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ORIGINAL ARTICLE

# Cerebellar volume and cerebellocerebral structural covariance in schizophrenia: a multisite mega-analysis of 983 patients and 1349 healthy controls

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Although cerebellar involvement across a wide range of cognitive and neuropsychiatric phenotypes is increasingly being recognized, previous large-scale studies in schizophrenia (SZ) have primarily focused on supratentorial structures. Hence, the across-sample reproducibility, regional distribution, associations with cerebrocortical morphology and effect sizes of cerebellar relative to cerebral morphological differences in SZ are unknown. We addressed these questions in 983 patients with SZ spectrum disorders and 1349 healthy controls (HCs) from 14 international samples, using state-of-the-art image analysis pipelines optimized for both the cerebellum and the cerebrum. Results showed that total cerebellar grey matter volume was robustly reduced in SZ relative to HCs (Cohens's $d = -0.35$), with the strongest effects in cerebellar regions showing functional connectivity with frontoparietal cortices ($d = -0.40$). Effect sizes for cerebellar volumes were similar to the most consistently reported cerebral structural changes in SZ (e.g., hippocampus volume and frontotemporal cortical thickness), and were highly consistent across samples. Within groups, we further observed positive correlations between cerebellar volume and cerebral cortical thickness in frontotemporal regions (i.e., overlapping with areas that also showed reductions in SZ). This cerebellocerebral structural covariance was strongest in SZ, suggesting common underlying disease processes jointly affecting the cerebellum and the cerebrum. Finally, cerebellar volume reduction in SZ was highly consistent across the included age span (16–66 years) and present already in the youngest patients, a finding that is more consistent with neurodevelopmental than neurodegenerative etiology. Taken together, these novel findings establish the cerebellum as a key node in the distributed brain networks underlying SZ.

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## INTRODUCTION

In parallel with emerging evidence documenting cerebellar involvement in complex mental operations, including cognitive[1,2] and emotional[3] functions, it has been proposed that the cerebellum also has an important part in the pathophysiology of schizophrenia (SZ).[4,5] According to this theory, and consistent with the wide range of clinical symptoms and signs seen in this disorder,[6] cerebellar dysfunction manifest clinically as poor coordination, or dysmetria, across both motor and cognitive domains.[5] Indeed, many of the most consistent sensorimotor deficits (or neurological soft signs[7,8]) in SZ, such as increased postural sway,[9–11] are strongly suggestive of cerebellar dysfunction.[9,10] In line with such clinical observations, performance on experimental tasks known to critically rely on cerebellar circuitry—such as classical conditioning of the eye-blink reflex[12]—has repeatedly been found to be impaired in both chronic[13] and first-episode unmedicated[14,15] SZ patients, as well as in their first-degree relatives.[16] Moreover, the growing evidence for cerebellar involvement beyond motor control[1,3] is consistent with the notion that cerebellar dysfunction may also underlie the core psychotic symptoms and cognitive deficits seen in SZ.[5]

Functional imaging studies add further evidence for cerebellar dysfunction and disrupted cerebrocerebellar connectivity in SZ (e.g., Whalley *et al.*[17]). Of particular note, several recent resting-state functional magnetic resonance imaging (fMRI) studies have independently replicated robust disruptions of cerebellothalamo-frontal functional connectivity in psychotic disorders[18–24] as well as in youth at high risk.[25,26] Indeed, one study reported that the most informative feature for distinguishing between cases and controls was the degree of cerebellar–prefrontal connectivity.[20]

In contrast, evidence from the structural imaging literature is more mixed.[27–30] While several studies have reported cerebellar

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structural differences in SZ,[31–39] including the largest multicenter study to date,[40] other studies report negative results.[41–45] Moreover, neither the specific cerebellar regions showing significant group differences nor the direction of the effects (decreases or increases) are consistent across studies (e.g., Levitt *et al*.[46]). These inconsistencies are likely partly due to methodological limitations, as most advanced analysis methods for structural brain imaging data are optimized for the cerebrum, not the cerebellum. One consequence is that while large collaborative studies have tested the robustness of other structural imaging phenotypes in severe mental disorders,[47,48] no similar studies exist for the cerebellum. Hence, the across-sample reproducibility, the regional specificity within the cerebellum, the relative effect sizes compared with other brain structures, associations between cerebellar and cerebral morphological features, and the clinical correlates of cerebellar structural differences in SZ remain largely unknown.

We addressed these questions using state-of-the-art analysis pipelines optimized for both the cerebellum and the cerebrum in a large multisite sample of 983 patients with SZ spectrum disorders and 1349 healthy controls (HCs). In contrast to previous reviews[27,29] and meta-analyses,[28,30] all included samples were processed in-house using identical analysis pipelines and quality control procedures, thus minimizing methodology-related heterogeneity. Our approach also allowed for comparison and ranking of effect sizes across cerebellar and cerebral features, as well as mapping of structural covariance[49] between the cerebellum and the cerebrum. We finally explored associations with available demographic and clinical data, and tested for possible confounding variables, such as MR image quality and harmful alcohol consumption.[35]

Based on findings from the largest meta-analysis of brain volumes in SZ to date,[28] we hypothesized that total cerebellar volume would be reduced in patients relative to controls, but remained agnostic regarding both the regional distribution and the relative effect size of cerebellar versus cerebral differences in SZ. Further, based on recent evidence for disorder-specific increases in cerebellocerebral structural covariance in neurodegenerative disorders,[50] we hypothesized a stronger association between cerebellar and cerebral anatomical features in SZ compared with HCs, reflecting the underlying disease processes jointly affecting closely integrated brain regions. Finally, as cerebellar functional deficits have been reported in first-episode SZ[15] and high-risk[25] samples, we expected to find cerebellar volume reductions already in the youngest patients, consistent with a neurodevelopmental etiology.

