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Epileptic Disorders

ORIGINAL ARTICLE

Automated volumetric brain MRI analysis reveals multiregional morphometric alterations in pediatric epilepsy

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Abstract

Objective: To quantitatively evaluate regional brain volume differences between pediatric patients with epilepsy and healthy controls using a fully automated volumetric magnetic resonance imaging (MRI) analysis performed with the Vol2Brain platform.

Methods: This retrospective study included 150 children (75 with epilepsy and 75 healthy controls) who underwent 1.5 T cranial MRI examinations. High-resolution three-dimensional T1-weighted images were processed using Vol2Brain, a fully automated segmentation tool based on SPM12 and CAT12 frameworks. Absolute and relative volumes of 135 cortical and subcortical structures were computed. Statistical comparisons between groups were performed using the Shapiro–Wilk and Mann–Whitney U tests ($p < .05$).

Results: Patients with epilepsy demonstrated significantly lower volumes in the hippocampus, frontal and temporal gray matter, thalamus, cerebellum, and total brain compared with controls, accompanied by a compensatory increase in cerebrospinal fluid volume. No significant volumetric differences were found in the remaining 128 brain structures, indicating a diffuse morphometric reorganization pattern extending beyond the epileptogenic focus.

Significance: Fully automated volumetric MRI analysis using vol2Brain can reliably detect widespread structural brain alterations in pediatric epilepsy. These findings support the concept of epilepsy as a diffuse network disorder extending beyond focal lesions. Quantitative morphometry provides an objective approach to characterize subtle structural reorganization and may serve as a basis for future studies investigating clinical and neurocognitive correlations in pediatric epileptology.

KEYWORDS

brain mapping, epilepsy, magnetic resonance imaging, volumetric analysis

1 | INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent, spontaneous epileptic seizures resulting from abnormal, synchronous electrical discharges of cerebral neurons.[1,2] Pathophysiologically, morphological alterations in the cortical gray matter and subcortical white matter, along with glial dysfunction and metabolic disturbances, can be observed.[3,4] The prevalence of epilepsy in childhood is approximately .5%–1%, making this period the most common age of onset.[1] In developed countries, the annual incidence ranges from 40 to 100 new cases per 100 000 individuals, and globally, nearly 10 million children and adolescents live with active epilepsy.[1,2] Childhood epilepsy does not represent a single disease entity but rather a heterogeneous group of disorders with diverse etiologies, clinical manifestations, seizure types, severities, and prognoses.[1,2] Pediatric epilepsies may arise from genetic, structural, metabolic, or immune-related causes, each associated with distinct pathophysiological mechanisms, and their clinical course varies widely among individuals. A key diagnostic challenge in epilepsy lies in its overlapping clinical presentation with other neurological and systemic conditions that can cause transient disturbances in consciousness, behavior, or motor function—such as syncope, migraine, psychogenic nonepileptic seizures, and metabolic disorders.[1] Therefore, establishing an accurate diagnosis requires a comprehensive clinical evaluation supported by detailed electrophysiological investigations and careful differential diagnosis.[1,2]

Epilepsy in children may lead to cognitive impairment, typically resulting from structural, functional, or biochemical alterations in the brain that occur after recurrent seizures.[5,6] Advanced neuroimaging techniques such as magnetic resonance imaging (MRI) can detect these alterations in nearly one-third of cases, providing an objective means of assessing the cerebral impact of epilepsy.[7–9] Consequently, MRI serves as a cornerstone in both the diagnostic work-up and the assessment of neurocognitive prognosis in pediatric epilepsy.[7–10] As the gold standard for detecting structural brain abnormalities, MRI enables precise visualization of epileptogenic foci.[11,12] In the context of surgical planning, MRI plays a critical role by delineating the lesion's location, extent, and relationship to eloquent cortical regions—factors essential for maximizing surgical success and minimizing neurological risk.[11,13] The use of dedicated, high-resolution, and multiplanar MRI protocols specifically tailored for epilepsy has been shown to significantly improve lesion detection rates, diagnostic accuracy, and overall clinical management compared with standard MRI examinations.[9,11]

