanatomical traits that more strongly influence diagnosis. In this report we looked at one specific structure, the cerebellum, that has been widely discussed in the literature. We performed a meta-analysis of the literature and an analysis of the data from the ABIDE project.

The meta-analysis of the literature did not show conclusive evidence for a difference between individuals with ASD and controls neither for the total cerebellar volume nor for its subregions. Whole cerebellum and cerebellar white matter volumes appeared slightly larger in ASD whereas vermal lobules VI-VII area was found to be slightly smaller in ASD, but the significance of these results would not survive correction for multiple comparisons. Compared with a previous meta-analysis on whole cerebellum volume and vermal areas (Stanfield et al. 2008), the effect sizes we computed were all smaller in absolute value. Specifically, Stanfield et al. (2008) reported a significant difference in the volume of the vermal lobules VIII-X. In our analysis, despite the fact that a larger number of studies was taken into account, we did not replicate their finding.

The combined effect sizes in the meta-analysis of the literature were small in general. The number of articles that reported statistically significant results was larger than expected given the mean achieved power. We investigated whether this excess could be due to publication bias or p-hacking. Publication bias occurs when studies with statistically significant results have higher chances to be published than those without. This is more likely to happen when the finding reported is central to the hypothesis made by an article. However, the main focus of many of the articles that we meta-analysed was not cerebellar volume, which should decrease the likelihood of bias. We studied publication bias by analysing the asymmetry of the funnel plot using Egger's test. This type of analysis is not very sensitive and is able to detect only strong publication bias. We observed statistically significant funnel plot asymmetry only for the vermis area. Whereas this result suggests the presence of publication bias, it could also be due to greater inter-study heterogeneity in this specific measurement (where a few large studies reported negative effect sizes, whereas the majority of the other studies reported positive effect sizes).

Table 9. ABIDE sites included in the meta-analysis

Site	N_{ASD} (F)	N_{Ctrl} (F)	Age_{ASD}	Age_{Ctrl}	IQ_{ASD}	IQ_{Ctrl}
CALTECH	14 (3)	14 (4)	27.4±10.7	30.1±12.2	108.0±13.4	111.9±8.7
KKI	17 (3)	29 (9)	10.1±1.5	10.1±1.3	95.5±15.7	114.4±9.0
LEUVEN	29 (3)	32 (5)	17.8±5.0	17.8±5.0	101.4±16.4	112.6±11.2
MAX	12 (0)	14 (0)	21.6±13.5	24.9±10.1	105.5±14.9	108.9±12.6
NYU	24 (4)	50 (16)	13.8±5.5	16.4±6.2	109.5±15.6	114.5±11.5
OHSU	9 (0)	15 (0)	10.5±1.5	10.1±1.1	101.3±21.7	115.7±11.1
OLIN	13 (0)	14 (0)	16.5±3.1	16.9±3.8	108.4±18.2	115.1±16.9
PITT	21 (3)	20 (4)	17.9±6.6	17.4±5.1	110.4±13.9	110.2±10.4
SDSU	6 (0)	12 (0)	15.1±1.7	14.5±1.6	114.3±19.3	112.5±9.5
TRINITY	22 (0)	23 (0)	17.7±3.4	17.2±3.8	109.2±15.6	111.9±12.2
UCLA	49 (6)	43 (6)	13.1±2.4	13.0±2.0	101.5±13.1	106.6±10.9
USM	52 (0)	38 (0)	22.6±7.9	21.8±7.9	99.6±15.6	114.9±13.1
YALE	25 (8)	24 (8)	13.0±3.0	12.8±2.8	93.7±21.3	106.2±17.7
Total	293 (30)	328 (52)	17.0±7.4	16.6±7.2	103.0±16.6	111.9±12.3

Table 10. Standardized Mean Difference: combination of effect sizes from ABIDE site.

