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RESEARCH ARTICLE

Patterns of subregional cerebellar atrophy across epilepsy syndromes: An ENIGMA-Epilepsy study

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Abstract

Objective: The intricate neuroanatomical structure of the cerebellum is of long-standing interest in epilepsy, but has been poorly characterized within the current corticocentric models of this disease. We quantified cross-sectional regional cerebellar lobule volumes using structural magnetic resonance imaging in 1602 adults with epilepsy and 1022 healthy controls across 22 sites from the global ENIGMA-Epilepsy working group.

Members of the ENIGMA-Epilepsy working group investigators are provided in the Appendix.

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Methods: A state-of-the-art deep learning-based approach was employed that parcellates the cerebellum into 28 neuroanatomical subregions. Linear mixed models compared total and regional cerebellar volume in (1) all epilepsies, (2) temporal lobe epilepsy with hippocampal sclerosis (TLE-HS), (3) nonlesional temporal lobe epilepsy, (4) genetic generalized epilepsy, and (5) extratemporal focal epilepsy (ETLE). Relationships were examined for cerebellar volume versus age at seizure onset, duration of epilepsy, phenytoin treatment, and cerebral cortical thickness.

Results: Across all epilepsies, reduced total cerebellar volume was observed ($d = .42$). Maximum volume loss was observed in the corpus medullare ($d_{max} = .49$) and posterior lobe gray matter regions, including bilateral lobules VIIB ($d_{max} = .47$), crus I/II ($d_{max} = .39$), VIIIA ($d_{max} = .45$), and VIIIB ($d_{max} = .40$). Earlier age at seizure onset ($\eta\rho^2_{max} = .05$) and longer epilepsy duration ($\eta\rho^2_{max} = .06$) correlated with reduced volume in these regions. Findings were most pronounced in TLE-HS and ETLE, with distinct neuroanatomical profiles observed in the posterior lobe. Phenytoin treatment was associated with reduced posterior lobe volume. Cerebellum volume correlated with cerebral cortical thinning more strongly in the epilepsy cohort than in controls.

Significance: We provide robust evidence of deep cerebellar and posterior lobe subregional gray matter volume loss in patients with chronic epilepsy. Volume loss was maximal for posterior subregions implicated in nonmotor functions, relative to motor regions of both the anterior and posterior lobe. Associations between cerebral and cerebellar changes, and variability of neuroanatomical profiles across epilepsy syndromes argue for more precise incorporation of cerebellar subregional damage into neurobiological models of epilepsy.

KEYWORDS

anterior lobe, cerebellum, epilepsy, MRI, posterior lobe

1 | INTRODUCTION

Epilepsy is a prevalent, chronic group of neurological diseases that affects more than 70 million people worldwide,[1] and encompasses many different disorders, of which temporal lobe epilepsy (TLE) is the most common in adults.[2] Current models of the disease conceptualize epilepsy as involving widespread cortical and subcortical network disturbances, including reduced cortical thickness and white matter abnormalities.[3,4] As such, studies have frequently overlooked the cerebellum. However, a plethora of evidence from electrophysiological and optogenetic studies in animals[5–7] as well as noninvasive imaging studies in humans[8,9] provide evidence for a role of the cerebellum in seizure generation. Furthermore, atrophy of the cerebellum is associated with poorer prognosis following therapeutic temporal resection.[10] These findings highlight the cerebellum as a potential target for therapeutic intervention in epilepsy and underscore the importance of incorporating the cerebellum into neurobiological models of epilepsy.

Structural magnetic resonance imaging (MRI) has increasingly been used to localize and quantify cerebellar gray and white matter volume changes in people with epilepsy. The most consistent finding has been reduced total cerebellar gray matter volume (GMV) in people with TLE compared to controls.[9,11–16] Many studies suggest a negative correlation between total cerebellar volume and duration of epilepsy[11–15] and earlier age at seizure onset.[11,17] Bilateral reduction of cerebellar GMV in TLE regardless of the side of seizure focus has been reported by some authors,[14,18–20] whereas others have found GMV cerebellar changes most pronounced ipsilateral to the side of the epileptogenic focus.[21,22] Evidence for changes in cerebellar white matter has been inconsistent.[15,16,23,24]

Collectively, these studies have highlighted the presence of global cerebellar atrophy in epilepsy. However,

Key Points

- All epilepsy types had corpus medullare and posterior lobe "nonmotor" volume reductions relative to controls, with maximal differences in bilateral VIIB and crus II lobules; anterior "motor lobe" regions were relatively spared
- Lower volume of bilateral VIIB and crus II lobules correlated with longer disease duration, independent of phenytoin use, suggesting progressive and additive damage
- Volume loss was most pronounced in TLE-HS and ETLE, with distinct neuroanatomical patterns: stronger superior "nonmotor" posterior lobe involvement in TLE-HS and stronger left lateralized inferior "motor" posterior lobe volume loss in ETLE
- Collectively, these findings argue for more precise incorporation of cerebellar subregional damage into neurobiological models of epilepsy

these studies are limited, as they have largely neglected the cerebellum's distinct underlying anatomical subregions (lobules) and associated functional heterogeneity. In addition, these studies have included modest sample sizes and typically have been confined to one epilepsy syndrome, limiting a thorough investigation of cerebellar subregions across epilepsy syndromes. Anatomically, the cerebellum is divided along its superior to inferior axis into three lobes: anterior, posterior (further divided into superior and inferior divisions), and flocculonodular.[25] Only a few studies have distinguished the cerebellar anterior and posterior lobes in epilepsy,[10,15,16] and largely report GMV reductions localized to the posterior lobes. Only one study has quantified cerebellar volume of 17 subregions and reported evidence for increased vermal and decreased posterior lobule volumes in TLE.[10] This work provides an initial indication that cerebellar changes in people with epilepsy are likely spatially nonuniform, supporting the need for larger, more spatially precise examinations of cerebellar atrophy across different epilepsy syndromes.

The development of new machine learning-based approaches for optimized and automated feature-based parcellation of the cerebellum allows for more spatially precise mapping of cerebellar anatomy. These approaches are superior to voxel-based approaches (including voxel-based morphometry [VBM]) for accurately quantifying cerebellar volume at the lobular level.[26] One such approach, called Automatic Cerebellum Anatomical Parcellation Using U-Net With Locally Constrained Optimization (ACAPULCO), uses a deep learning algorithm to automatically parcellate the cerebellum into 28 anatomical subunits.[27] In contrast to registration-based approaches such as VBM, feature-based segmentation ACAPULCO performs on par with leading approaches for automatic cerebellar parcellation, has broad applicability to both healthy and atrophied cerebellums, and is more time-efficient than other approaches.[27]

Here, in the largest study of cerebellar volume in epilepsy to date, we applied ACAPULCO to quantify cerebellar lobule volumes from 1602 individuals with epilepsy and 1022 healthy controls from the global ENIGMA-Epilepsy working group. We undertook multisite mega-analyses to infer regional cerebellar volumetric differences in (1) all epilepsies; (2) hippocampal sclerosis-related TLE, considering left-sided (TLE-HS-L) and right-sided (TLE-HS-R) sclerosis as independent groups; (3) nonlesional TLE (TLE-NL-L and TLE-NL-R); (4) genetic generalized epilepsy (GGE); and (5) extratemporal focal epilepsy (ETLE), compared to controls. As a secondary aim, epilepsy syndromes were directly compared, to assess for syndrome-specific changes in total and regional cerebellar volume. Relationships between cerebellar regional volume, age at seizure onset, and epilepsy duration were examined. Finally, given reports of a relationship between chronic phenytoin treatment and cerebellar atrophy,[12,28] we examined associations between cerebellar volume and phenytoin treatment.

