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ABSTRACT

BACKGROUND: The neuroanatomical bases of autism spectrum disorder remain largely unknown. Among the most widely discussed candidate endophenotypes, differences in cerebellar volume have been often reported as statistically significant.

METHODS: We aimed at objectifying this possible alteration by performing a systematic meta-analysis of the literature and an analysis of the ABIDE (Autism Brain Imaging Data Exchange) cohort. Our meta-analysis sought to determine a combined effect size of autism spectrum disorder diagnosis on different measures of the cerebellar anatomy as well as the effect of possible factors of variability across studies. We then analyzed the cerebellar volume of 328 patients and 353 control subjects from the ABIDE project.

RESULTS: The meta-analysis of the literature suggested a weak but significant association between autism spectrum disorder diagnosis and increased cerebellar volume ($p = .049$, uncorrected), but the analysis of ABIDE did not show any relationship. The studies meta-analyzed were generally underpowered; however, the number of statistically significant findings was larger than expected.

CONCLUSIONS: 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, although independent of autism diagnosis.

Keywords: Autism, Cerebellum, Cohort study, Computational neuroanatomy, Meta-analysis, Neuroimaging

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Autism spectrum disorder (ASD) affect 1% of the population and is characterized by impairments in social interactions and the variety of interests. Through the years, many reports have suggested that cerebellar abnormalities were implicated in the onset of ASD [reviewed in (1)]. The cerebellum exhibits a highly regular arrangement of neurons and connections, supposed to support massive parallel computing capabilities, in particular through long-term synaptic plasticity (2,3). It has been traditionally involved in the performance of precise motor behavior, and patients with ASD also present with varying degrees of dyspraxia (4,5). There is also growing evidence for involvement of the cerebellum in cognitive and affective functions, which could be impaired in autism (6–9).

The first case report of abnormal cerebellar anatomy in autism was published in 1980 (10) and described a reduced number of Purkinje cells in the cerebellar vermis of a patient with autism. In 1987, Courchesne *et al.* (11), using in vivo magnetic resonance imaging (MRI), were the first to report a cerebellar abnormality in a patient with ASD. Since then, various studies comparing the volumes and areas of cerebellar subregions between patients with ASD and control subjects have reported significant differences. However, whereas many articles report statistically significant differences, many others fail to detect differences. These discrepancies could be due to many factors, for example, the high heterogeneity in the etiology of ASD, differences in the inclusion criteria across studies, or 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.

Our aim was to objectify the alterations of cerebellar volumes in ASD. In the first part of this article, we present a systematic meta-analysis of the literature, examining the differences across previous reports and determining a combined effect size. In the second part, we describe our analysis of cerebellar volume in the ABIDE (Autism Brain Imaging Data Exchange) cohort (12) and study the consistency of these results with results 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 control subjects.

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METHODS AND MATERIALS

Meta-analysis of the Literature

Collection and Selection of Articles. We queried PubMed on October 12, 2016, for all articles that met the search criteria "cerebell* AND autis*". We included articles reporting volumetric or area MRI measurements (mean and standard deviation) on at least one region of the cerebellum for patients with ASD and control subjects (Supplemental Methods).

Meta-analysis. We conducted two meta-analyses. The first compared mean cerebellar volume between patients with ASD and control subjects. Effect sizes were computed as standardized mean differences (Cohen's *d*) using Hedges' *g* as estimator (13). The second compared the variability of cerebellar volumes between patients and control subjects by computing the log-variance ratio (14). We combined effect sizes using a random-effects model, where the global estimate is obtained as the average of each estimate weighted by the inverse of its variance (15). The between-study variance τ^2 was estimated using the restricted maximum likelihood 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 (15).

We then evaluated publication bias and *p*-hacking in several ways. Publication bias is the tendency to publish preferentially studies reporting statistically significant results. *p*-Hacking describes the different methods used to achieve significance in a statistical test, such as flexible choice of covariates, flexible inclusion/exclusion criteria, and selective reporting. First, we calculated the rate of studies showing statistically significant differences between patients and control subjects. We compared this rate with the average statistical power obtained by assuming that the actual effect was equal to the effect estimated after meta-regression. Second, we evaluated the asymmetry of the funnel plot (16) using Egger's test. In a funnel plot, the x axis represents effect size, and the y axis represents standard error. The interpretation of Egger's test relies on the assumption that studies with small sample sizes are more affected by publication bias than studies with large sample sizes. Publication bias could then appear as an asymmetric distribution of points in the funnel plot, with an excess of small studies reporting large effect sizes (17). Finally, we plotted the *p* curve, which shows the distribution of significant *p* values (18). We evaluated *p* curves for inferred power—the most likely statistical power of the studies to get the observed *p* curve. Computations were performed using R (https://www.r-project.org) with the packages meta (19) and metafor (20) along with the *p* curve app 4.0 (http://www.p-curve.com/app4/). We report statistical significance for an α level of .05. *p* values were not corrected for multiple comparisons.