		Random Effects model			Meta-regression		
Region	**Number of sites**	**Effect size (Cohen's d)**	**p-value**	**Heterogeneity (I^2)**	**Age impact ($year^{-1}$)**	**IQ impact (IQ^{-1})**	**Residual heterogeneity (I^2)**
Cerebellum	13	0.06 (-0.12, 0.24)	0.532	33% (0%, 65%)	0.003 (-0.045, 0.052)	0.007 (-0.032, 0.046)	38% p=0.063
Cerebellum WM	13	0.01 (-0.15, 0.17)	0.924	5% (0%, 59%)	-0.014 (-0.051, 0.023)	-0.003 (-0.033, 0.027)	0% p=0.296
Cerebellum GM	13	0.06 (-0.11, 0.23)	0.497	31% (0%, 64%)	0.006 (-0.041, 0.053)	0.009 (-0.029, 0.047)	34% p=0.074

Values in parentheses represent 95% confidence intervals; WM White matter; GM: Grey matter.

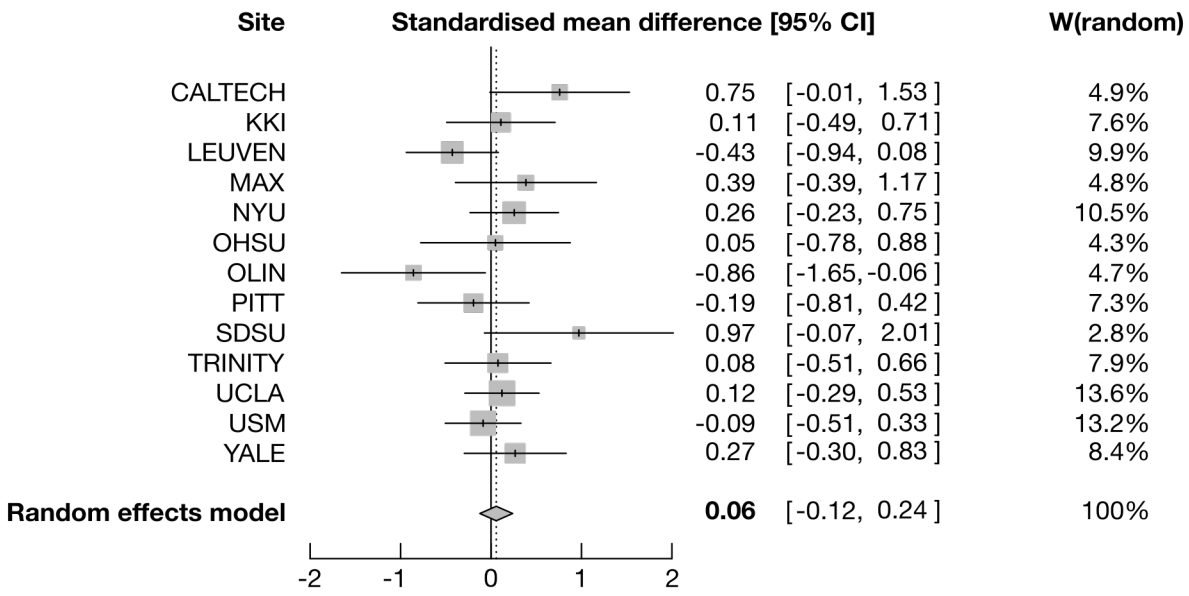

Figure 11. Forest plot for standardized mean difference on the cerebellar volume involving the different ABIDE sites. For each site, the grey square is centred on the estimated standardized mean difference (SMD), the black segment illustrates the confidence interval (95%-CI), and the surface of the square is proportional to the number of subjects in the site. SMD is positive when the cerebellum volume is greater in ASD. W(random) represents the weight given to each site for the combination of effect sizes. Heterogeneity: I^2=32.6%, τ^2=0.0192, p=0.1219.

We aimed at testing for p-hacking by analysing the p-curves: the distribution of p-values smaller than 0.05. The numbers of significant p-values reported, however, were not sufficient to draw a definite conclusion. In the case of the total cerebellar volume, where 7 out of 16 articles reported statistically significant findings, p-curve analysis did not reveal evidence for p-hacking. Overall, the analysis of the literature alone does not allow us to provide a definitive explanation for the excess of statistically significant findings.