## MATERIALS AND METHODS

### Participants

Supplementary Note 1 describes participant inclusion and MR image quality control procedures, whereas demographic information for all included participants is given in Supplementary Table S1. Briefly, we combined T1-weighted MRIs from 14 different cohorts, including seven samples in the IMAGEMEND consortium (http://www.imagemend.eu/) and seven freely available data sets from OpenfMRI[51] (http: //openfmri.org) and SchizConnect[52] (http: //chizconnect.org), yielding a final data set of 983 patients and 1349 controls after quality control. Mean age (HCs = 33.6 years, s.d. = 10.0, range: 16–66; SZ: 33.3 years, s.d.: 10.4, range: 16–65) did not differ significantly between groups ($t = 0.715$, $P = 0.48$). Control and patient samples comprised on average 59% and 67% males, respectively, with a larger proportion of males in the SZ than in the HC group ($\chi^2 = 13.88$, $P = 1.95^{e-4}$). Information on handedness was available from 12 samples, and did not indicate any significant group differences (percent right-handed: HCs = 91.3, SZ = 89.7, $\chi^2 = 1.56^{e-4}$, $P = 0.99$). As expected, mean IQ estimates (available from seven samples) were significantly lower in SZ (96.8) than in HCs (111.3; $t = 15.181$, $P = 1.2^{e-44}$). Data on harmful alcohol consumption, a potential confound in studies of cerebellar volume,[35] was available from five samples and revealed a higher incidence in SZ (36.3%) than in HCs (19.8%, $\chi^2 = 43.875$, $P = 3.5^{e-11}$).

Clinical information for all included patients is summarized in Supplementary Table S2. Positive and Negative Syndrome Scale scores for positive and negative symptoms were available for eight samples, and in five samples we estimated these scores from Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptom scores using a validated conversion equation.[53] Mean Positive and Negative Syndrome Scale positive score was 15.3 (s.d.: 5.0), whereas the mean Positive and Negative Syndrome Scale negative score was 15.9 (s.d.: 6.0). Nine samples had information on age at illness-onset (mean: 23.2 years) and duration of illness (mean: 12.4 years). Each study sample was collected with participants' written informed consent approved by local Institutional Review Boards.

### MRI acquisition and preprocessing

Please see Supplementary Table S3 for specific technical details concerning scanners and acquisition parameters. T1-weighted MRI volumes were analyzed using a dual processing steam, respectively, optimized for the cerebrum and the cerebellum. FreeSurfer v.5.3 (http://surfer.nmr.mgh.harvard.edu) was used to derive anatomical segmentations of cortical[54] and subcortical structures[55] of the cerebrum, estimates of total intracranial volume (eTIV[56]), an index of white matter signal-to-noise ratio and surface maps of vertex-wise cortical thickness.[57] We chose cortical thickness as the cerebrocortical structural index based on recommendations in the imaging literature.[58] However, as volumetric indices could in theory be more sensitive to group differences (being products of both cortical thickness and surface area), we compared effect sizes based on thickness and volume indices in *post hoc* control analyses (see Supplementary Note 2). To limit the number of tested variables, we computed the mean across left and right hemisphere cerebral regions of interest (ROIs), resulting in 34 bilateral cerebral measures of regional cortical thickness (based on the Desikan-Killiany Atlas[54]) and eight bilateral subcortical volumes (thalamus, hippocampus, amygdala, pallidum, putamen, nucleus caudatus, nucleus accumbens, lateral ventricles). *Post hoc* control analyses evaluated the validity of this approach by comparing effect sizes between left and right ROIs. Cortical thickness maps were smoothed with a two-dimensional Gaussian kernel of 15 mm full-width at half-maximum before being subjected to analyses.

The cerebellum-optimized analysis pipeline was performed with the SUIT toolbox[59] (see Supplementary Note 3). In brief, SUIT isolates the cerebellum and brainstem, segments images into grey matter maps and normalizes these maps to a cerebellar template, ensuring superior cerebellar alignment across subjects compared with whole-brain procedures.[59] Normalized cerebellar grey matter maps were modulated by the Jacobian of the transformation matrix to preserve absolute grey matter volume. We extracted the summed modulated grey matter value (i.e., a measure of regional volume) for 28 cerebellar lobules defined in the probabilistic SUIT Atlas,[59] and computed total cerebellar grey matter volume by summing these indices. Further, as the functional anatomy of the cerebellum does not strictly correspond to this gross anatomical parcellation,[60] we also extracted grey matter volume from seven functionally defined ROIs from a large-scale fMRI study of cerebrocerebellar functional connectivity.[60] Finally, the modulated gray matter (GM) maps were smoothed with a three-dimensional 4 mm full-width at half-maximum Gaussian kernel before being subjected to voxel-wise analyses.