Analysis of ABIDE

We analyzed data from the ABIDE I project (the original release of ABIDE), which include MRI scans for 539 patients with ASD and 573 control subjects. From the information provided in the ABIDE website, we concluded that there was no overlap between their subject groups and those included in our meta-analysis. Cerebellar volumes were automatically segmented using FreeSurfer 5.1 (https://surfer.nmr.mgh.harvard.edu). We developed a tool for visual quality control of the segmentations (Figure 1 and Supplemental Methods). We included only subjects for whom the segmentation quality was clearly good. Our quality control focused on the cerebellum, but we combined its results with our previous quality control of the whole brain (21) and conserved only the subjects that passed both.

From the original 1112 subjects, 328 patients (61% of the subjects) and 353 control subjects (62% of the subjects) were retained for further analysis after quality control (see Table 1 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 full-scale IQ.

Following our previous results showing the nonlinear variation of brain anatomy relative to brain volume (21–23), we studied the allometric scaling of cerebellar volume. The division of regional volume measurements by total brain volume (normalization) is often used to control for differences in brain volume between groups. This strategy would be appropriate only if the volume of the cerebellum scaled proportionally to total brain volume. We assessed the scaling factor of the cerebellum with total brain volume using a linear regression.

We evaluated the effect of diagnosis and other factors on total cerebellar volume, cerebellar white matter volume, and cerebellar gray 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 in addition the interactions of group with age, IQ, scanning site, sex, and brain volume. Because these statistical models were not the same as the models used in the meta-analysis of the literature, we also analyzed 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. 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 (https://www.jmp.com) for fitting linear models and R version 3.3.1 for the meta-analytical approach. The R scripts that we used for the computation of the meta-analysis are available on the web (https://github.com/neuroanatomy/Cerebellum).

RESULTS

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 (24) and a meta-analysis on cerebellum in ASD (25). We also added two studies (26,27) that we found by other means. We selected studies in two steps, first based on their titles and abstracts and then based on their full text (see Supplemental Figure S1 for the Preferred Reporting Items for Systematic Reviews