One result that appeared very clearly was the strong heterogeneity of the findings in the literature. A certain degree of variability in the estimations of volume is expected, especially with the small sample sizes used. Heterogeneity tests aim at detecting a degree of variability that would go beyond this expectation. We found statistically significant heterogeneity for the estimations of 4 out of the 7 meta-analysed regions (i.e., whole cerebellar volume, lob I-V, lob VI-VII and lob VIII-IX, see table 2). Heterogeneity may be due to a combination of technical and physiological causes, for example, differences in MRI equipment, acquisition sequences, segmentation protocol, but also the age of the subjects, IQ distribution, etc. We analysed the effect of 2 of these factors, age and IQ, using meta-regression. First, our analysis did not reveal a differential effect of age or IQ on cerebellar volume for patients and controls. Second, residual heterogeneity was still statistically significant for 3 out of the 7 regions studied (whole cerebellar volume, lob VI-VII, lob VIII-IX). This indicates that sources other than age and IQ level may be causing significant heterogeneity in the literature.

The ABIDE project data provides a very interesting point of comparison for previous findings in the literature. The subjects in ABIDE come in most cases from research projects that had already been published, and should be then of similar characteristics as those in our literature meta-analysis. However, because the raw MRI and behavioural data is available, there is no issue of publication bias or p-hacking having an effect on the cohort selection. Additionally, the availability of raw data makes it possible to run methodologically homogenous analyses: same segmentation protocol, quality control procedures, and statistical analyses. There still remain, of course, many additional sources of heterogeneity due to the grassroots nature of the project (some of them being currently addressed in ABIDE II through an important harmonisation effort). Overall, the analyses of ABIDE data should provide a more precise, less heterogeneous estimation. The availability of raw data makes it also possible to engage a community effort to assess the impact of different methodological choices on the very same dataset.

We analysed all 1112 subjects from ABIDE using validated automatic computational neuroanatomy tools. After quality control and additional inclusion criteria we retained a group of 681 subjects. We had 85% power to detect the Cohen's d=0.23 effect obtained from our meta-analysis of the literature (2-sided t-test, alpha=0.05). We did not find any statistically significant result, neither for mean total volumes, interaction with age or IQ. Our statistical analysis here was a linear model including group, age, sex, IQ and site as main effects, or additionally the interaction between group and the other covariates. Although the absence of group effect was clear, we repeated our analyses using the same meta-analytical procedure used to study the literature to rule out an eventual methodological artefact. Every ABIDE site was considered as a different source of data and we computed a meta-analytical effect size using a random effects model weighting of each site's estimations by the inverse of the

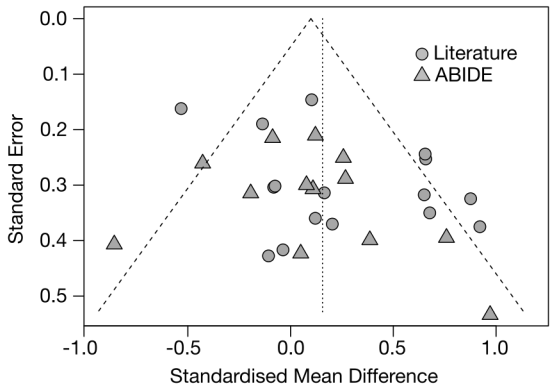

Figure 12. Funnel plot for the total cerebellum volume combining articles of the literature and ABIDE sites.

variance (thus giving more weight to sites with larger sample sizes, as in the case of the literature meta-analysis). Our meta-analysis was in agreement with the results of our linear models: a clear absence of group differences.

We can also use the ABIDE results to better understand publication bias in the literature. Figure 12 shows a funnel plot combining the results for total cerebellar volume in the literature and the different ABIDE centres. Egger's test for funnel plot asymmetry provides again a suggestion of publication bias (p=0.0478). More research, probably expanding the scope of our analyses to encompass more brain regions, would be required to better understand the underlying reasons of the excess of significant reports in the literature.

Interestingly, and although the site effect was substantial, the estimations from the ABIDE data were more precise than those from the literature (tighter confidence intervals), less heterogeneous. One reason for the lack of power in the literature (in addition to the small sample sizes) could stem from the significant heterogeneity across studies. This may be an important source of discordant reports, and makes it more difficult to draw conclusions from the literature. The public availability of raw data should greatly enhance our ability to understand neuroanatomical variability and increase our chances of detecting reliable neuroimaging phenotypes for neurodevelopmental disorders such as autism. Towards this aim, all our analysis scripts, our software for quality control, and the list of subjects we included have been made openly available on the Web, to facilitate the replication, critical appraisal and extension of our current results: https://github.com/neuroanatomy/Cerebellum.