### Meta-analysis of ROI measures

See Supplementary Figure S1 for histograms depicting the distributions of all analyzed cerebellar and cerebral ROI measures across the 14 samples and 2332 included subjects. Group differences for all ROI measures were examined using univariate linear regression analysis (R's linear model function *lm*) within each sample. The main analyses included group (HCs, SZ) and sex (male, female) as fixed factors and age as a covariate, with eTIV added as an additional covariate in the analyses of volumetric measures. For each sample, Cohen's *d* effect sizes for each ROI were computed based on the group contrast t-statistics.[61] Pooled effect size estimates, as well as indices of sample heterogeneity (the $I^2$ statistic[62]), were computed across samples using the r-package *metafor*.[63] See Supplementary Note 4 for details on the meta-analytical framework and computed statistics, and Supplementary Note 5 for descriptions of control analyses testing for possible confounding effects of MRI data quality and harmful alcohol consumption. Alpha-levels ($P < 0.05$, two-tailed) were adjusted for the total number (78) of tested ROIs using Bonferroni correction, yielding a corrected critical *P*-value $< 0.00064$.

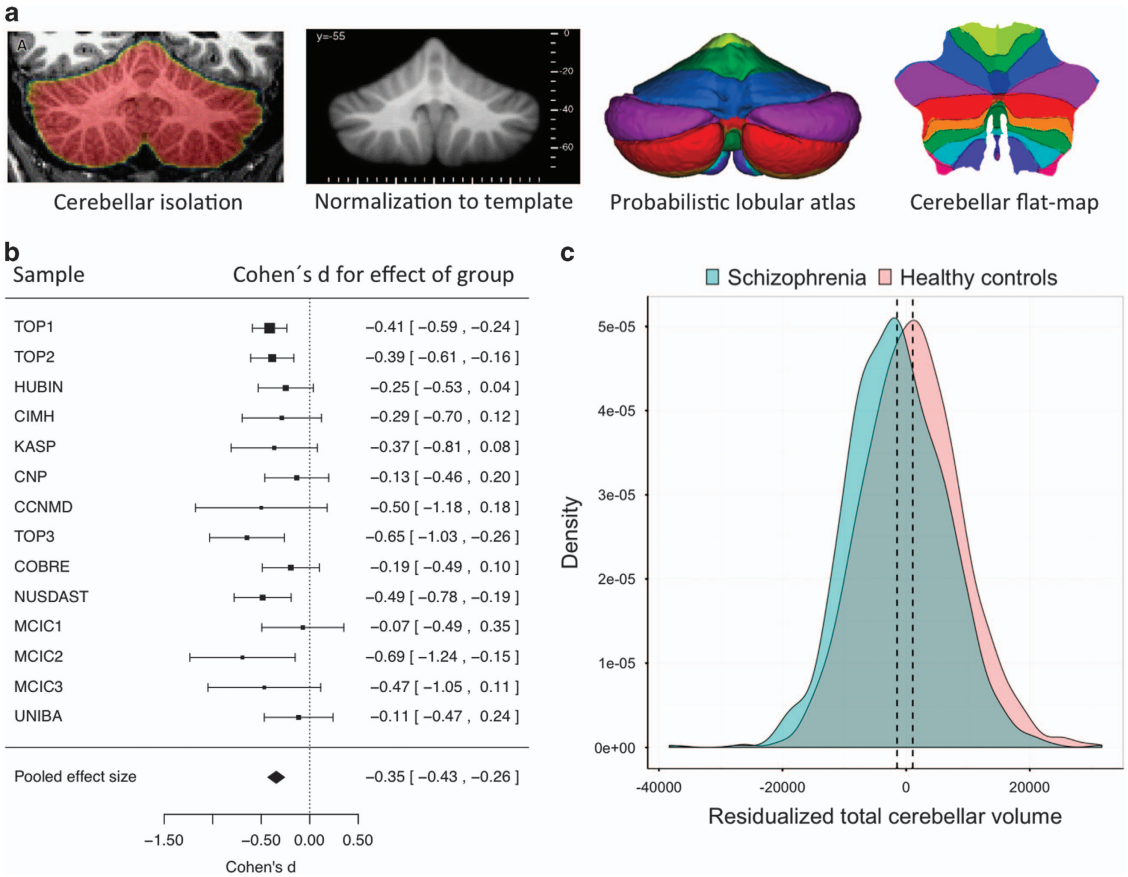


**Figure 1.** Total cerebellar gray matter volume is robustly reduced in schizophrenia (SZ). (**a**) Cartoon depicting the SUIT pipeline:[59] (1) cerebellar isolation, (2) normalization to a detailed cerebellar template, (3) assigment of lobular labels and (4) projection of cerebellar grey matter onto a flat-map of the cerebellar surface.[77] Total cerbellar volume was computed by summing all lobular grey matter volumes. (**b**) Forest plot showing effect sizes (Cohen's *d*) of the group effect (healthy controls (HCs) vs SZ) on total cerebellar volume across the 14 included samples. (**c**) Density plots showing the distribution of residualized total cerebellar volumes in SZ and HCs (after regressing out effect of sample, age and sex). Dotted lines represent the means of each group. Figure **a** is adapted with permission from Diedrichsen 2006[59] and Diedrichsen and Sotov 2015.[77]

### Voxel-wise mega-analysis of group differences in cerebellar grey matter volume

Voxel-wise analyses were performed on the full set (983 SZ, 1349 HCs) of QC'ed SUIT-normalized, modulated and smoothed grey matter maps using nonparametric permutation testing as implemented in FSL randomize.[64] Voxels were included if they overlapped both (1) the probabilistic cerebellar grey matter ROIs in SUIT and (2) a mask created by thresholding the mean of the normalized (unmodulated and unsmoothed) grey matter maps at 0.1. We tested for main effects of group while including sex, estimated total intracranial volume, age and sample as covariates in a general linear model (see Supplementary Note 6 for model specification). Five thousand permutations were performed for each contrast and voxels surviving a conservative voxel-wise family-wise error-corrected statistical threshold of $P < 0.05$ (two-tailed, permutation-based) were considered significant.