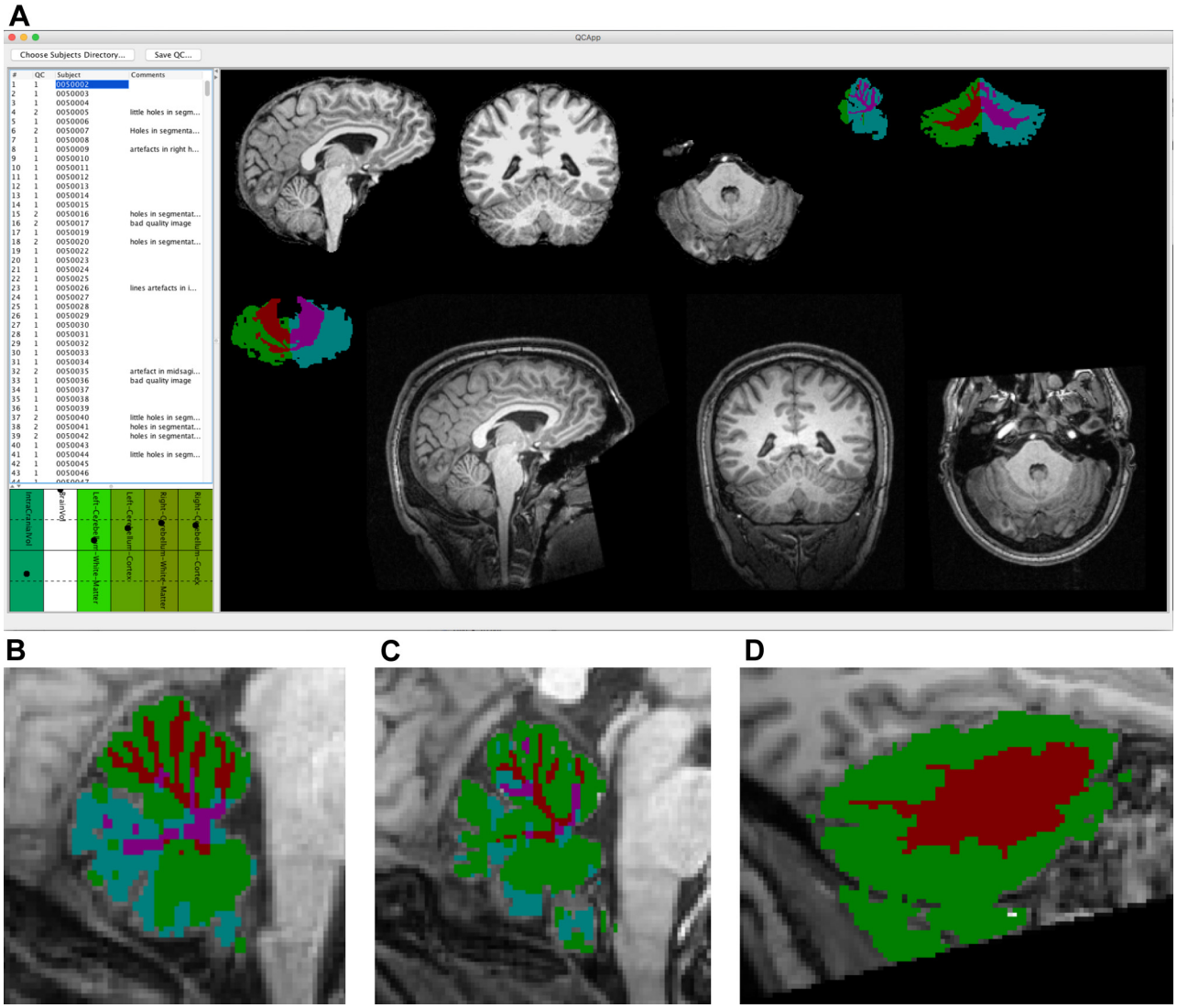

Figure 1. Quality control (QC) of the cerebellum automatic segmentation. **(A)** QC tool. For each subject, we evaluated the quality of the segmentation in comparison with the original image in the three different planes. The values of the different measured volumes along with their deviation from the overall mean is represented in the graph at the bottom left. **(B)** A segmentation evaluated as correct. **(C)** A segmentation with an excess of unlabeled regions. **(D)** A segmentation with major labeling errors.

and Meta-Analyses workflow). Our final analyses were based on 30 articles covering seven different regions of interest. The three most reported measures were total cerebellar volume (1050 subjects in total), vermal lobules VI–VII area (965 subjects in total), and vermal lobules I–V area (861 subjects in total) (see Table 2 for a description of the selected articles).

Mean Effect Size. Significant mean effects were found for three of the seven regions studied: total cerebellum (p = .049), white matter (p = .011), and vermal lobules VI–VII (p = .022) (Table 3). Compared with control subjects, patients with ASD displayed larger cerebellar white matter volume (Cohen's d = 0.31, 95% confidence interval [CI] [0.07, 0.55]) and smaller areas for vermal lobules VI–VII (Cohen's d = −0.24, 95% CI [−0.44, −0.03]). The effect of diagnosis on total cerebellar volume was barely statistically significant (Cohen's d = 0.23, 95% CI [0.00, 0.45]) (see forest plot in Figure 2A).

Heterogeneity and Meta-regression. A statistically significant heterogeneity was found for four of the seven regions under study: total cerebellar volume (p = .0001), vermal lobules I–V area (p = .0049), vermal lobules VI–VII area (p = .0081), and vermal lobules VIII–X area (p = .019). Despite this high heterogeneity, our meta-regression did not show a significant impact of age or IQ on total cerebellar volume. The age of patients with ASD correlated with a reduced volume of cerebellar white matter (p = .025) and an increased volume of cerebellar gray matter (p = .024) compared with control

Table 1. Demographics of ABIDE Subjects Retained for Statistical Analyses (Allometry and Linear Models)

Site/Institution	N_{ASD} (F)[a]	N_{Ctrl} (F)[a]	Age_{ASD}, Years	Age_{Ctrl}, Years	IQ_{ASD}	IQ_{Ctrl}
Caltech/California Institute of Technology, California	14/19 (3/4)	14/19 (4/4)	27.4 ± 10.7	30.1 ± 12.2	108 ± 13	112 ± 9
CMU/Carnegie Mellon University, Pennsylvania	0/14 (0/3)	0/13 (0/3)	—	—	—	—
KKI/Kennedy Krieger Institute, Maryland	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, New York	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, Oregon	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, Connecticut	15/20 (2/3)	16/16 (2/2)	16.5 ± 3.0	16.9 ± 3.7	110 ± 18	115 ± 17
Pitt/University of Pittsburgh, School of Medicine, Pennsylvania	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, California	7/14 (1/1)	17/22 (5/6)	14.8 ± 1.9	14.1 ± 2.1	111 ± 19	109 ± 11
Stanford/Stanford University, California	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, California	49/62 (6/7)	43/47 (6/6)	13.1 ± 2.4	13.0 ± 2.0	101 ± 13	107 ± 11
UM/University of Michigan, Michigan	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, Utah	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, Connecticut	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

Age and IQ data are presented as mean ± SD.
ABIDE, Autism Brain Imaging Data Exchange; ASD, patients with autism spectrum disorder; Ctrl, control subjects; F, female.
[a]Number of subjects retained/Number of subjects segmented (Number of female subjects retained/Number of female subjects segmented).

subjects. However, the number of studies included in the meta-regression may be insufficient to obtain reliable results. The IQ of patients with ASD correlated with increased volume of the cerebellar white matter ($p = .0176$) and increased area of vermal lobules I–V ($p = .019$). Age and IQ did not seem to be the only factors producing heterogeneity: after the meta-regression, residual heterogeneity was still statistically significant for total cerebellar volume ($p = .0020$), vermal lobules VI–VII area ($p = .039$), and vermal lobules VIII–X area ($p = .013$). Table 3 shows the results of the random-effects models and meta-regressions for the cerebellum regions, and Supplemental Figure S2 shows the observed effect sizes versus the expected effect from the meta-regression on total cerebellar volume.