In conclusion, we did not find evidence for a difference in cerebellar volume between subjects with ASD and controls, neither in the literature nor in the ABIDE cohort. This result does not rule out a possible involvement of the cerebellum in the aetiology of ASD. We could also imagine that some other measurement of cerebellar anatomy, more sophisticated than simple volume measurements, may be linked to autism in a future. However our current results do not provide evidence to justify a specific focus on the study of the cerebellum instead of any other brain structures. We reached a similar conclusion after a similar analysis of the corpus callosum (Lefebvre et al. 2015), another structure that had traditionally captured the interest of the research community. Based on these experiences, we can only advocate for a broad analysis of all neuroanatomical phenotypes available. For this effort to be successful, our community needs to continue developing the data sharing initiatives that will allow us to increase statistical power, decrease heterogeneity, and avoid the biases preventing researchers from benefiting from the work of each other.

Acknowledgements

The research leading to these results has received funding from the Fondation de France project "Développement du plissement cortical dans les troubles du spectre autistique : caractérisation morphométrique et génétique", ERA-Net NEURON Cofund Programme under "Horizon 2020" (SynPathy project), Institut Pasteur, Bettencourt-Schueller Foundation, Centre National de la Recherche Scientifique, University Paris Diderot, Agence Nationale de la Recherche programme "Investissements d'avenir", Labex BioPsy, ANR-10-LABX-BioPsy, ANR-11-IDEX-0004-02, Labex GenMed, ANR SynDiv, Conny-Maeva Charitable Foundation, Cognacq Jay Foundation, Orange Foundation, Fondamental Foundation. The group of LRR is member of the Labex BioPsy and ENP Foundation.

References

Åhsgren, Ingegerd, Ingela Baldwin, Christina Goetzinger-Falk, Anders Erikson, Olof Flodmark, and Christopher Gillberg. 2005. "Ataxia, Autism, and the Cerebellum: A Clinical Study of 32 Individuals with Congenital Ataxia." *Developmental Medicine & Child Neurology* 47 (3): 193–98. doi:10.1017/S0012162205000356.

Akshoomoff, Natacha, Catherine Lord, Alan J. Lincoln, Rachel Y. Courchesne, Ruth A. Carper, Jeanne Townsend, and Eric Courchesne. 2004. "Outcome Classification of Preschool Children with Autism Spectrum Disorders Using MRI Brain Measures." *Journal of the American Academy of Child and Adolescent Psychiatry* 43 (3): 349–57. doi:10.1097/00004583-200403000-00018.

Bloss, Cinnamon S., and Eric Courchesne. 2007. "MRI Neuroanatomy in Young Girls with Autism: A Preliminary Study." *Journal of the American Academy of Child and Adolescent Psychiatry* 46 (4): 515–23. doi:10.1097/chi.0b013e318030e28b.

Borenstein, Michael, Larry V. Hedges, Julian P. T. Higgins, and Hannah R. Rothstein. 2009. *Introduction to Meta-Analysis*. Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/9780470743386.

Brambilla, Paolo, Antonio Hardan, Stefania Ucelli di Nemi, Jorge Perez, Jair C Soares, and Francesco Barale. 2003. "Brain Anatomy and Development in Autism: Review of Structural MRI Studies." *Brain Research Bulletin* 61 (6): 557–69. doi:10.1016/j.brainresbull.2003.06.001.

Carper, Ruth A., and Eric Courchesne. 2000. "Inverse

Correlation between Frontal Lobe and Cerebellum Sizes in Children with Autism." *Brain* 123 (4): 836–44. doi:10.1093/brain/123.4.836.

Catani, Marco, Derek K. Jones, Eileen Daly, Nitzia Embiricos, Quinton Deeley, Luca Pugliese, Sarah Curran, Dene Robertson, and Declan G. M. Murphy. 2008. "Altered Cerebellar Feedback Projections in Asperger Syndrome." *NeuroImage* 41 (4): 1184–91. doi:10.1016/j.neuroimage.2008.03.041.