2 | MATERIALS AND METHODS

2.1 | Study sample

Sixteen sites were included in this cross-sectional study, totaling 1602 adult people with epilepsy and 1022 age- and sex-matched controls. Demographic and clinical characteristics of the sample are listed in Tables 1 and S1. Exclusion criteria included participants with a comorbid progressive disease (e.g., Rasmussen encephalitis) or MRI-visible lesions in the cerebellum; however, patients with supratentorial cortical dysplasia-related epilepsy or cortical lesions were not excluded. An epilepsy specialist assessed seizure and syndrome classifications at each center, using International League Against Epilepsy (ILAE) terminology.[29,30] For TLE, all individuals presenting with the typical electroclinical constellation and clinical semiology of this disorder were included.[30] For the TLE-HS subgroups, people with unilateral HS had a neuroradiologically confirmed diagnosis of hippocampal atrophy and increased T2 signal on an epilepsy protocol clinical MRI. TLE-L and TLE-R disorders without HS (as indicated by a normal MRI) were considered as independent groups (TLE-NL-L and

TABLE 1 Demographic and clinical characteristics of the total sample.

Characteristic	*n*	Age (SD)	Sex, % female	Age at onset, years (SD)	Duration epilepsy, years (SD)
Controls	1022				
All epilepsies	1602	36.2 (11.8)	56.5	18.3 (13.6)	17.5 (14.1)
TLE-HS-L	320	38.8 (10.8)	54	13.8 (11.5)	25.1 (14.3)
TLE-HS-R	242	40.3 (10.9)	57	15.2 (12.1)	24.6 (14.7)
TLE-NL-L	153	37.8 (12.5)	63	26.0 (15.3)	12.2 (11.9)
TLE-NL-R	131	37.3 (11.5)	59	26.5 (13.7)	10.3 (10.3)
GGE	186	29.2 (9.7)	66	13.4 (8.3)	15.4 (10.5)
ETLE	251	32.1 (10.8)	54	15.1 (10.6)	16.5 (12.1)
All other epilepsies	317	36.4 (12.3)	50	24.2 (15.1)	12.5 (11.0)

Abbreviations: ETLE, extratemporal focal epilepsy; GGE, genetic generalized epilepsy; TLE, temporal lobe epilepsy; TLE-HS-L, left-sided hippocampal sclerosis-related TLE; TLE-HS-R, right-sided hippocampal sclerosis-related TLE; TLE-NL-L, left-sided nonlesional TLE; TLE-NL-R, right-sided nonlesional TLE.

TLE-NL-R, respectively). For GGE, people with juvenile onset myoclonic epilepsy, absence, or myoclonic seizures with generalized spike–wave discharges on electroencephalogram, were included in this group. The ETLE group included people with epileptogenic foci identified outside of the temporal lobe. All remaining epilepsies that could not be classified into the predefined syndrome groups were combined into an "all other epilepsies" group (Table S2).

2.2 | Image processing and analysis: ACAPULCO

Whole-brain, T1-weighted magnetic resonance images were collected from each participant. Scanner descriptions and acquisition protocols for all sites are reported in Table S3. We treated each individual scanner and/or data acquisition protocol used in the collection of MRI scans as a separate "site" during statistical analysis (see below). Each image was processed in accordance with the ENIGMA cerebellum parcellation protocol, as fully described elsewhere (https://enigma.ini.usc.edu/protocols/imaging-protocols/).[31] In brief, the cerebellum was parceled into 28 subregions (left and right lobules I–III, IV, V, VI, crus I, crus II, VIIB, VIIIA, VIIIB, IX, and X; bilateral vermis VI, VII, VIII, IX, and X), and bilateral corpus medullare (central white matter and deep cerebellar nuclei) using the deep learning-based algorithm ACAPULCO (version 0.2.1; https://gitlab.com/shuohan/acapulco).[27] Outputs were quality checked by visual inspection followed by quantitative identification of outlier volumes that were greater or less than 2.698 SD from the group mean.

2.3 | Statistical analysis

All statistical analyses of cerebellar volume were carried out using R version 4.1.0.[32] We fit linear mixed effects regression models (LMMs) using *lme4* and *lmerTest* packages in R, with diagnosis (Dx; i.e., control or epilepsy), age, age^2, sex, and intracranial volume (ICV) as fixed factors and site as a random factor. Age^2 was included given evidence of nonlinear effects of age on brain volume loss in the cerebellum and cerebral cortex.[33] Model 1 was fit for total cerebellar volume (sum of all 28 cerebellar regions of interest [ROIs]) and each cerebellar lobule individually and repeated for the total sample (all epilepsy vs. controls) and each subgroup of interest: TLE-HS-L, TLE-HS-R, TLE-NL-L, TLE-NL-R, GGE, and ETLE.

$$\text{Volume} \sim \text{Dx} + \text{Age} + \text{Age}^2 + \text{Sex} + \text{ICV} + 1 \mid \text{site} \quad (1)$$

LMMs were repeated to compare epilepsy syndromes to one another. For all analyses, results were false discovery rate (FDR)-corrected ($p < .05$) for multiple comparisons. Cohen *d* effect sizes with 95% confidence intervals (CIs) were calculated for each of the ROIs, based on the estimated marginal means and Satterthwaite's approximation for degrees of freedom.[34] Positive effect size values correspond to people with epilepsy having *lower* values relative to controls.

2.4 | Regression with clinical variables and phenytoin therapy

LMMs were used to test for associations between each ROI volume (and total cerebellar volume) and (1) duration of

epilepsy and (2) age at onset in all epilepsies, as well as in each epilepsy disorder subtype. Partial η^2 is reported as a measure of effect size. To investigate the association between phenytoin treatment and volume of each ROI in all epilepsies, a binary variable indicating exposure to phenytoin ("Yes" = have been treated with phenytoin at some point for any duration; "No" = have never been treated with phenytoin) was treated as the predictor of interest, with age, age^2, duration of epilepsy, and ICV included as fixed factors and site as a random factor. To examine site-specific effects, we also fit LMMs separately for each site.

2.5 | Laterality

In addition, we investigated whether the side of seizure focus in patients with TLE (e.g., TLE-HS-L vs. TLE-HS-R) was associated with left/right asymmetry of cerebellar volumes. Methodological details can be found in the supplementary material.