Statistical Power. Despite a small mean effect size estimated at Cohen's $d = 0.23$ for the total cerebellar 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 detected a statistically significant funnel plot asymmetry only for the whole vermis area ($p = .002$). None of the remaining regions presented a significant funnel plot asymmetry (Figure 3).

Our analyses of the *p* curves were not conclusive on the presence of *p*-hacking. In five of the seven regions studied, there were only two or three *p* values $< .05$, which resulted in very imprecise estimations with wide confidence intervals. Total cerebellar volume and area of lobules VI–VII each had seven *p* values $< .05$, which still produced unreliable estimations. *p* curve analyses suggested low statistical power for both regions (total 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 again, confidence intervals were very wide. Supplemental Table S1 summarizes the results for the different publication bias and *p*-hacking analyses. Figure 4 shows the observed *p* curve for the total cerebellar volume.

Meta-analysis of Variability (Log-Variance Ratio). A barely statistically significant (uncorrected) effect was found for vermal lobules VIII–X area, suggesting larger volume variations for the ASD groups ($p = .049$). No significant effect was found for any other region. Heterogeneity was statistically significant only for the total cerebellar volume ($p = .0052$, 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 (Supplemental Table S2).

Analysis of ABIDE Data

Allometry. The scaling between cerebellar volume and brain volume was not isometric, i.e., the volume of the cerebellum was not directly proportional to brain volume. Indeed, the scaling factor was estimated at 0.518 (95% CI [0.457, 0.578]), showing that large brains have a proportionally smaller