Ciesielski, K.T., R.J. Harris, B.L. Hart, and H.F. Pabst. 1997. "Cerebellar Hypoplasia and Frontal Lobe Cognitive Deficits in Disorders of Early Childhood." *Neuropsychologia* 35 (5): 643–55. doi:10.1016/S0028-3932(96)00119-4.

Cleavinger, Howard B., Erin D. Bigler, Jamie L. Johnson, Jeffrey Lu, William McMahon, and Janet E. Lainhart. 2008. "Quantitative Magnetic Resonance Image Analysis of the Cerebellum in Macrocephalic and Normocephalic Children and Adults with Autism." *Journal of the International Neuropsychological Society : JINS* 14 (3): 401–13. doi:10.1017/S1355617708080594.

Courchesne, E., C. M. Karns, H. R. Davis, R. Ziccardi, R. A. Carper, Z. D. Tigue, H. J. Chisum, et al. 2001. "Unusual Brain Growth Patterns in Early Life in Patients with Autistic Disorder An MRI Study." *Neurology* 57 (2): 245–54. doi:10.1212/WNL.57.2.245.

Courchesne, E., O. Saitoh, R. Yeung-Courchesne, G. A. Press, A. J. Lincoln, R. H. Haas, and L. Schreibman. 1994. "Abnormality of Cerebellar Vermian Lobules VI and VII in Patients with Infantile Autism: Identification of Hypoplastic and Hyperplastic Subgroups with MR Imaging." *AJR. American Journal of Roentgenology* 162 (1): 123–30. doi:10.2214/ajr.162.1.8273650.

Courchesne, Eric, John R. Hesselink, Terry L. Jernigan, and Rachel Yeung-Courchesne. 1987. "Abnormal Neuroanatomy in a Nonretarded Person With Autism: Unusual Findings With Magnetic Resonance Imaging." *Archives of Neurology* 44 (3): 335–41. doi:10.1001/archneur.1987.00520150073028.

D'Angelo, Egidio. 2014. "Chapter 2 - The Organization of Plasticity in the Cerebellar Cortex: From Synapses to Control." In *Progress in Brain Research*, edited by Narender Ramnani, 210:31–58. Cerebellar Learning. Elsevier. http://www.sciencedirect.com/science/article/pii/B9780444633569000029.

Dean, Paul, John Porrill, Carl-Fredrik Ekerot, and Henrik Jörntell. 2010. "The Cerebellar Microcircuit as an Adaptive Filter: Experimental and Computational Evidence." *Nature Reviews Neuroscience* 11 (1): 30–43. doi:10.1038/nrn2756.

Di Martino, A., C.-G. Yan, Q. Li, E. Denio, F. X. Castellanos, K. Alaerts, J. S. Anderson, et al. 2014. "The Autism Brain Imaging Data Exchange: Towards a Large-Scale Evaluation of the Intrinsic Brain Architecture in Autism." *Molecular Psychiatry* 19 (6): 659–67. doi:10.1038/mp.2013.78.

Dziuk, M.A., J.C.G. Larson, A. Apostu, E.M. Mahone, M.B. Denckla, and S.H. Mostofsky. 2007. "Dyspraxia in Autism: Association with Motor, Social, and Communicative Deficits." *Developmental Medicine and Child Neurology* 49 (10): 734–39. doi:10.1111/j.1469-8749.2007.00734.x.

Egger, Matthias, George Davey Smith, Martin Schneider, and Christoph Minder. 1997. "Bias in Meta-Analysis Detected by a Simple, Graphical Test." *BMJ* 315 (7109): 629–34. doi:10.1136/bmj.315.7109.629.

Elia, Maurizio, Raffaele Ferri, Sebastiano A. Musumeci, Simonetta Panerai, Maria Bottitta, and Carmela Scuderi. 2000. "Clinical Correlates of Brain Morphometric Features of Subjects With Low-Functioning Autistic Disorder." *Journal of Child Neurology* 15 (8): 504–8. doi:10.1177/088307380001500802.

Evans, David W., Steven M. Lazar, K. B. Boomer, Aaron D. Mitchel, Andrew M. Michael, and Gregory J. Moore. 2014. "Social Cognition and Brain Morphology: Implications for Developmental Brain Dysfunction." *Brain Imaging and Behavior*, May. doi:10.1007/s11682-014-9304-1.