3 | RESULTS

3.1 | Participant demographics

A one-way analyses of variance (ANOVA) with group as a fixed effect revealed differences across the eight groups in age ($F[7, 2614] = 27.76$, $p < .001$). Two one-way ANOVAs across the seven patient groups revealed group differences in age at seizure onset ($F[6, 1235] = 37.12$, $p < .001$) and duration of epilepsy ($F[6, 1248] = 45.06$, $p < .001$). Post hoc comparisons revealed that controls were younger than the TLE-L, TLE-R, TLE-NL-L, and "all other epilepsies" groups, but significantly older than the GGE group ($p < .05$). The TLE-NL-L, TLE-NL-R, and "all other epilepsies" groups had a later age at seizure onset compared to all other syndromes ($p < .05$). In addition, TLE-HS-L and TLE-HS-R had a longer duration of epilepsy compared to all other groups.

Four of the 16 data collection sites used more than one imaging sequence across their cohort; these sites were also broken into subsites, resulting in a total of 22 sites included in our mixed linear regression models.

3.2 | All epilepsies group

3.2.1 | All epilepsies versus healthy controls

Compared to controls, people with epilepsy had significantly reduced total cerebellar (gray and corpus medullare) volume ($d = .42$, 95% CI = .33–.52). ROI analyses revealed significantly reduced volume of the corpus medullare ($d = .49$, 95% CI = .39–.58) and reduced GMV in 21 cerebellar lobules, with small to moderate effect sizes ($d_{min} = .11$, $d_{max} = .40$, all $p < .05$ FDR-corrected; Figure 1). The largest effect sizes were observed in predominantly bilateral superior and inferior posterior lobe regions including left and right VIIB, right and left crus II, right V, left VIIIB, left crus I, and right VIIIB. There were no significant between-group differences for the remaining cerebellar lobules (Figure 1 and Table S5).

3.2.2 | Duration of epilepsy and age at seizure onset

Longer duration of epilepsy corresponded with smaller total cerebellar volume across all epilepsies (partial $\eta^2 = .032$, 95% CI = .017–.061, $p < .001$; Figure 2A). Analyses of individual cerebellar subregions revealed significant negative correlations between duration of epilepsy and regions that also showed reduced GMV (all $p < .05$ FDR-corrected; Table S10). To further control for the effects of phenytoin use on the relationship between duration of epilepsy and cerebellar volume, we repeated this analysis in a subset of phenytoin-naïve individuals. The negative correlation with total and posterior cerebellar volume remained significant (Table S11). Earlier age at onset corresponded with smaller total cerebellar volume (partial $\eta^2 = .024$, 95% CI = .051–.011, $p < .001$; Figure 2B). Nineteen cerebellar subregions showed a significant positive association with age at disease onset. The strongest effects were seen for regions that showed reduced gray matter in people with epilepsy (vs. controls; all $p < .05$ FDR-corrected; Table S12).

3.3 | TLE-HS group

3.3.1 | TLE-HS versus healthy controls

In TLE-HS-L ($n = 320$), there was significantly reduced total cerebellar volume ($d = .56$, 95% CI = .40–.71). ROI analyses revealed significantly reduced volume of the corpus medullare compared to healthy controls ($d = .56$, 95% CI = .40–.72). In addition, the TLE-HS-L group also showed reduced GMV in 22 cerebellar lobules, with small to moderate effect sizes ($d_{min} = .15$, $d_{max} = .48$, all $p < .05$ FDR-corrected; Figure 3), with the largest effect sizes seen in left and right VIIB, right crus II, and right V. The TLE-HS-L group also showed increased cerebellar volume in left IV ($d = -.16$, 95% CI = −.32 to −.01). There were no significant between-group differences for the remaining cerebellar lobules (Figure 3 and Table S6).

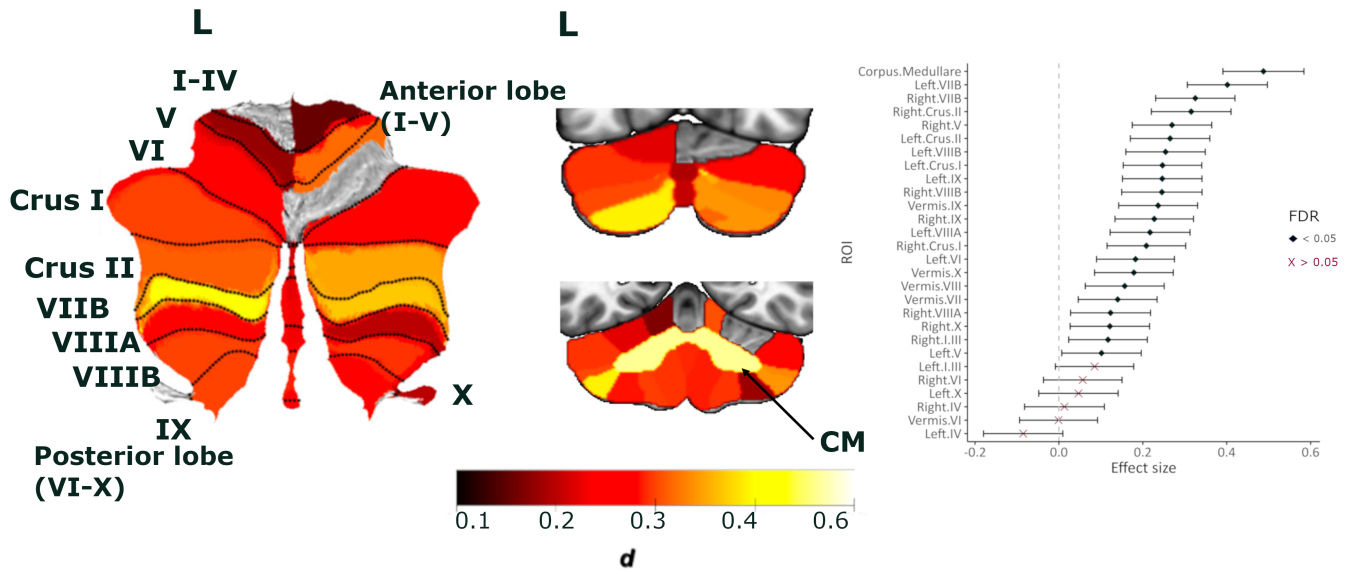

FIGURE 1 Atlas-based effect size (Cohen *d*) maps, Montreal Neurological Institute-based coronal slices (top: $y = -72$; bottom: $y = -54$), and forest plots (Cohen $d \pm 95\%$ confidence interval) of the significant between-group differences for all epilepsies versus healthy controls (HC). Positive effect sizes reflect epilepsy patients < HC. Regions significant at $p < .05$ false discovery rate (FDR)-corrected are depicted in color (see Table S5 for full tabulation). CM, corpus medullare; L, left; ROI, region of interest.