Table 2. Studies Included in Meta-analysis

Study	N_{ASD} (F)	N_{Ctrl} (F)	Age_{ASD}, Years	Age_{Ctrl}, Years	IQ_{ASD}	IQ_{Ctrl}	Regions of Interest
Hodge *et al.*, 2010 (30)	22 (0)	11 (0)	9.4 ± 2.0	10.4 ± 2.7	87 ± 22	114 ± 11	Cb, WM, GM, vermis, I–V, VI–VII, VIII–X
Scott *et al.*, 2009 (31)	48 (0)	14 (0)	12.4 ± 3.1	12.5 ± 3.1	79 ± 23	113 ± 12	Cb, vermis, I–V, VI–VII, VIII–X
Hallahan *et al.*, 2009 (32)	114 (18)	60 (7)	31.9 ± 10.1	32.0 ± 9.0	97 ± 18	114 ± 12	Cb
Webb *et al.*, 2009 (33)	45 (7)	26 (8)	3.9 ± 0.3	3.9 ± 0.5	59 ± 21	115 ± 15[a]	Cb, vermis, I–V, VI–VII, VIII–X
Langen *et al.*, 2009 (26)	99 (8)	89 (7)	12.9 ± 4.5	12.4 ± 4.8	108 ± 14	110 ± 13	Cb
Lahuis *et al.*, 2008 (34)	21 (0)	21 (0)	11.1 ± 2.2	10.4 ± 1.8	107 ± 14	103 ± 15	Cb
Cleavinger *et al.*, 2008 (35)	28 (0)	16 (0)	13.9 ± 5.3	13.9 ± 5.4	99 ± 18	102 ± 14	Cb, WM, GM, vermis, I–V, VI–VII, VIII–X
Catani *et al.*, 2008 (36)	15 (0)	16 (0)	31.0 ± 9.0	35.0 ± 11.0	109 ± 17	120 ± 21	Cb
Bloss and Courchesne, 2007 (37)	9 (9)	14 (14)	3.7 ± 0.9	3.8 ± 1.1	83 ± 18	119 ± 13	Cb, WM, GM
Hazlett *et al.*, 2005 (38)	51 (5)	14 (4)	2.7 ± 0.3	2.4 ± 0.4	54 ± 9	108 ± 19	Cb, WM, GM
Palmen *et al.*, 2004 (39)	21 (2)	21 (1)	20.1 ± 3.1	20.3 ± 2.2	115 ± 19	113 ± 10	Cb
Kates *et al.*, 2004 (40)	9 (1)	16 (2)	7.6 ± 2.4	8.3 ± 2.4	70 ± 19	124 ± 10	Cb, WM, GM
Akshoomoff *et al.*, 2004 (41)	52 (0)	15 (0)	3.8 ± 0.8	3.6 ± 1.1	82 ± 24	108 ± 18[b]	I–V, VI–VII
Herbert *et al.*, 2003 (42)	17 (0)	15 (0)	9.0[b] ± 1.4[b]	9.0[b] ± 1.4[b]	100 ± 15[c]	115 ± 15[a]	Cb
Kaufmann *et al.*, 2003 (43)	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 (44)	14 (2)	14 (4)	3.8 ± 1.1	4.4 ± 1.2	84 ± 24	110 ± 12	I–V, VI–VII
Courchesne *et al.*, 2001 (45)	60 (0)	52 (0)	6.2 ± 3.5	8.1 ± 3.5	79 ± 26	115[b] ± 15[b]	Cb, WM, GM
Hardan *et al.*, 2001 (46)	22 (0)[d]	22 (0)[d]	22.4 ± 10.1	22.4 ± 10.0	100 ± 15	100 ± 14	Vermis, I–V, VI–VII, VIII–X, Cb
Elia *et al.*, 2000 (47)	22 (0)	11 (0)	10.9 ± 4.0	10.9 ± 2.9	55 ± 10[e]	115 ± 15[a]	Vermis, VI–VII
Carper and Courchesne, 2000 (48)	42 (0)	29 (0)	5.4 ± 1.7	6.0 ± 1.8	80 ± 22	114 ± 12	VI–VII
Levitt *et al.*, 1999 (49)	8 (NR)	21 (NR)	12.5 ± 2.2	12.0 ± 2.8	83 ± 12	115 ± 11	VIII–X
Piven *et al.*, 1997 (50)	35 (9)	36 (16)	18.0 ± 4.5	20.2 ± 3.8	91 ± 20	102 ± 13	Cb
Ciesielski *et al.*, 1997 (51)	9 (4)	10 (3)	16.8 ± 5.2[b]	16.6 ± 5.4[b]	93[b] ± 13[b]	119[b] ± 10[b]	I–V, VI–VII
Hashimoto *et al.*, 1995 (52)	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 (53)	50 (9)	53 (10)	16.5 ± 11.6[b]	18.8 ± 10.4[b]	81[b] ± 31[b]	115 ± 15[a]	I–V, VI–VII
Piven *et al.*, 1992 (54)	15 (0)	15 (0)	27.7 ± 10.7	28.8 ± 5.6	92 ± 23	130 ± 0	I–V, VI–VII
Holttum *et al.*, 1992 (55)	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 (56)	12 (3)	12 (4)	27.2 ± 5.3	26.4 ± 3.6	95 ± 15[f]	115 ± 15[a]	Vermis, I–V, VI–VII
Kleiman *et al.*, 1992 (57)	13 (3)	17 (8)	7.7 ± 5.7	7.0 ± 4.3[b]	52 ± 17	115 ± 15[a]	I–V, VI–VII
Ritvo *et al.*, 1988 (58)	15 (4)	15 (4)	11.6 ± 4.1	11.6 ± 4.1	75 ± 15	115 ± 15[a]	Vermis, I–V, VI–VII

Age and IQ data are presented as mean ± SD. Regions of interest include volumes (Cb, WM, and GM) and midsagittal areas (whole vermis and its lobules numbered I–V, anterior; VI–VII, superior-posterior; and VIII–X, inferior-posterior).

ASD, patients with autism spectrum disorder; Cb, cerebellum; Ctrl, normal control subjects; F, female; GM, cerebellum gray matter; NR, not reported; WM, cerebellum white matter.

[a]IQ for normal control group supposed to be 115 ± 15.

[b]Mean and/or SD extrapolated from minimum and maximum.

[c]IQ for high-functioning autism group supposed to be 100 ± 15.

[d]Cerebellar volume was estimated for only 16 patients with ASD and 19 control subjects in Hardan *et al.* (46).

[e]IQ for low-functioning autism group supposed to be 55 ± 10.

[f]IQ for medium- to high-functioning autism group supposed to be 95 ± 15.

cerebellum (Figure 5). This replicates a recent result by Mankiw *et al.* (28). Because of this nonproportional relationship, the normalization of cerebellar volumes by total brain volume should not be used to control for group differences. Instead, we used 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 control subjects for total cerebellar volume and cerebellum gray matter volume. The effect of diagnosis group for the total cerebellar 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; estimated 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 control subjects. We did not find 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 gray matter volumes) did not reveal a statistically significant group effect. See Supplemental Table S3 for the results of the linear model with group as main effect and Supplemental Table S4 for the results