### Vertex-wise mega-analysis of cerebellocerebral structural covariance

To assess group differences in cortical thickness and to identify patterns of covarying cerebellar and cerebral morphological changes in SZ, we first tested for group differences in cortical thickness (see Supplementary Note 6 for model specification). Next, we tested for associations between cerebellar volume and cortical thickness within each group. For these analyses, we selected the cerebellar functional ROI showing the strongest effect of group (HCs vs SZ) and residualized this measure with respect to age, sex, sample and eTIV. Residualized cerebellar ROI volumes were then entered together with age, sex and sample in a general linear model predicting vertex-wise cortical thickness within each group (see Supplementary Note 6 for model specification). For group comparisons and cerebrocerebellar association analyses, we used nonparametric statistical testing using PALM,[65] with 5000 permutations for each contrast. Vertices surviving a conservative vertex-wise family-wise error-corrected statistical threshold of $P < 0.05$ (two-tailed, permutation-based) were considered significant. We finally quantified the similarity between (uncorrected) t-maps representing (1) case–control differences in cortical thickness and (2) associations between cerebellar volume and cortical thickness within each group, by computing their spatial (i.e., across all vertices) Pearson's correlation coefficients.

### Associations with demographic and clinical variables

For total cerebellar GM and functionally defined ROI[60] volumes, we used general linear models to test for associations with age and estimated IQ within HCs and SZ. Within SZ we also tested for associations with positive and negative symptom scores and medication status (unmedicated, typical, atypical or both typical and atypical antipsychotic medication). In addition to the demographic/clinical variable of interest, these analyses included sample and sex (male, female) as fixed factors and eTIV and age (except for in the analyses targeting this feature) as covariates. The α-level ($P < 0.05$, two-tailed) was adjusted for the 40 conducted tests (eight cerebellar features × five demographic/clinical indices) using Bonferroni correction (corrected critical *P*-value = $1.25^{e-3}$), but we also report uncorrected values. We finally explored the age dependence of any group effects (HCs vs SZ) by computing *t*-tests on total and regional cerebellar volumes (after regressing out effects of sex, sample and eTIV) in sliding windows (each including 500 participants) covering the age range between 16 and 66 in steps of 100 participants.

## RESULTS

### Total and lobule-wise cerebellar grey matter volume

Results from the meta-analysis of total cerebellar grey matter volume are given in Figure 1. We observed a highly significant ($P = 2.7^{e-15}$) pooled effect size (Cohen's *d*) of −0.35, indicating reduced total cerebellar grey matter volume in SZ relative to HCs. Notably, the heterogeneity across the 14 samples was low ($I^2$ statistic = 0%).

Relative to HCs, patients showed significantly reduced grey matter volume in 17 out of 28 lobules (see Supplementary Figure 2).

As expected, our index of MR image quality (white matter signal-to-noise ratio, white matter signal-to-noise ratio) was lower in SZ relative to HCs (pooled Cohen's $d = -0.14$, $P < 0.005$). Further, in the five samples with this information, we observed a higher incidence of harmful alcohol consumption in SZ than in HCs (36.3% versus 19.8%, Pearson's $\chi^2 = 43.9$, $P = 3.5^{e-11}$). Crucially, however, including white matter signal-to-noise ratio as an additional covariate in the models or restricting the analyses to participants without evidence of harmful alcohol consumption only increased the group effects (see Supplementary Note 7 for further details).

### Volumes of functionally defined cerebellar ROIs

Ranked effect sizes across the seven functionally defined cerebellar ROIs[60] are displayed in Figure 2.

Patients showed significantly reduced grey matter volume in five ROIs, with the largest effect sizes for the cerebellar nodes of the frontoparietal (Cohen's $d = -0.40$) and default mode (Cohen's $d = -0.33$) networks. Heterogeneity across samples was low, with the $I^2$ statistic ranging from 0 to 4.85%. Including SNR as a covariate, or restricting analyses to participants without alcohol abuse, did not reduce the group effects (see Supplementary Note 7 and Supplementary Figure 4).

### Ranked effect sizes across cerebellar and cerebral ROIs

Figure 3 displays ranked effect sizes and heterogeneity indices across cerebellar, subcortical and cortical ROIs.

Compared with HCs, patients with SZ showed significant volume or cortical thickness reductions in 30 ROIs (Cohen's *d* ranging from −0.15 to −0.41; mean: −0.31), and significant volume increases for the basal ganglia and lateral ventricles (Cohen's *d* ranging from 0.23 to 0.47; mean: 0.31). Across all 50 included brain morphology indices, total cerebellar GM volume ranked as the ninth strongest, whereas the regional volume of cerebellar functional ROI6 (frontoparietal network) ranked as the second strongest negative effect size (after mean hippocampus volume). *Post hoc* control analyses of cerebrocortical ROI volumes overall yielded somewhat weaker group effects than ROI mean cortical thickness (see Supplementary Note 8 and Supplementary Figure 5), and we observed no consistent differences in the magnitude of effect sizes between left and right hemisphere ROIs (see Supplementary Figure 6), justifying our *a priori* choice of cortical thickness averaged over left and right ROIs as sensitive indices of cerebral changes in SZ.