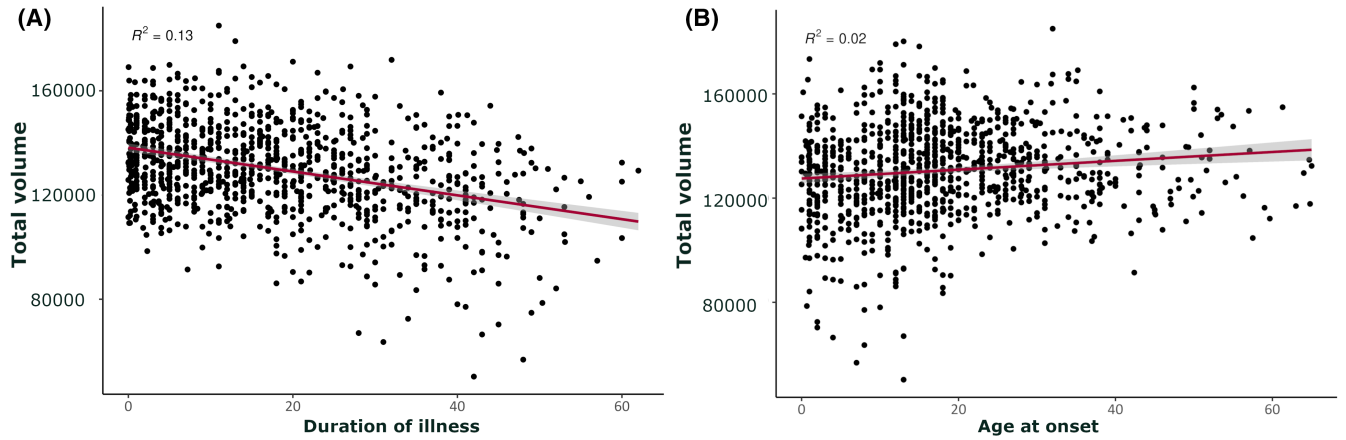

FIGURE 2 Scatterplots showing the association between (A) duration of illness and (B) age at seizure onset, and total cerebellar volume in epilepsy patients ($p < .001$).

In TLE-HS-R ($n = 242$) total cerebellar volume was significantly reduced ($d = .48$, 95% CI = .30–.64). ROI analyses significantly reduced volume of the corpus medullare compared to healthy controls ($d = .63$, 95% CI = .45–.80; Figure 3). However, the TLE-HS-R group showed less pronounced (compared to the TLE-HS-L group) cerebellar volume loss across individual cerebellar lobules. Reduced gray matter was found for 14 cerebellar lobules ($d_{min} = .19$, $d_{max} = .42$, all $p < .05$ FDR-corrected; Figure 3), with the largest effect sizes seen for left and right VIIB, left crus I, and right V (Table S6).

3.3.2 | Duration of epilepsy and age at seizure onset

There were no significant relationships between duration of epilepsy or age at onset and total cerebellar volume in the TLE-HS-L group (Tables S10 and S12). In the right TLE-HS group, however, longer duration of epilepsy corresponded with smaller total cerebellar volume (partial $\eta^2 = .06$, 95% CI = .01–.15, $p = .010$; Table S10); in addition, later age at disease onset corresponded with higher total cerebellar volume (partial $\eta^2 = .06$, 95% CI = .01–.14, $p = .016$; Table S12).

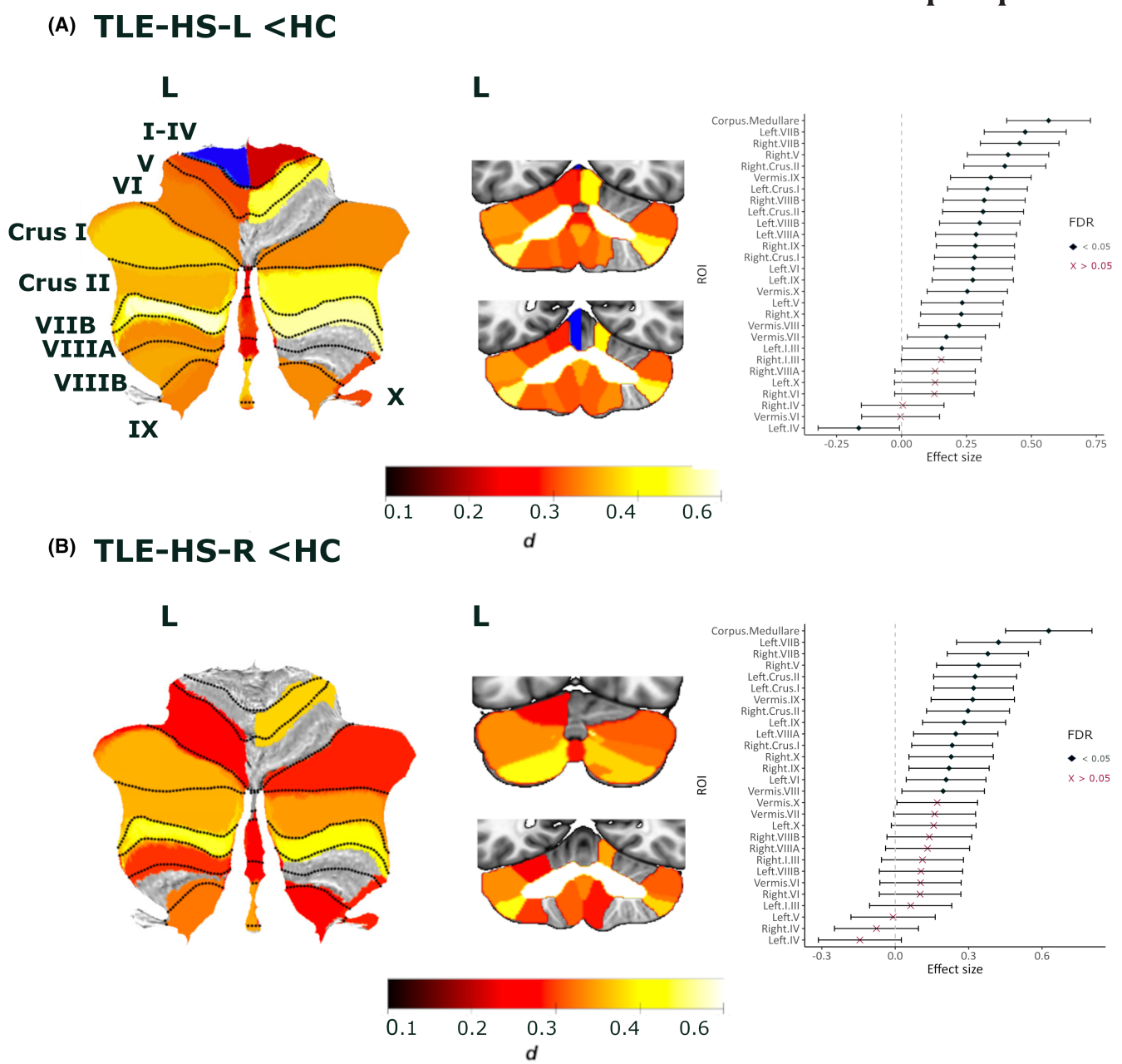

FIGURE 3 Atlas-based effect size (Cohen *d*) maps, Montreal Neurological Institute-based coronal slices (top: $y = -72$; bottom: $y = -54$), and forest plots (Cohen $d \pm 95\%$ confidence interval) of the significant between-group differences for left-sided hippocampal sclerosis-related temporal lobe epilepsy (TLE-HS-L; A) and right-sided hippocampal sclerosis-related TLE (TLE-HS-R; B) versus healthy controls (HC). Positive effect sizes reflect TLE-HS-L and TLE-HS-R < HC, respectively. Regions significant at $p < .05$ false discovery rate (FDR)-corrected are depicted in color (red–yellow for epilepsy < HC; blue for epilepsy > HC; see Table S6 for full tabulation). L, left; ROI, region of interest.