Garber, H. Jordan, and Edward R. Ritvo. 1992. "Magnetic Resonance Imaging of the Posterior Fossa in Autistic Adults." *The American Journal of Psychiatry* 149 (2): 245–47. doi:10.1176/ajp.149.2.245.

Hallahan, B., E. M. Daly, G. McAlonan, E. Loth, F. Toal, F. O'Brien, D. Robertson, et al. 2009. "Brain Morphometry Volume in Autistic Spectrum Disorder: A Magnetic Resonance Imaging Study of Adults." *Psychological Medicine* 39 (2): 337–46. doi:10.1017/S0033291708003383.

Hardan, A. Y., N. J. Minshew, K. Harenski, and M. S. Keshavan. 2001. "Posterior Fossa Magnetic Resonance Imaging in Autism." *Journal of the American Academy of Child and Adolescent Psychiatry* 40 (6): 666–72. doi:10.1097/00004583-200106000-00011.

Hashimoto, Toshiaki, Masanobu Tayama, Kazuyosi Murakawa, Tsutomu Yoshimoto, Masahito Miyazaki, Midori Harada, and Yasuhiro Kuroda. 1995. "Development of the Brainstem and Cerebellum in Autistic Patients." *Journal of Autism and Developmental Disorders* 25 (1): 1–18. doi:10.1007/BF02178163.

Hazlett, H.C., M. Poe, G. Gerig, R.G. Smith, J. Provenzale, A. Ross, J. Gilmore, and J. Piven. 2005. "Magnetic Resonance Imaging and Head Circumference Study of Brain Size in Autism: Birth through Age 2 Years." *Archives of General Psychiatry* 62 (12): 1366–76. doi:10.1001/archpsyc.62.12.1366.

Hedges, Larry V. 1981. "Distribution Theory for Glass's Estimator of Effect Size and Related Estimators." *Journal of Educational and Behavioral Statistics* 6 (2): 107–28. doi:10.3102/10769986006002107.

Herbert, M. R., D. A. Ziegler, C. K. Deutsch, L. M. O'Brien, N. Lange, A. Bakardjiev, J. Hodgson, et al. 2003. "Dissociations of Cerebral Cortex, Subcortical and Cerebral White Matter Volumes in Autistic Boys." *Brain* 126 (5): 1182–92. doi:10.1093/brain/awg110.

Hodge, Steven M., Nikos Makris, David N. Kennedy, Verne S. Jr Caviness, James Howard, Lauren McGrath, Shelly Steele, Jean A. Frazier, Helen Tager-Flusberg, and Gordon J. Harris. 2010. "Cerebellum, Language, and Cognition in Autism and Specific Language Impairment." *Journal of Autism and Developmental Disorders* 40 (3): 300–316. doi:10.1007/s10803-009-0872-7.

Holttum, J. R., N. J. Minshew, R. S. Sanders, and N. E.

Phillips. 1992. "Magnetic Resonance Imaging of the Posterior Fossa in Autism." *Biological Psychiatry* 32 (12): 1091–1101.

Kates, Wendy R., Courtney P. Burnette, Stephan Eliez, Leslie Abbott Strunge, Desmond Kaplan, Rebecca Landa, Allan L. Reiss, and Godfrey D. Pearlson. 2004. "Neuroanatomic Variation in Monozygotic Twin Pairs Discordant for the Narrow Phenotype for Autism." *American Journal of Psychiatry* 161 (3): 539–46. doi:10.1176/appi.ajp.161.3.539.

Kaufmann, W.E., K.L. Cooper, S.H. Mostofsky, G.T. Capone, W.R. Kates, C.J. Newschaffer, I. Bukelis, M.H. Stump, A.E. Jann, and D.C. Lanham. 2003. "Specificity of Cerebellar Vermian Abnormalities in Autism: A Quantitative Magnetic Resonance Imaging Study." *Journal of Child Neurology* 18 (7): 463–70.

Kleiman, Michele D., Samuel Neff, and N. Paul Rosman. 1992. "The Brain in Infantile Autism Are Posterior Fossa Structures Abnormal?" *Neurology* 42 (4): 753–753. doi:10.1212/WNL.42.4.753.