Epilepsy is increasingly regarded as a neurodegenerative process in which pathological changes are not confined to the epileptogenic zone but instead extend to distant cortical and subcortical regions, leading to widespread structural and volumetric alterations.[10,12–14] This concept supports the view that epilepsy is not merely a focal disorder but a dynamic and diffuse neuropathological process that disrupts entire brain networks.[10,12] The morphometric changes observed in epilepsy are multifactorial in origin. Volumetric alterations may result not only from the direct effects of recurrent seizures but also from secondary mechanisms, such as hypoxia, glutamate-mediated excitotoxicity, and oxidative stress, all of which contribute to neuronal injury.[13,15] Furthermore, long-term use of antiseizure medications may influence neuronal metabolism and synaptic plasticity, thereby promoting structural and volumetric modifications.[10,13]

Key points

- Fully automated Vol2Brain analysis detected widespread brain volume loss in pediatric epilepsy.
- Hippocampal, frontal, temporal, thalamic, and cerebellar volumes were significantly reduced.
- Findings support epilepsy as a diffuse network disorder beyond focal lesions.
- Automated volumetric analysis enhance reproducibility and minimize observer variability.

Volumetric analysis of brain structures was initially performed using manual segmentation techniques, which, although accurate, were time-consuming and limited in clinical applicability.[16,17] To overcome these challenges, automated segmentation software such as Vol2Brain has been developed, enabling rapid, reproducible, and user-independent volumetric measurements from brain MRI data.[3,16,18] While Vol2Brain operates on principles similar to those of the volBrain platform,[8,19] it incorporates more advanced algorithms and offers enhanced regional segmentation capabilities, providing a more comprehensive framework for both clinical and research-based volumetric assessments.[3,16,18]

The present study aimed to evaluate differences in brain volumes between pediatric patients with epilepsy and healthy controls using the Vol2Brain software and to characterize voxel-based volumetric alterations derived from automated segmentation in detail.[3,8,18]

2 | MATERIALS AND METHODS

2.1 | Patient population

This retrospective study was conducted with approval from the local institutional ethics committee. A

retrospective analysis was performed on pediatric patients diagnosed with epilepsy who underwent cranial MRI at Balikesir University Faculty of Medicine, Health Practice and Research Hospital between January 2019 and July 2024. During the same period, healthy children who underwent cranial MRI for non-neurological complaints such as headache, vertigo, or syncope and whose examinations were reported as normal served as the control group.

The diagnosis of epilepsy was established by an experienced pediatric neurologist based on the 2017 classification of the International League Against Epilepsy (ILAE 2017).[1] All participants had complete clinical and imaging data, which were retrospectively obtained from the institutional digital archive. The final study cohort consisted of 150 children, including 75 patients with epilepsy and 75 age-matched healthy controls. Inclusion and exclusion criteria were determined to ensure a homogeneous study population and to eliminate potential confounding factors.

2.1.1 | Inclusion criteria

Epilepsy group:

- Age below 18 years
- Definite diagnosis of epilepsy according to ILAE 2017 criteria
- Availability of complete clinical and imaging documentation
- Cranial MRI performed at our institution

Control group:

- Age below 18 years
- Cranial MRI performed for benign non-neurological indications such as headache, vertigo, or syncope and absence of a epilepsy history
- Normal neurological examination findings
- No chronic systemic illness or regular medication use
- Cranial MRI obtained at our institution

Exclusion Criteria (applied to both groups):

- History of psychiatric disorders
- Chronic illness requiring long-term medication
- Known vascular or demyelinating disease
- MRI performed at an external institution
- Incomplete clinical or imaging data
- For the epilepsy group, etiologies related to trauma, hemorrhage, hypoxic ischemic injury, hydrocephalus, neoplasm, arteriovenous malformation, genetic syndromes, or developmental delay

2.2 | Magnetic resonance imaging protocol

All examinations were performed using a standardized cranial MRI protocol on a 1.5 Tesla scanner (Ingenia, Philips Medical Systems, the Netherlands). The detailed MRI sequence parameters used in the epilepsy protocol and the routine brain MRI protocol are provided in Supporting Information S1. For volumetric analysis, a high-resolution three-dimensional (3D) T1-weighted sequence was used in all participants.

No contrast agent was administered in any of the cases.