3.4 | TLE-NL group

3.4.1 | TLE-NL versus healthy controls

Compared to healthy controls, the left TLE-NL group ($n = 153$) did not show significant differences in total cerebellar volume or individual cerebellar lobule volumes (all $p > .05$ FDR-corrected). The TLE-NL-L group did however, show significantly reduced white matter volume of the corpus medullare ($d = .58$, 95% CI = .37–.79; Figure S1a and Table S7).

The right TLE-NL-R group ($n = 131$) did not show significant differences in total cerebellar volume compared to healthy controls ($p > .05$ FDR-corrected); however, they

showed reduced volume of the corpus medullare ($d = .57$, 95% CI = .33–.80). TLE-NL-R also showed significantly increased GMV of left lobule IV ($d = -.38$, 95% CI = −.61 to −.15; Figure S1b and Table S7).

3.4.2 | Duration of epilepsy and age at seizure onset

There were no significant relationships between duration of epilepsy or age at disease onset and total cerebellar volume in the TLE-NL groups (all $p > .05$; Tables S10 and S12).

3.5 | GGE group

People with GGE ($n = 186$) showed significantly reduced total cerebellar volume ($d = .42$, 95% CI = .23–.61) and reduced volume of the corpus medullare ($d = .47$, 95% CI = .27–.66) compared to healthy controls. Additionally, they showed reduced GMV in nine cerebellar lobules with small to moderate effect sizes ($d_{min} = .24$, $d_{max} = .38$, all $p < .05$ FDR-corrected; Figure 4). Differences were seen for predominantly bilateral posterior regions including left and right VIIB, right crus I, left VIIIA, and right VIIIB (Figure 4 and Table S8).

3.5.1 | Duration of epilepsy and age at seizure onset

There was no significant relationship between duration of epilepsy or age at seizure onset and total cerebellar volume in people with GGE (all $p > .05$; Tables S10 and S12).

3.6 | ETLE group

Individuals with ETLE ($n = 251$) showed significantly reduced total cerebellar volume ($d = .58$, 95% CI = .40–.76) and reduced volume of the corpus medullare ($d = .86$, 95% CI = .67–1.0) compared to healthy controls. ROI analyses showed reduced GMV in 17 cerebellar lobules with small to moderate effect sizes ($d_{min} = .12$, $d_{max} = .52$, all $p < .05$ FDR-corrected; Figure 5). The largest effect sizes were seen for predominantly left-sided posterior nonmotor and motor regions: left VIIB, left VIIIA, and left IX. People with ETLE also showed increased GMV of left anterior lobule IV compared

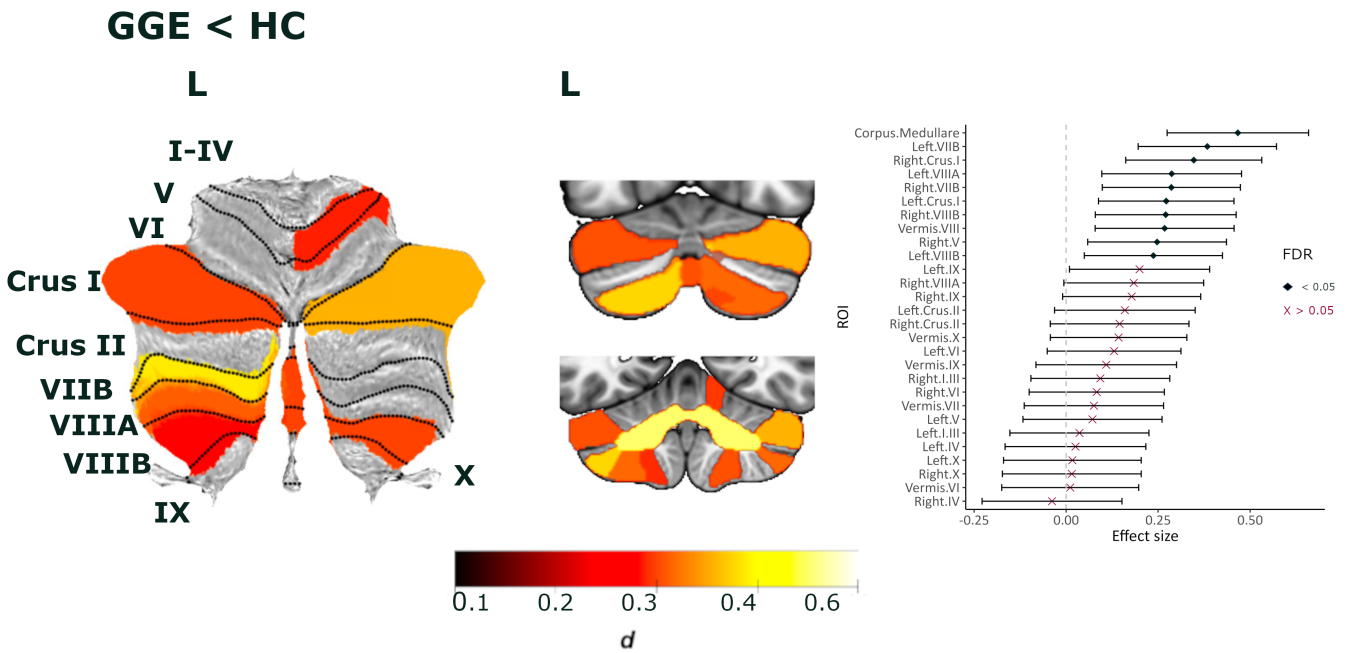

FIGURE 4 Atlas-based effect size (Cohen) maps, Montreal Neurological Institute-based coronal slices (top: $y = -72$; bottom: $y = -54$), and forest plots (Cohen $d \pm 95\%$ confidence interval) of the significant between-group differences for genetic generalized epilepsy (GGE) versus healthy controls (HC). Positive effect sizes reflect epilepsy < HC. Regions significant at $p < .05$ false discovery rate (FDR)-corrected are depicted in color. See Table S8 for full tabulation. L, left; ROI, region of interest.