### Voxel-based mega-analysis of cerebellar grey matter volume

Results from the voxel-based analyses are given in Figure 4a, Supplementary Figure 7 and Supplementary Table 4. Confirming the ROI-based analyses, group effects (HC > SZ) were most pronounced in posterior cerebellar regions. The opposite contrast (SZ > HC) yielded one small cluster (27 voxels) located in right lobule VIIIb, and four smaller clusters (5 voxels or less) bilaterally in the superior cerebellar peduncles and in right Crus II.

### Cerebrocortical group differences and cerebellocerebral structural covariance

Confirming previous reports,[66] permutation testing revealed widespread significant group differences in cerebral cortical thickness, with the strongest reductions in SZ in frontotemporal regions (Figure 4b). Figures 4c and d show the associations between regional cerebellar volume (ROI6) and cortical thickness, revealing significant positive cerebellocerebral structural covariation in frontotemporal areas, in particular in patients (Figure 4c). The spatial Pearson's correlations between uncorrected t-maps (see Supplementary Figure 8) for the (1) case–control comparison

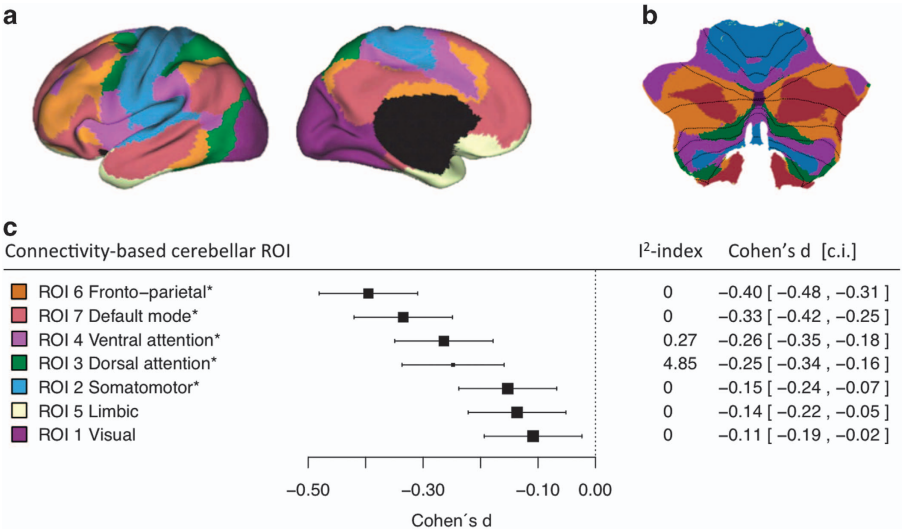


**Figure 2.** Cerebellar grey matter reductions in schizophrenia (SZ) are most prominent in regions that show functional connectivity with associative regions of the cerebral cortex. (**a**) Seven color-coded cerebrocortical functional connectivity networks based on resting-state functional magnetic resonance imaging (fMRI) data from 1000 subjects.[78] (**b**) Cerebellar regions showing functional connectivity with the seven cerebrocortical networks in the same 1000 subjects[60] displayed on a flat-map representation of the cerebellar cortex.[77] (**c**) Forest plot displaying ranked effect sizes, $I^2$ indices and confidence intervals (c.i.) for the difference between healthy controls and SZ across the seven cerebellar networks shown in (**b**). Asterisks mark significant effects at a Bonferroni-corrected threshold of $P < 0.00064$ (0.05/78). ROI, regions of interest. Figure **a** is adapted with permission from Buckner 2013.[1] Figure **b** is adapted with permission from Diedrichsen and Sotov 2015.[77]