2.3 | Automated volumetric brain MRI analysis using the Vol2Brain platform

MRI data were processed using Vol2Brain, a fully automated, web-based volumetric analysis software developed by the Neuroimaging Laboratory of the University of Castilla-La Mancha, Spain.[3] This platform is built upon the SPM12 and CAT12 frameworks[4,20] and employs high-resolution voxel-based morphometric segmentation and volumetric quantification algorithms. It enables standardized analysis of T1-weighted brain MRI data in either DICOM or NIfTI formats. All MRI examinations were retrieved in DICOM format from the institutional imaging archive. To ensure optimal segmentation accuracy, only high-resolution three-dimensional T1-weighted sequences with isotropic voxel sizes of $\leq 1\,mm^3$ were included.[3,20]

Prior to segmentation, all MRI datasets were carefully reviewed by a board-certified neuroradiologist with 9 years of experience in diagnostic brain imaging to assess motion artifacts, field inhomogeneity, and anatomical coverage integrity. Only technically adequate scans were accepted for analysis. After anonymization, DICOM files were converted to NIfTI format using the dcm2niix software.[21]

Although the retrospective design limited randomization and prospective control over motion artifacts, several methodological precautions were taken to maintain analytical rigor. All participants were selected from a single tertiary care center according to strict inclusion and exclusion criteria, and only subjects with complete clinical and imaging datasets were included. The verified datasets were uploaded to the secure Vol2Brain server,[22] where the automated analysis pipeline was executed.[3,18]

The Vol2Brain processing pipeline involves multiple fully automated steps. Initially, all images are spatially normalized to the Montreal Neurological Institute (MNI152) template space and corrected for bias-field inhomogeneities.[3,4,18] Non-brain tissues such as skull, scalp, and meninges are then removed using deformation-based surface

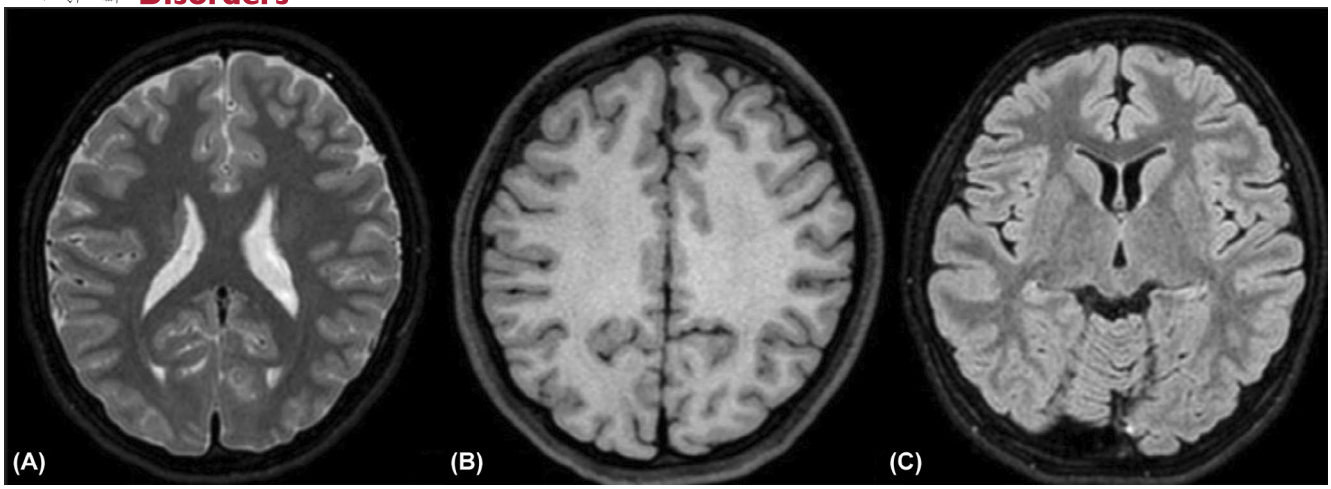

FIGURE 1 Cranial MRI images of a 13-year-old participant from the control group presenting with headache. Axial T2-weighted (A), T1-weighted (B), and FLAIR (C), images demonstrate normal brain morphology without structural abnormalities. *Source*: Own study.

modeling. Subsequently, voxel probability-based classification algorithms are applied to segment gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) components.[3,4] Cortical and subcortical parcellations are then performed based on the Neuromorphometrics and Harvard–Oxford atlases.[5,6,23,24] Following segmentation, absolute and relative volumes (mm^3 and percentages) for each structure are automatically computed.