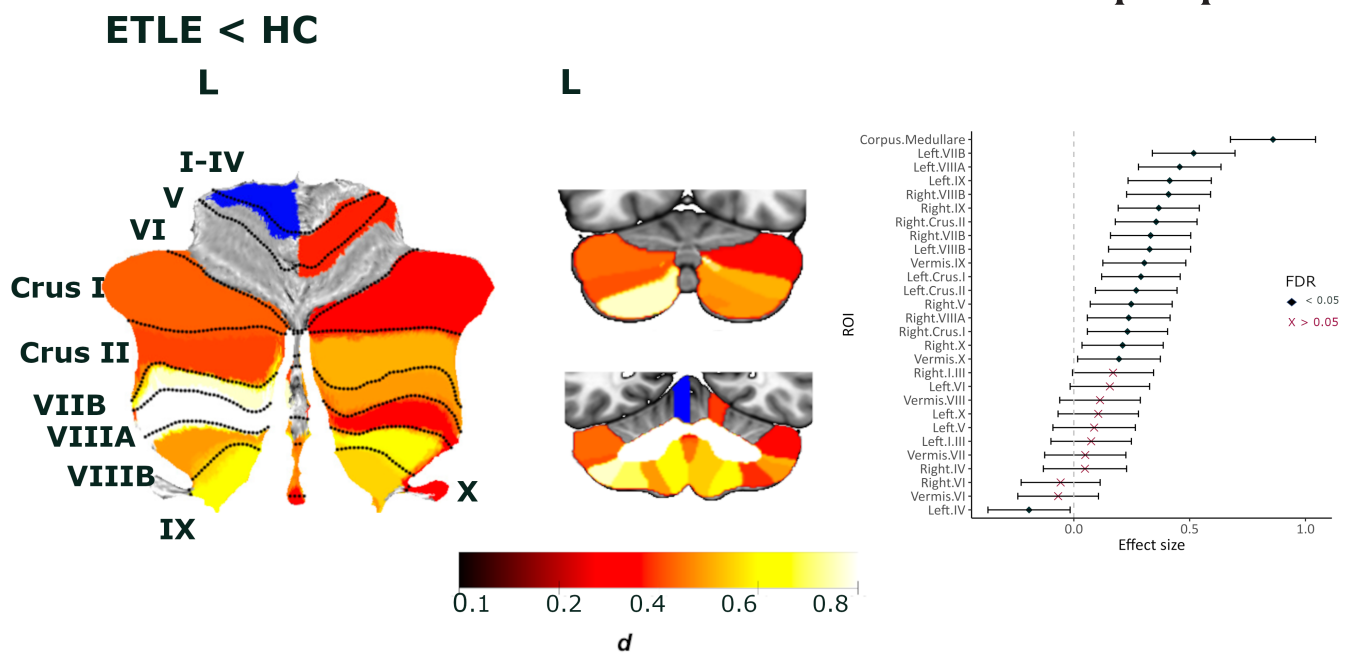

FIGURE 5 Atlas-based effect size (Cohen *d*) maps, Montreal Neurological Institute-based coronal slices (top: $y = -72$; bottom: $y = -54$), and forest plots (Cohen $d \pm 95\%$ confidence interval) of the significant between-group differences for extratemporal focal epilepsy (ETLE) versus healthy controls (HC). Positive effect sizes reflect epilepsy patients < HC. Regions significant at $p < .05$ false discovery rate (FDR)-corrected are depicted in color (red–yellow for ETLE < HC; blue for ETLE > HC); see Table S9 for full tabulation. L, left; ROI, region of interest.

to controls ($d = -.19$, 95% CI = −.37 to −.01; Figure 5 and Table S9).

3.6.1 | Duration of epilepsy and age at seizure onset

Longer duration of epilepsy was associated with smaller total cerebellar volume (partial $\eta^2 = .05$, 95% CI = .01–.13, $p < .05$ FDR-corrected; Table S10). In addition, later age at onset was associated with larger total cerebellar volume (partial $\eta^2 = .05$, 95% CI = .01–.13, $p < .05$ FDR-corrected; Table S12).

3.7 | Comparisons between epilepsy syndromes

The most significant differences were observed between the TLE-HS-L and TLE-NL-L groups in posterior lobe regions, where the TLE-HS-L group had significantly lower right VIIB ($d = .51$, 95% CI = .20–.77) and right crus II ($d = .39$, 95% CI = .11–.67) volumes. The ETLE group showed significantly lower volume of right VIIB ($d = .60$, 95% CI = .20–.89) and left and right lobule IX ($d = .40$, 95% CI = .14–.65; and $d = .46$, 95% CI = .16–.76, respectively) compared to the TLE-NL-L group. Finally, compared to the GGE group, people with ETLE showed significantly decreased volume of left IX ($d = .28$, 95% CI = .10–.50). A qualitative summary of the results can be found in Figure S4.

3.8 | Relationships between cerebellar and cerebral structural changes

We explored cerebrocerebellar relationships to assess whether the magnitude of cerebellar volume loss observed in people with epilepsy mirrored that seen in the cerebral cortex. FreeSurfer-derived cortical thickness measures were available for 1586 individuals across eight sites (controls = 804, epilepsies = 782). Methodological details are provided in the supplementary material. Results showed a significant interaction between cortical thickness and diagnosis on predicting cerebellar total volume ($p = .01$). Marginal effects plots (controlling for all other covariates) showed that a reduction in mean cortical thickness was associated with a more pronounced decrease in cerebellar volume for those with epilepsy (Figure S2). Additionally, we explored the interaction of subdiagnosis with cortical thickness. Of the epilepsy syndromes, a significant interaction between cortical thickness and subdiagnosis was only observed for the TLE-HS-R and TLE-HS-L cohorts ($p = .003$), suggesting that the reduction in cerebellum volume relative to cortical thickness is more pronounced in TLE-HS.

3.9 | Volume changes associated with phenytoin therapy

Phenytoin therapy data ($n = 802$; Yes = 161, No = 641) was derived from seven sites. People treated with phenytoin were all affected by focal epilepsy. In contrast, the phenytoin-naïve group consisted of focal, generalized, and unspecified epilepsy cases. We therefore restricted analyses of phenytoin use to focal epilepsies only. Independent sample *t*-tests showed that people treated with phenytoin had a significantly longer duration of illness than phenytoin-naïve individuals at four of the sites (Table S13). Linear regression controlling for duration of epilepsy revealed that phenytoin therapy was associated with reduced total cerebellum volume ($d = .39$, 95% CI = .12–.63) and reduced gray matter of 10 posterior lobe regions (all $p < .05$ FDR-corrected; Figure S3). Post hoc analyses for each site independently showed cerebellar volume loss in phenytoin-treated individuals to be associated with medium to large effect sizes for three sites; however, there was substantial variability in effect sizes across sites ($d_{min} = .25$, $d_{max} = .86$).

3.10 | Laterality

There were no significant associations between laterality of disease (right vs. left) and total cerebellar volume asymmetry or individual cerebellar lobule asymmetry for any of the epilepsy syndromes (all $p > .05$). Furthermore, these findings were replicated in a phenytoin-naïve subgroup (Table S4).

4 | DISCUSSION

In the largest quantitative study of cerebellum morphometry in epilepsy to date, we performed a comprehensive assessment of regional cerebellar atrophy in >1600 adults with epilepsy. We report significant cerebellar volume reductions, principally weighted to the posterior cerebellar lobe. These differences were observed across epilepsy syndromes, although they were most pronounced in TLE-HS and ETLE. Smaller volumes in posterior lobe regions were associated with longer duration of epilepsy. Exploration of cerebrocerebellar volume ratios demonstrated that cortical thinning was associated with a more pronounced decrease in cerebellar volume in individuals with epilepsy relative to controls. Collectively, these findings suggest involvement of the cerebellum in epilepsy and raise important questions about the potential vulnerability of different cerebellar subregions in the causes, consequences, and clinical expression of specific disease features in epilepsy.