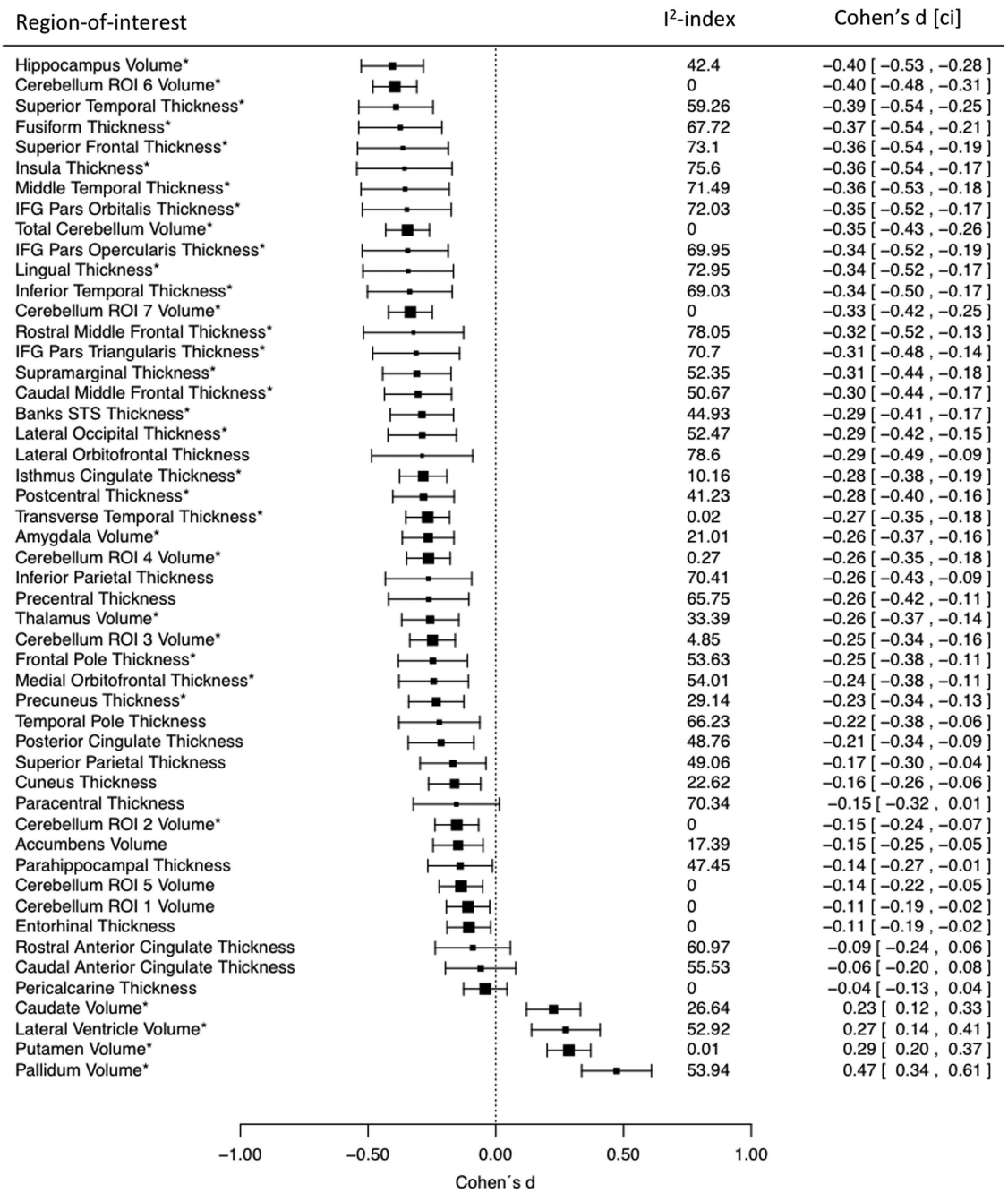


**Figure 3.** Cerebellar effect sizes are comparable in magnitude to the most consistently reported cerebrocortical and subcortical brain alterations in schizophrenia (SZ). The forest plot displays ranked pooled effect sizes (healthy control (HC) > SZ) and heterogeneity indices ($I^2$) for 34 (bilateral) cerebrocortical regions of interest (ROI) measures of cortical thickness, 8 subcortical volumes, total cerebellar volume and the volume of 7 cerebellar ROIs. ci, Confidence intervals. Asterisks mark significant effects at a Bonferroni-corrected threshold of $P < 0.00064$ (0.05/78).

and (2) the within-group cerebellar volume associations was 0.57 in SZ and 0.38 in HCs (Figures 4e–f), indicating considerable overlap between the effects of group (HC > SZ) and cerebellar volume on cortical thickness.

### Associations with demographic and clinical variables

See Supplementary Note 9 for more detailed description of these results. In brief, total and regional cerebellar volumes showed robust negative associations with age in both groups. In SZ, we also observed nominally significant ($P < 0.05$, uncorrected) positive associations between estimated IQ and total cerebellar volume, ROI2, ROI6 and ROI7, whereas ROI3 showed a nominally significant positive association with estimated IQ in HCs. No associations were observed with the severity of positive or negative symptoms or medication status in SZ (all uncorrected *P*-values > 0.134).

Notably, for the ROI showing the strongest effect of group (ROI6), estimated age curves for patients and controls were highly parallel (Figure 5a), with sliding-window *t*-tests revealing consistent effects of diagnosis across the age range (Figure 5b and see Supplementary Figure 9 for the remaining tested ROIs).