Lahuis, B. E., S. Durston, H. Nederveen, M. Zeegers, S. J. M. C. Palmen, and H. Van Engeland. 2008. "MRI-Based Morphometry in Children with Multiple Complex Developmental Disorder, a Phenotypically Defined Subtype of Pervasive Developmental Disorder Not Otherwise Specified." *Psychological Medicine* 38 (9): 1361–67. doi:10.1017/S0033291707001481.

Langen, Marieke, Hugo G. Schnack, Hilde Nederveen, Dienke Bos, Bertine E. Lahuis, Maretha V. de Jonge, Herman van Engeland, and Sarah Durston. 2009. "Changes in the Developmental Trajectories of Striatum in Autism." *Biological Psychiatry* 66 (4): 327–33. doi:10.1016/j.biopsych.2009.03.017.

Lefebvre, Aline, Anita Beggiato, Thomas Bourgeron, and Roberto Toro. 2015. "Neuroanatomical Diversity of Corpus Callosum and Brain Volume in Autism: Meta-Analysis, Analysis of the Autism Brain Imaging Data Exchange Project, and Simulation." *Biological Psychiatry*, Autism and Brain Development, 78 (2): 126–34. doi:10.1016/j.biopsych.2015.02.010.

Leiner, Henrietta C., Alan L. Leiner, and Robert S. Dow. 1993. "Cognitive and Language Functions of the Human Cerebellum." *Trends in Neurosciences* 16 (11): 444–47. doi:10.1016/0166-2236(93)90072-T.

Levitt, Jennifer G., Rebecca Blanton, Linda Capetillo-Cunliffe, Donald Guthrie, Arthur Toga, and James T. McCracken. 1999. "Cerebellar Vermis Lobules VIII-X in Autism." *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 23 (4): 625–33. doi:10.1016/S0278-5846(99)00021-4.

Light, Richard J., and David B. Pillemer. 1984. *Summing Up: The Science of Reviewing Research*. Highlighting edition. Cambridge, Mass: Harvard University Press.

Manni, Ermanno, and Laura Petrosini. 2004. "A Century of Cerebellar Somatotopy: A Debated Representation." *Nature Reviews Neuroscience* 5 (3): 241–49. doi:10.1038/nrn1347.

Moher, David, Alessandro Liberati, Jennifer Tetzlaff, Douglas G. Altman, and PRISMA Group. 2009. "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement." *PLoS Medicine* 6 (7): e1000097. doi:10.1371/journal.pmed.1000097.

Palmen, Saskia J. M. C., Hilleke E. Hulshoff Pol, Chantal Kemner, Hugo G. Schnack, Joost Janssen, René S. Kahn, and Herman van Engeland. 2004. "Larger Brains in Medication Naive High-Functioning Subjects with Pervasive Developmental Disorder." *Journal of Autism and Developmental Disorders* 34 (6): 603–13. doi:10.1007/s10803-004-5282-2.

Pierce, Karen, and Eric Courchesne. 2001. "Evidence for a Cerebellar Role in Reduced Exploration and Stereotyped Behavior in Autism." *Biological Psychiatry* 49 (8): 655–64. doi:10.1016/S0006-3223(00)01008-8.

Piven, J., E. Nehme, J. Simon, P. Barta, G. Pearlson, and S.E. Folstein. 1992. "Magnetic Resonance Imaging in Autism: Measurement of the Cerebellum, Pons, and Fourth Ventricle." *Biological Psychiatry* 31 (5): 491–504. doi:10.1016/0006-3223(92)90260-7.

Piven, Joseph, Khalil Saliba, James Bailey, and Stephan Arndt. 1997. "An MRI Study of Autism: The Cerebellum Revisited." *Neurology* 49 (2): 546–51. doi:10.1212/WNL.49.2.546.

Ritvo, E.R., H.J. Garber, A.L. Reiss, L. Garcia-Bunuel, C.T. Hayden, P.S. Lichtenberg, R.C. Woody, et al. 1988. "Cerebellar Hypoplasia and Autism." *New England Journal of Medicine* 319 (17): 1152–54. doi:10.1056/NEJM198810273191709.