4.1 | Dissociation in anterior "motor" versus posterior "nonmotor" cerebellar lobe involvement across epilepsies

The spatial nonuniformity of the observed anatomical changes provides evidence for a dissociation in anterior (motor) versus posterior (nonmotor) lobe involvement in epilepsy. Previous studies report evidence for reduced superior[15] and inferior posterior lobe[16] volume in epilepsy, alongside spared or increased anterior lobe volume. The posterior lobe, particularly lobules VII (crus I/II and VIIB), where the observed anatomical changes were maximal, are predominantly "nonmotor" regions of the cerebellar cortex, and are preferentially connected to prefrontal and posterior parietal regions of the cerebral cortex.[35,36] Functional mapping studies ascribe these areas to cognitive, language, and attentional processes.[37,38] Functionally, these regions are also part of the frontoparietal and salience resting state networks that are selectively vulnerable to neurodegeneration in Alzheimer disease and related conditions that show evidence of cerebellar functional changes and associated cognitive decline. In contrast, the cerebellar anterior lobe ("motor cerebellum"), flocculonodular lobe, and vermis were relatively spared. This is perhaps surprising when drawing parallels to *cerebral cortical* thickness changes of cerebral motor regions that are functionally and anatomically connected to motor regions of the cerebellar cortex in people with epilepsy.[4] Specifically, reduced bilateral cortical thickness of the pre- and postcentral gyri–motor cortical regions connected to anterior lobe and motor regions of the posterior lobe, namely, lobule VIII–has been reported in TLE-HS and GGE epilepsy disorders.[4] It is important to note that although volumetric changes were maximal in superior posterior (predominantly nonmotor) regions, the anterior and inferior posterior (motor/premotor) lobes were still significantly affected. Given strong evidence of the cerebellum being a brain region particularly vulnerable to injury and neurodegeneration,[39,40] and our observations of a negative relationship between posterior lobe volume loss and illness duration, we speculate that the posterior lobe may be particularly vulnerable to epilepsy-related cell loss. Clinically, such pathology of the nonmotor posterior lobe could be associated with cognitive and emotional comorbidities in people with epilepsy, and future imaging studies in epilepsy should further explore this possibility.

4.2 | Shared and distinct patterns of cerebellar gray and white matter atrophy across epilepsy syndromes

The most robust finding across all epilepsy disorders was reduced corpus medullare volume, suggesting that atrophy of the corpus medullare represents a global/shared feature of the disease. In contrast, regional gray matter atrophy across the cerebellum showed different patterns across epilepsy syndromes, suggesting unique neuroanatomical profiles of cerebellum volume changes. We do, however, refrain from interpreting all volumetric changes in the corpus medullare as unambiguously reflecting white matter atrophy. The dentate (and other deep cerebellar) nuclei cannot be delineated on structural T1-weighted images; therefore, the corpus medullare label includes these structures. Nonetheless, our findings broadly align with previous investigations that report robust changes to white matter structure,[3] and more mild changes in gray matter cortical thickness,[4] in people with TLE.

In contrast to white matter changes, the specific pattern and magnitude of volume changes in the posterior lobe gray matter (and underlying white matter) varied across the subgroups. Reduced GMV was most pronounced in the TLE-HS groups and least pronounced in TLE-NL groups (with the ETLE and GGE groups in between). TLE is the most common and best characterized subtype of epilepsy[2] and is associated with unilateral or bilateral hippocampal sclerosis in up to 60%–70% of adult cases.[41] Previous reports showed that even among people with drug-resistant TLE, NL individuals have less severe cortical[42,43] and white matter[3,44] abnormalities. The current work indicates that this distinction, with its implications, is recapitulated in the cerebellum. Importantly, the TLE-HS group in our study had a more chronic course of illness (longer duration of epilepsy), with a largely childhood/early adolescent onset, compared to NL individuals (Table 1). The TLE-HS group also represented the largest group of individuals to be treated with phenytoin in our study. Analyses comparing the lesional (TLE-HS) and nonlesional (TSE-NL), groups controlling for duration of illness, showed that TLE-HS-L subjects have marked volume loss of right VIIB and right crus II that distinguishes them from individuals without HS. The cross-sectional nature of our study, however, precludes us from drawing causal statements on volumetric changes in people with chronic epilepsy. For example, we cannot rule out pre-existing cerebellar brain injury that may have occurred from the initial epileptogenic insult. Moreover, the observed distinctions in cerebellar morphology likely reflect the influences of illness chronicity, phenytoin exposure, neurodevelopmental factors, and/or pathophysiological distinctions in TLE-HS versus TLE-NL.

People with GGE showed a similar but much less pronounced pattern of cerebellar GMV reduction compared to the TLE-HS groups, alongside reduced white matter volume, as is observed in all epilepsy syndromes. The ETLE group showed a similar magnitude of cerebellum gray matter loss to the TLE-HS and TLE-NL groups, but—in an important qualitative distinction—they showed a stronger involvement of left-lateralized "motor" *inferior* posterior cerebellar regions (VIIIA, VIIIB, IX). Notably, our analyses directly comparing epilepsy syndromes (controlling for the duration of disease) showed that left lobule IX volume in the ETLE group was significantly lower than the nonlesional TLE and GGE groups (but not when compared to the TLE-HS groups). Our results suggest that people with ETLE harbor unique cerebellar neuroanatomical features that are not common to focal epilepsy in general. In summary, our findings point to shared and unique cerebellar anatomical changes across epilepsy disorders.

4.3 | Clinical implications

Our findings have clinical implications in the context of advancing treatment in epilepsy and clinical management of the disease. Our finding of an association between posterior cerebellar volume and duration of illness across all epilepsies, in particular, demonstrates a common and potentially progressive neurodegeneration in patients with epilepsy. Importantly, this finding remained after controlling for phenytoin use, suggesting that the neurobiological mechanisms underlying cerebellar neurodegeneration in epilepsy are (at least partially) independent of phenytoin-induced neurotoxicity of the cerebellum. Together with our finding of greater cerebellar volume loss relative to cerebral cortical thinning in epilepsy (compared to controls), this suggests the cerebellum, particularly the posterior lobe, is especially vulnerable to seizure-related atrophy. As recognized by the ILAE, a major challenge for the field is to develop disease-modifying or antiepileptogenesis treatments.[45] As these medications reach late stage clinical trials, objective measures of the presence or progress of disease will be needed to support long-term claims of disease modification or antiepileptogenesis. Posterior cerebellar volume, in this case, may be a useful additional biomarker of disease severity and progression. In addition, the cerebellum has advantages in potentially being a generalized marker of continued disease burden, as we show it is uninfluenced by laterality of seizure onset or the lesion itself. Given the cerebellum has a role in both cognitive and emotional processing,[38] reduced cerebellar (particularly posterior) volumes could be associated with

the common mood and cognitive comorbidities observed in epilepsy.[46] If this hypothesized association was found to be correct, cerebellar volumes could be considered when managing the disease, specifically when deciding on antiseizure medications (ASMs), with ASMs with substantial known effects on mood or cognition not prescribed as first-line therapies for patients with smaller cerebellar volumes.