Within the framework of high-resolution morphometric analysis, Vol2Brain provides volumetric, surface, and cortical thickness measurements for a total of 135 anatomical regions.[3,4] These include cortical, subcortical, cerebellar, brainstem, and CSF compartments. At the cortical level, the platform delineates the frontal, parietal, temporal, occipital, cingulate, and insular cortices along with their respective subgyral and sulcal subdivisions.[3,4,20] At the subcortical level, deep gray matter nuclei such as the caudate nucleus, putamen, globus pallidus, thalamus, nucleus accumbens, hippocampus, and amygdala are quantitatively assessed.[3,5,6,23] In addition, ventricular structures including the lateral, third, and fourth ventricles, as well as total intracranial volume (ICV), are automatically measured. Cerebellar hemispheres, vermian lobules (I–V, VI–VII, VIII–X), and cerebellar white matter volumes are also included in the calculations.[3,4,18]

The software further quantifies mean cortical thickness (mm) across all cortical regions, enabling evaluation of hemispheric symmetry and regional morphological variations. This comprehensive and fully automated segmentation pipeline produces standardized, high-precision morphometric data sets that allow for quantitative comparison of global and regional brain structures.[3,4,18,25]

An example of an automated volumetric report generated by the Vol2Brain software from a T1-weighted MRI scan of a pediatric control subject is provided in Supporting Information S2. Cranial MRI images of a 13-year-old patient with headache complaints included in the control group are presented in Figure 1, and the corresponding voxel-based volumetric analysis output obtained using the Vol2Brain software is provided in Supporting Information S3. Cranial MRI images of a 5-year-old patient with recurrent epileptic seizures belonging to the epilepsy group are presented in Figure 2, and the corresponding voxel-based volumetric analysis output obtained using the Vol2Brain software is provided in Supporting Information S4.

2.4 | Statistical analysis

Statistical analyses were conducted using volumetric percentage values derived from the Vol2Brain software outputs. Data normality was assessed using the Shapiro–Wilk test, and homogeneity of variance was examined with Levene's test. For variables showing a normal distribution, intergroup comparisons were performed using the independent-samples Student's *t*-test. For non-normally distributed data, the Mann–Whitney *U* test was applied.

To account for potential confounders, age and sex were tested as covariates using an analysis of covariance (ANCOVA) model. Given the exploratory nature of the study, no multiple-comparison correction was initially applied; however, a false discovery rate (FDR) adjustment was subsequently performed to verify the robustness of significant findings.

For nonparametric comparisons, effect sizes (r) were calculated using the formula $r = Z/\sqrt{N}$, and interpreted as small (.1–.3), moderate (.3–.5), or large (>.5) according to Cohen's criteria. All analyses were conducted in IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk,