Table 3. Standardized Mean Difference: Combination of Effect Sizes

Region	Number of Studies	Random-Effects Model			Meta-regression		
		Effect Size (Cohen's *d*)	*p* Value	Heterogeneity (I^2)	Age Impact ($Year^{-1}$)	IQ Impact (IQ^{-1})	Residual Heterogeneity (I^2)
Meta-analysis of Literature							
Cerebellum	16	0.23 (0.00, 0.45)[a]	.049[a]	66% (42%, 80%)	−0.026 (−0.057, 0.005)	0.014 (−0.002, 0.030)	57%, p = .002[a]
White Matter	6	0.31 (0.07, 0.55)[a]	.011[a]	19% (0%, 64%)	−0.153 (−0.287, −0.019)[a]	0.042 (0.007, 0.077)[a]	0%, p = .943
Gray Matter	6	−0.22 (−0.47, 0.03)	.085	16% (0%, 79%)	0.152 (0.020, 0.284)[a]	−0.033 (−0.067, 0.002)	0%, p = .837
Whole vermis	11	−0.09 (−0.30, 0.13)	.416	21% (0%, 60%)	0.011 (−0.039, 0.062)	0.009 (−0.010, 0.029)	0%, p = .657
Lobules I–V	16	0.00 (−0.22, 0.23)	.971	54% (20%, 74%)[a]	−0.019 (−0.054, 0.016)	0.020 (0.003, 0.038)	29%, p = .061
Lobules VI–VII	18	−0.24 (−0.44, −0.03)[a]	.022[a]	50% (14%, 71%)[a]	0.009 (−0.024, 0.041)	0.010 (−0.006, 0.026)	36%, p = .039[a]
Lobules VIII–X	9	−0.20 (−0.50, 0.10)	.192	56% (8%, 79%)[a]	−0.043 (−0.167, 0.080)	0.008 (−0.038, 0.055)	65%, p = .013[a]
Meta-analysis of ABIDE							
Cerebellum	13	0.06 (−0.12, 0.24)	.532	33% (0%, 65%)	0.003 (−0.045, 0.052)	0.007 (−0.032, 0.046)	38%, p = .063
White Matter	13	0.01 (−0.15, 0.17)	.924	5% (0%, 59%)	−0.014 (−0.051, 0.023)	−0.003 (−0.033, 0.027)	0%, p = .296
Gray Matter	13	0.06 (−0.11, 0.23)	.497	31% (0%, 64%)	0.006 (−0.041, 0.053)	0.009 (−0.029, 0.047)	34%, p = .074

Values in parentheses represent 95% confidence intervals.
ABIDE, Autism Brain Imaging Data Exchange.
[a]$p < .05$.

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 the results of the direct fit of linear models. Despite a smaller number of subjects than in the meta-analysis of the literature (Supplemental Table S5), 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 control subjects: Cohen's d = 0.06, 95% CI (−0.12, 0.24). In the meta-regression, no significant effect was found for age (p = .888) or IQ (p = .726). Supplemental Table S5 describes the characteristics of the subjects selected for the preservation of age and sex matching between patients and control subjects. Figure 2B shows the forest plot of ABIDE sites combined with the random-effects model. The meta-analytical approach did not show any statistically significant difference in the variability of volume measures between patients and control subjects (log-variance ratio = 0.17, 95% CI [−0.18, 0.52]). The results of the ABIDE meta-analysis on standardized mean difference are summarized in Table 3, and Supplemental Table S6 summarizes the results of the ABIDE meta-analysis on log-variance ratio.

DISCUSSION

Neuroanatomical diversity appears to account for a substantial proportion of the risk for ASD (29). However, and even though several candidate neuroanatomical biomarkers have been proposed, it is not yet clear exactly which neuroanatomical traits 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 data from the ABIDE project.

The meta-analysis of the literature did not show conclusive evidence for a difference between patients with ASD and control subjects either for the total cerebellar volume or for its subregions. Total cerebellar volume and cerebellar white matter volume appeared slightly larger in ASD, whereas the area of vermal lobules VI–VII was found to be slightly smaller in ASD, but the significance of these results did not survive correction for multiple comparisons. Compared with a previous meta-analysis on total cerebellar volume and vermal areas (25), the effect sizes we computed were all smaller in absolute value. Specifically, Stanfield *et al.* (25) reported a significant difference in the volume of 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 studies without statistically significant results. This is