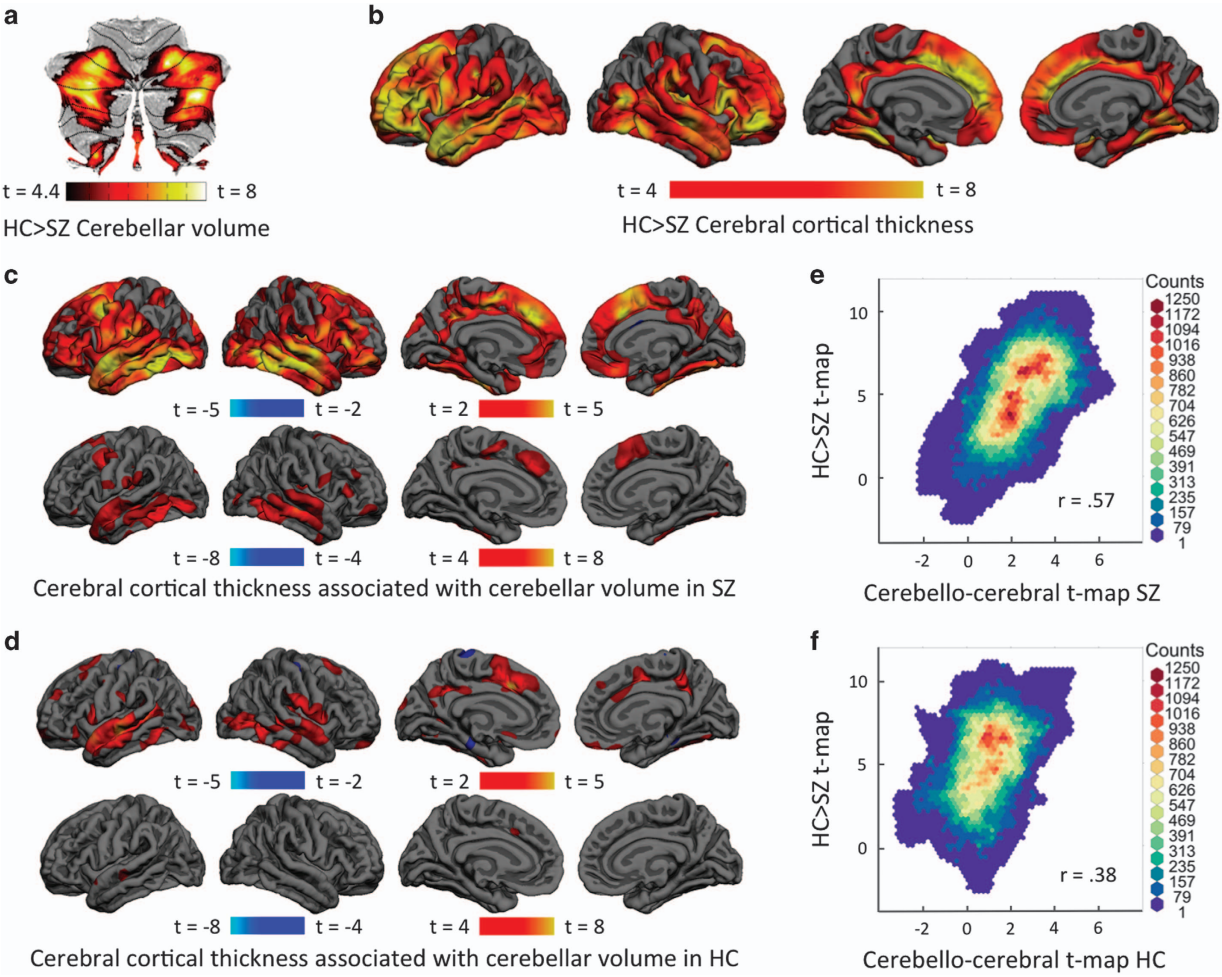


**Figure 4.** Voxel- and vertex-wise mega-analyses reveal regional patterns of (**a**) cerebellar and (**b**) cerebral structural changes, as well as (**c–f**) cerebellocerebral structural covariation in schizophrenia (SZ). (**a**) Cerebellar grey matter reductions in SZ; (**b**) cortical thickness reductions in SZ; (**c** and **d**) regions of cortical thickness associated with regional cerebellar volume (regions of interest (ROI) 6) in SZ and healthy controls (HCs). Top rows display t-maps ranging from 2 to 5, whereas the bottom row displays regions surviving vertex-wise family-wise error (FWE) correction ($P < 0.05$, two-tailed). (**e** and **f**) Color-coded scatter plots showing the spatial correlations (across all 299 881 cortical vertices) between the group difference map (**a**) and the cerebellocerebral associations in SZ (**c** and **e**) and HCs (**d** and **f**).

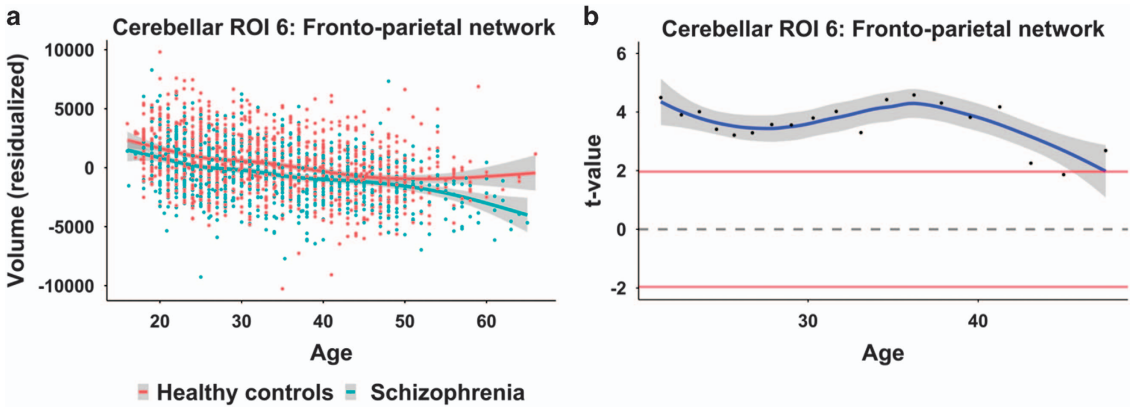


**Figure 5.** Cerebellar volume reductions in schizophrenia (SZ) are consistent across the age range. (**a**) Mean residualized volumes of cerebellar regions of interest (ROI) 6 (after correcting for effects of estimates of total intracranial volume (eTIV), sex and sample) plotted against age for healthy controls (HCs) and SZ. (**b**) Results from a sliding windows *t*-test (each including 500 participants) covering the age range between 16 and 66 in steps of 100 participants. The position of each dot on the x axis denotes the mean age of the respective sliding-window subsample and *t*-values are plotted on the y axis. The red horizontal lines denote critical *t*-values for $P < 0.05$ (two-tailed).