4.4 | Laterality of cerebellar changes across epilepsy

We did not find any significant evidence for lateralized differences in the degree of cerebellar volume loss between the left versus right cerebellum, including when the same analysis was restricted to phenytoin-naïve individuals. Notably, however, we did find that right-sided crus II and VIIB volume in the TLE-HS-L group statistically differed from the TLE-NL group, providing some support for cross-cerebellar changes. Evidence for lateralization of cerebellar volume asymmetry in epilepsy disorders has been inconsistent, with several studies reporting bilateral cerebellar volume reduction, regardless of laterality of seizure onset.[20] These findings may suggest that cerebellar involvement is not driven by diaschisis via cerebrocerebellar connectivity, but represents another element of more widespread intracranial derangement associated with the consequences of seizures and their treatment.

4.5 | Associations with phenytoin

An association between phenytoin exposure and reduced cerebellar posterior lobe volume in TLE-HS individuals was also observed. Our study is the most robust and largest evaluation of phenytoin therapy in epilepsy disorders to date. The pattern of atrophy—notably almost exclusively localized to the posterior lobe—suggests that although phenytoin is associated with pronounced targeted cerebellar atrophy, it cannot explain atrophy occurring across the breadth of the cerebellum in these patients and speaks to independent disease-related cerebellar pathology. Although our post hoc analyses revealed that the findings were driven by three sites that were associated with medium to large effect sizes, the variability in sample sizes across sites for which information on phenytoin therapy was available may have rendered the analysis underpowered to detect statistically significant effects for smaller sites. Future studies will be required to conduct a more fine-grained assessment of phenytoin-mediated effects on cerebellum atrophy.

4.6 | Limitations and future considerations

Our study has several limitations. The inconsistency of data availability across sites precluded particular analyses of disease features (e.g., cognitive impairments, comprehensive ASM history). The GGE and ETLE groups also represented heterogeneous cohorts, perhaps contributing to greater variability and weaker effects compared to the TLE-HS groups. We did not have available information on seizure frequency and severity, which precluded analyses of the relationship between cerebellar volume and cumulative seizure burden. Finally, although we report strong volumetric changes of the corpus medullare across all epilepsies, we cannot interpret these findings as reflecting pure white matter. Given that the dentate nucleus and other deep cerebellar nuclei cannot be delineated from structural T1-weighted images, these structures were also captured in our segmentation of the corpus medullare. Future studies using quantitative susceptibility mapping are required to rule out or rule in volumetric changes in the dentate nucleus as a feature of epilepsy.

In summary, we provide evidence of shared and unique cerebellar atrophy profiles in a large, international cohort of people with epilepsy across epilepsy syndromes. Shared atrophy was observed in the corpus medullare and bilateral posterior lobes, with the strongest effects in the TLE-HS groups, whereas volume loss in other regions (i.e., VIIIA, VIIIB, IX) were only observed in patients with ETLE. Importantly, cerebellar atrophy was associated with longer disease duration and phenytoin therapy, raising concerns for a neurodegenerative aspect to this loss. Future studies examining cerebrocerebellar spatial covariance will extend upon this work and provide insights into the prominence of cerebellar changes within current corticocentric neurobiological models of the disease.

AUTHOR CONTRIBUTIONS

Rebecca Kerestes, Andrew Perry, Carrie R. McDonald, Sanjay M. Sisodiya, and Ian H. Harding contributed to the conception and design of the study and methods. Marina K. M. Alvim, Alice Ballerini, Gabriel F. Baltazar, Núria Bargalló, Benjamin Bender, Renzo Guerrini, John S. Duncan, Jerome P. Engel Jr., Francesco Fortunato, Antonio Gambardella, Renzo Guerrini, Victoria Ives-Deliperi, Rafael B. João, Simon S. Keller, Benedict Kleiser, Angelo Labate, Pascal Martin, Mario Mascalchi, Stefano Meletti, Costanza B. Parodi, Jun Rao, Michael Rebsamen, Antonella Riva, Theodor Rüber, Christian Rummel, Mariasavina Severino, Lucas S. Silva, Richard J. Staba, Peter N. Taylor, Domenico Tortora, Anna Elisabetta Vaudano, Gavin P. Winston, and Clarissa L. Yasuda contributed to the imaging data collection. Rebecca Kerestes, Donatello Arienzo, Ítalo K. Aventurato, Alice

Ballerini, Benjamin Bender, Eva Bürkle, Maria Eugenia Caligiuri, Sonya Foley, Francesco Fortunato, Gerard Hall, Victoria Ives-Deliperi, Rafael B. João, Simon S. Keller, Matteo Lenge, Conor Owens-Walton, Costanza B. Parodi, Saül Pascual-Diaz, Michael Rebsamen, Johannes Reiter, Christian Rummel, Freda Scheffler, Richard J. Staba, Peter N. Taylor, Anna Elisabetta Vaudano, Clarissa L. Yasuda, and Hong Zheng contributed to imaging data analysis. Fernando Cendes, Antonio Gambardella, Renzo Guerrini, Khalid Hamandi, Simon S. Keller, Angelo Labate, Pascal Martin, Stefano Meletti, Theodor Rüber, Richard J. Staba, Pasquale Striano, Bernd Weber, Gavin P. Winston, Roland Wiest, Carrie R. McDonald, and Sanjay M. Sisodiya were principal investigators at each site. Rebecca Kerestes, Andrew Perry, David Powell, and Ian H. Harding were the core analysts, and Rebecca Kerestes and Ian H. Harding were the core writing group. Andrew Perry, Terence J. O'Brien, Lucy Vivash, Núria Bargalló, Benjamin Bender, Eva Bürkle, John S. Duncan, Francesco Fortunato, Simon S. Keller, Benedict Kleiser, Mario Mascalchi, Mariasavina Severino, Richard J. Staba, Pasquale Striano, Peter N. Taylor, Sophia I. Thomopoulos, Paul M. Thompson, Domenico Tortora, Gavin P. Winston, Clarissa L. Yasuda, Carrie R. McDonald, and Sanjay M. Sisodiya contributed to editing of the manuscript. Cassandra Marotta, Jane de Tisi, Ricardo Brioschi and Thea Giacomini contributed to the imaging data collection. Dan J. Stein contributed to the imaging data collection and was a principal investigator.

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CONFLICT OF INTEREST STATEMENT

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PATIENT CONSENT STATEMENT

All study participants provided written informed consent for the local study, and the local institutional review boards and ethics committees approved each included cohort study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not all publicly available in a repository, as they contain information that could compromise the privacy of research participants. Although there are data-sharing restrictions imposed by (1) ethical review boards of the participating sites, and consent documents; (2) national and transnational data-sharing laws, such as GDPR; and (3) institutional processes, some of which require a signed material transfer agreement for limited and predefined data use, we welcome sharing data with researchers, requiring only that they submit an analysis plan for a secondary project to the leading team of the Working Group (http://enigma.ini.usc.edu).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX A

ENIGMA-Epilepsy working group members

Name	Primary affiliation(s)	Role	Contribution
A. Aguila	UCL, London, UK	Member	Lab member in charge of data collection and/or analysis
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Name	Primary affiliation(s)	Role	Contribution
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Name	Primary affiliation(s)	Role	Contribution
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Name	Primary affiliation(s)	Role	Contribution
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Abbreviations: ERN, European Reference Network; IRCCS, Scientific Institute for Research and Health Care; PI, principal investigator; QIMR, Queensland Institute of Medical Research; UCL, University College London.