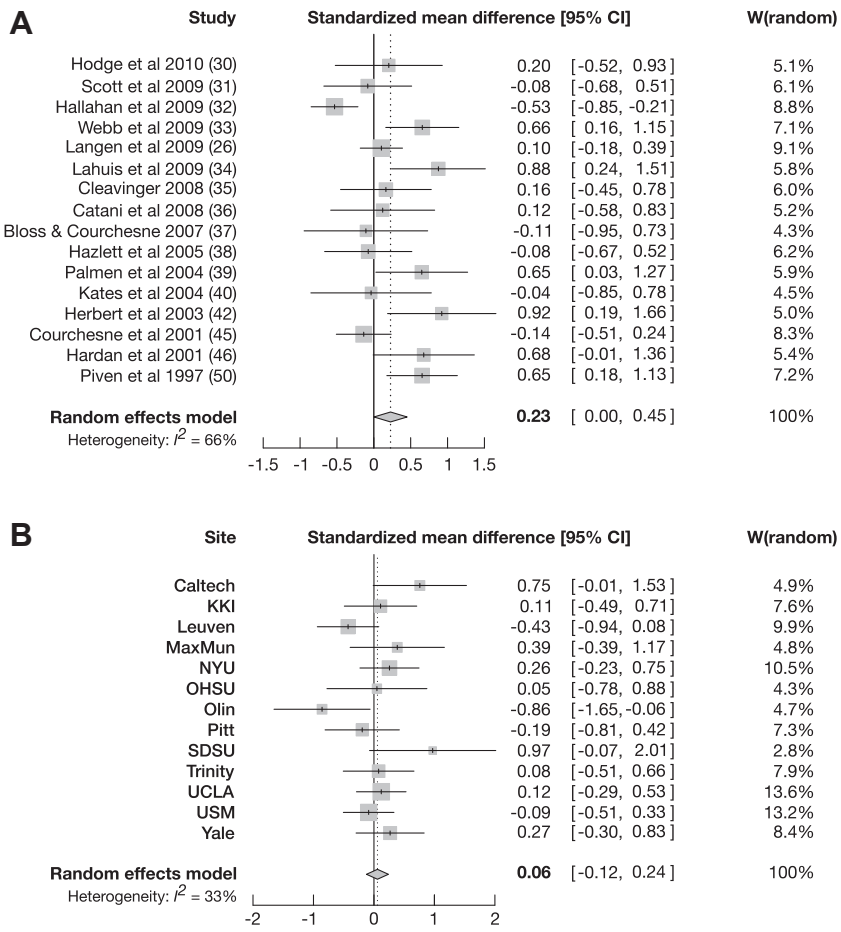

Figure 2. Forest plots for the cerebellar volume. For each study, the gray square is centered on the estimated standardized mean difference, the black segment illustrates the 95% confidence interval (CI), and the surface of the square is proportional to the number of subjects in the study. Standardized mean difference is positive when the cerebellar volume is greater in autism spectrum disorder. W(random) represents the weight given to each study for the combination of effect sizes. **(A)** Meta-analysis of the literature. Heterogeneity: $I^2 = 65.9\%$, $\tau^2 = 0.1235$, $p = .0001$. **(B)** Meta-analysis of ABIDE (Autism Brain Imaging Data Exchange) sites. Heterogeneity: $I^2 = 32.6\%$, $\tau^2 = 0.0192$, $p = .1219$.

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 in our meta-analysis was not cerebellar volume, which should decrease the likelihood of bias. We studied publication bias by analyzing 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 (uncorrected). Whereas this result suggests the presence of publication bias, it could also be due to greater interstudy 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).

We aimed at testing for *p*-hacking by analyzing the *p* curves: the distribution of *p* values $< .05$. The numbers of significant *p* values reported, however, were not sufficient to

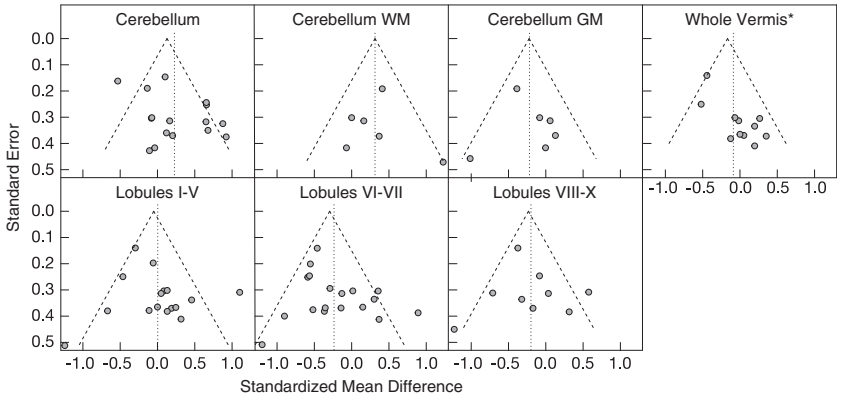

Figure 3. Funnel plots for the different cerebellar regions. The dotted line represents the meta-analytic effect size, whereas the two dashed lines represent the boundaries of the 95% confidence interval for effect combined with the fixed effect model. *statistically significant asymmetry of the funnel plot ($p = .002$). GM, gray matter; WM, white matter.