Rondi-Reig, Laure, Anne-Lise Paradis, Julie M. Lefort, Benedicte M. Babayan, and Christine Tobin. 2014. "How the Cerebellum May Monitor Sensory Information for Spatial Representation." *Frontiers in Systems Neuroscience* 8. doi:10.3389/fnsys.2014.00205.

Sabuncu, Mert R., Tian Ge, Avram J. Holmes, Jordan W. Smoller, Randy L. Buckner, Bruce Fischl, the Alzheimer's Disease Neuroimaging Initiative, et al. 2016. "Morphometricity as a Measure of the Neuroanatomical Signature of a Trait." *Proceedings of the National Academy of Sciences* 113 (39): E5749–56. doi:10.1073/pnas.1604378113.

Schmahmann, J. D., and J. C. Sherman. 1998. "The Cerebellar Cognitive Affective Syndrome." *Brain* 121 (4): 561–79. doi:10.1093/brain/121.4.561.

Scott, Julia A., Cynthia Mills Schumann, Beth L. Goodlin-Jones, and David G. Amaral. 2009. "A Comprehensive Volumetric Analysis of the Cerebellum in Children and Adolescents with Autism Spectrum Disorder." *Autism Research : Official Journal of the International Society for Autism Research* 2 (5): 246–57. doi:10.1002/aur.97.

Simonsohn, Uri, Leif D. Nelson, and Joseph P. Simmons. 2014. "P-Curve: A Key to the File-Drawer." *Journal of Experimental Psychology: General* 143 (2): 534–47. doi:10.1037/a0033242.

Stanfield, Andrew C., Andrew M. McIntosh, Michael D. Spencer, Ruth Philip, Sonia Gaur, and Stephen M. Lawrie. 2008. "Towards a Neuroanatomy of Autism: A Systematic Review and Meta-Analysis of Structural Magnetic Resonance Imaging Studies." *European Psychiatry : The Journal of the Association of European Psychiatrists* 23 (4): 289–99. doi:10.1016/j.eurpsy.2007.05.006.

Thompson, Simon G., and Julian P. T. Higgins. 2002. "How Should Meta-Regression Analyses Be Undertaken and

Interpreted?" *Statistics in Medicine* 21 (11): 1559–73. doi:10.1002/sim.1187.
Toro, Roberto, Marie Chupin, Line Garnero, Gabriel Leonard, Michel Perron, Bruce Pike, Alain Pitiot, et al. 2009. "Brain Volumes and Val66Met Polymorphism of the BDNF Gene: Local or Global Effects?" *Brain Structure and Function* 213 (6): 501. doi:10.1007/s00429-009-0203-y.
Toro, Roberto, Michel Perron, Bruce Pike, Louis Richer, Suzanne Veillette, Zdenka Pausova, and Tomáš Paus. 2008. "Brain Size and Folding of the Human Cerebral Cortex." *Cerebral Cortex* 18 (10): 2352–57. doi:10.1093/cercor/bhm261.
Traut, Nicolas. 2017. "Meta-Analysis of the Variance Ratio." *bioRxiv*, January, 104695. doi:10.1101/104695.
Wang, Samuel S.-H., Alexander D. Kloth, and Aleksandra Badura. 2014. "The Cerebellum, Sensitive Periods, and Autism." *Neuron* 83 (3): 518–32. doi:10.1016/j.neuron.2014.07.016.
Webb, Sara Jane, Bobbi-Faun Sparks, Seth D. Friedman, Dennis W. W. Shaw, Jay Giedd, Geraldine Dawson, and Stephen R. Dager. 2009. "Cerebellar Vermal Volumes and Behavioral Correlates in Children with Autism Spectrum Disorder." *Psychiatry Research: Neuroimaging* 172 (1): 61–67. doi:10.1016/j.pscychresns.2008.06.001.
Williams, Roger S., Stephen L. Hauser, Dominick P. Purpura, G. Robert DeLong, and Charles N. Swisher. 1980. "Autism and Mental Retardation: Neuropathologic Studies Performed in Four Retarded Persons With Autistic Behavior." *Archives of Neurology* 37 (12): 749–53. doi:10.1001/archneur.1980.00500610029003.