## DISCUSSION

The current large-scale international multisite effort analyzing data from over 2300 participants yielded three main findings. First, compared with HCs, cerebellar grey matter volume was robustly reduced in patients with SZ, with the strongest effects seen in cerebellar regions associated with higher-level cognitive functions. Effect sizes were comparable in magnitude to the most consistently reported cerebral alterations in SZ and showed low heterogeneity across the 14 samples. Second, we document robust positive correlations between regional cerebellar grey matter volume and cerebral cortical thickness. This association was more pronounced in patients than in controls, and primarily involved frontotemporal regions, that is, highly overlapping with the case–control difference maps. Third, we found that the cerebellar volume reduction in SZ was highly consistent across age, and present already in the youngest patients. In combination, these results provide robust empirical support for the classical hypothesis of cerebellar involvement in SZ pathophysiology,[4,5] and further provide novel evidence suggesting coordinated cerebellar and cerebral changes and a neurodevelopmental etiology for the cerebellar structural alterations seen in SZ.

Combining data from 983 SZ patients and 1349 HCs across 14 sites allowed us to both calculate robust pooled estimates of effect size and assess the variability across sites. For total cerebellar GM volume, the pooled effect size across all samples (Cohen's $d = -0.35$) was highly significant ($P = 2.7^{e-15}$) and the $I^2$-statistic (0%) indicated low heterogeneity across samples. In line with previously reported supratentorial effects (e.g., Rimol *et al*.[66] and Shah *et al*.[67]), our ROI and voxel-wise analyses further revealed that cerebellar grey matter reductions in SZ show a regional pattern of preferential affectedness. Notably, the largest group effects were seen in posterior cerebellar regions, which are associated with high-level cognitive function[68] and show functional connectivity with associative regions of the cerebral cortex (e.g., frontoparietal and default mode networks[60]). Conversely, markedly smaller—but still significant—differences between SZ and HCs were observed in anterior cerebellar regions more strongly linked to motor function.[60,68]

Importantly, the magnitude of cerebellar effect sizes were comparable to or larger than several previous findings in large-scale studies of SZ brain morphometry,[47] such as decreased hippocampal volumes and enlarged basal ganglia and ventricle volumes.[47] Note also that analyses of these cerebral anatomical features in the current sample yielded considerably larger $I^2$ indices (mean: 42.4%) than analyses of cerebellar features (mean: 0.27%), indicating more pronounced heterogeneity across samples. While it must be emphasized that the magnitude of all consistently reported MRI-based structural brain differences in SZ are relatively modest (Cohen's $d < 1$),[69] the cerebellum thus appears to be among the brain areas showing the strongest and most consistent differences in SZ.

Our cerebrocerebellar structural covariance analyses were partly motivated by recent reports of network-specific cerebrocerebellar correlations of GM atrophy in neurodegenerative disorders[50] and disrupted supratentorial development following focal cerebellar lesions in childhood.[70–72] Taken together, these findings suggest that cerebellar and cerebral regions are linked through developmental and/or pathological processes.[49] The current findings of significant associations between cerebellar volume and cerebral cortical thickness are in line with such a coordinated network perspective, and the stronger associations in patients suggest that SZ jointly affects the cerebellum and the cerebrum. Indeed, such correlated structural perturbations may reflect common causal factors,[49,73] and further research efforts targeting the genetic and environmental impact on cerebellar structure and cerebellocerebral structural covariance may thus provide new leads towards a more comprehensive understanding of the complex SZ pathophysiology.

The estimated group difference in cerebellar GM volume was remarkably stationary across an age range from 16 to 66 years, indicating that cerebellar volume reductions are present already at disease onset, and does not show evidence of progressive deterioration with increasing age and duration of disease. Thus, our cerebellar findings fit better with a neurodevelopmental[74] than with a neurodegenerative account[75] of SZ, and highlight the need for future studies of cerebellar development in younger cohorts of high-risk populations. Based on the current results, we hypothesize that cerebellar volume, especially in posterior regions, will emerge as a predictor (rather than a consequence) of developing SZ.

Notable strengths of the current study include the large sample size of 983 SZ patients and 1349 HCs, identical in-house analysis pipelines optimized for both the cerebellum and the cerebrum, and the prospective nature of our meta-analyses of cerebellar features that were previously unexamined in all samples (protecting against effects of publication bias). Its main weaknesses are different acquisition parameters across sites and the lack of detailed and consistent demographic and clinical information across all samples. Moreover, the use of different analysis methods (cerebellar voxel-based morphometry, subcortical segmentation and cerebral surface-based estimates of cortical thickness) warrants some caution in the interpretation of the relative effect sizes presented in Figure 3. We find it highly unlikely, however, that these limitations affect our main findings, as (1) the difference between SZ and HCs were remarkably homogenous across samples and (2) the analyses of cerebral morphological features closely replicate existing multisite studies (e.g., van Erp *et al*.[47] and Okada *et al*.[76]). More plausibly, the variability in cognitive and clinical evaluation, resulting in few common measures across sites, may have contributed to our failure to detect any robust behavioral correlates of cerebellar volume, but note that such significant structure–function associations are generally rare in multisite studies.[40,47]

In summary, our results provide strong evidence for cerebellar structural abnormalities in SZ, primarily in regions associated with advanced cognitive functions. We also show robust correlations between cerebellar volume and cerebral cortical thickness in patients, suggestive of common underlying disease processes. Finally, our results reveal that cerebellar volume reductions are present already at disease onset, thus highlighting the need for future studies on cerebellocerebral structural networks in developmental and high-risk samples.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)