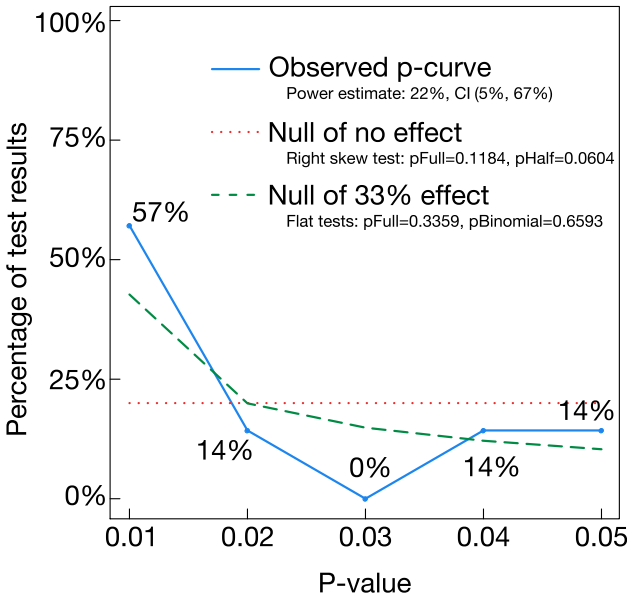

Figure 4. *p* curve of studies with a significant result for the cerebellar volume. Note the observed *p* curve includes seven studies with statistically significant results ($p < .05$). Among them, five had $p < .025$. Eight additional studies were excluded from the *p* curve analysis because their results did not pass significance ($p > .05$). Null of, expected *p* curve in case of.

draw a definite conclusion. In the case of the total cerebellar volume, where seven of 16 articles reported statistically significant findings, *p* curve analysis did not reveal evidence for *p*-hacking. Overall, the analysis of the literature alone did 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, even compared with the multisite data from the ABIDE project. For cerebellar volume, *p* value for heterogeneity was .0001, which would remain

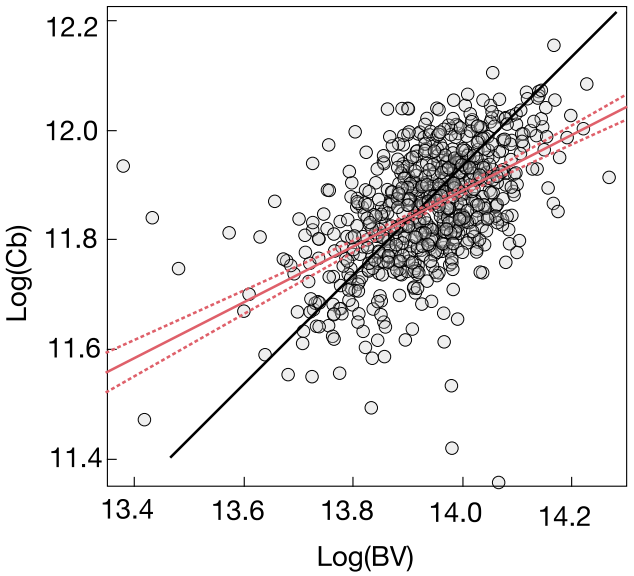

Figure 5. Log of cerebellar volume (Cb) vs. log of total brain volume (BV).

significant even after correction for multiple testing. A certain degree of variability in the estimations of volume is expected, especially given 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 four of the seven meta-analyzed regions (i.e., total cerebellar volume, lobules I–V, lobules VI–VII, and lobules VIII–IX) (Table 3). Heterogeneity may be due to a combination of technical and physiological causes; for example, differences in MRI equipment, acquisition sequences, and segmentation protocol as well as the age of the subjects, IQ distribution, and so forth. We analyzed the effect of two 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 control subjects. Second, residual heterogeneity was still statistically significant for three of the seven regions studied (total cerebellar volume, lobules VI–VII, and lobules VIII–IX). This indicates that sources other than age and IQ level may be causing significant heterogeneity in the literature.

The ABIDE project data provide 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 thus should be of similar characteristics as those in our literature meta-analysis. However, because the raw MRI and behavioral data are available, there is no issue of publication bias or *p*-hacking having an effect on cohort selection. Additionally, the availability of raw data makes it possible to run methodologically homogeneous analyses: same segmentation protocol, quality control procedures, and statistical analyses. There still remain, of course, many additional sources of heterogeneity owing to the grassroots nature of the project (some of them being currently addressed in ABIDE II through an important harmonization 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 same dataset.

We analyzed 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 (two-sided *t* test, $\alpha = .05$). We did not find any statistically significant effect of ASD diagnosis on mean volumes. 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 artifact. 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 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.

Interestingly, and although the site effect was substantial, the estimations from the ABIDE data were more precise than

the estimations from the literature (tighter confidence intervals) and less heterogeneous. One reason for the lack of power in the literature (in addition to the small sample sizes) could be 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. Toward 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, either in the literature or in the ABIDE cohort, for a difference in cerebellar volume between patients with ASD and control subjects. This result does not rule out possible involvement of the cerebellum in the etiology of ASD. In particular, ABIDE includes only subjects without intellectual disability, and a difference could still appear in a population with a wider IQ range (although the meta-analysis of the literature did not suggest such a link). Also, it is possible that some other measurement of cerebellar anatomy, more sophisticated than mere volume measurements, may be linked to autism in the 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 structure. We reached a similar conclusion after analyzing the corpus callosum (21), another structure that had traditionally captured the attention of the research community. Based on these experiences, we can advocate only 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 that prevent researchers from benefiting from the work of each other.

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