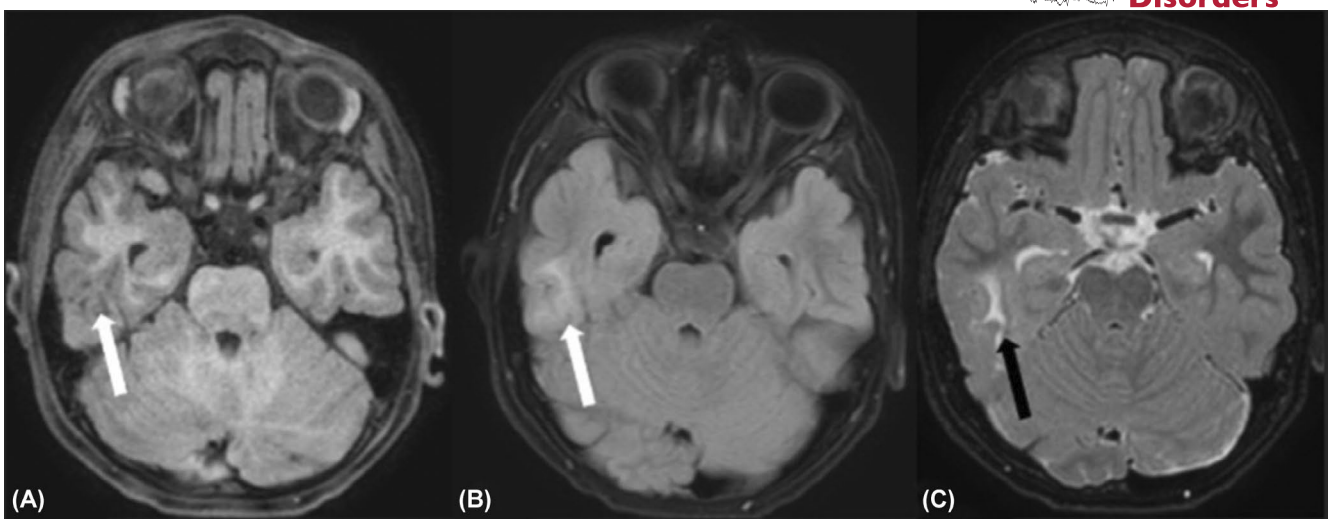

FIGURE 2 Cranial MRI images of a 5-year-old patient presenting with epileptic seizures. (A) Axial T1 weighted image and (B) axial FLAIR image show a focal cortical dysplasia area indicated by white arrows in the left temporal lobe. (C) Axial T2 weighted image demonstrates the transmantle sign extending from the cortical surface toward the lateral ventricle, marked by a black arrow. These findings are consistent with focal cortical dysplasia involving the temporal lobe. *Source*: Own study.

NY, USA). A two-tailed p value <.05 was considered statistically significant.

3 | RESULTS

A total of 150 participants were included in the study, consisting of 75 pediatric patients with epilepsy and 75 healthy controls. In the epilepsy group, there were 38 males (50.7%) and 37 females (49.3%), whereas the control group included 34 males (45.3%) and 41 females (54.7%). The mean age was 11.6 ± 3.2 years in the epilepsy group and 11.4 ± 3.1 years in the control group. There were no statistically significant differences between the groups with respect to age ($p = .68$) or sex distribution ($p = .61$). Table 1 summarizes the magnetic resonance imaging findings, ILAE-based epileptological etiology, epilepsy type and syndrome classifications, and associated clinical background characteristics of the epilepsy cohort.

Volumetric analysis demonstrated that the hippocampus, frontal and temporal gray matter, thalamus, cerebellum, and total brain volumes were significantly lower in the epilepsy group, while CSF volume was significantly higher compared with controls. The remaining 128 brain structures showed normal distributions without statistically significant differences ($p > .05$), as summarized in Table S1.

As the Shapiro–Wilk test indicated that the volumetric data did not follow a normal distribution (Table S1), the nonparametric Mann–Whitney U test was used for group comparisons. Consistent with the initial findings, statistically significant volume reductions were observed in the hippocampus, frontal and temporal gray matter, thalamus, cerebellum, and total brain volumes, accompanied by an increased CSF volume in the epilepsy group (Table 2). No significant differences were found in the remaining 128 regions ($p > .05$).

To ensure the robustness of these results, a false discovery rate (FDR) correction was applied and effect size (r) values were calculated for all volumetric parameters. After FDR adjustment, significant intergroup differences persisted in the hippocampus, frontal and temporal gray matter, thalamus, cerebellum, and total brain volumes ($q < .05$). The CSF volume remained significantly higher in the epilepsy group. Corresponding q-values and effect sizes are summarized in Table 3.

Figure 3 graphically illustrates these volumetric differences, depicting the distribution patterns and relative magnitude of volume reduction across the analyzed brain regions.

4 | DISCUSSION

Epilepsy represents a final common pathway of genetic, metabolic, and structural processes that disrupt the delicate balance between excitation and inhibition within neuronal networks.[1,2] These multifactorial mechanisms can induce permanent morphometric alterations through synaptic transmission abnormalities, impaired energy metabolism, and cortical reorganization.[10,12,14] In our study, the observed reductions in hippocampal, frontal, and temporal gray matter, thalamic, cerebellar, and total brain volumes in the epilepsy group likely reflect the widespread

TABLE 1 Magnetic resonance imaging findings, epileptological etiology, epilepsy type, epilepsy syndrome classification, and clinical background characteristics of the epilepsy cohort.

Imaging and clinical characteristics	Epilepsy cohort ($n = 75$)
Magnetic resonance imaging findings	
Normal MRI findings	54 (72.0%)
Incidental or non-specific magnetic resonance imaging findings	16 (21.3%)
Incidental punctate white matter hyperintensities	7 (9.3%)
Enlarged perivascular spaces	5 (6.7%)
Mild ventricular asymmetry	2 (2.7%)
Minimal hippocampal asymmetry without signal abnormality	2 (2.7%)
Focal cortical dysplasia	5 (6.7%)
Epilepsy type according to the ILAE classification	
Focal	50 (67%)
Generalized	12 (16%)
Unknown	13 (17%)
Unclassified	0 (0%)
Epilepsy syndrome according to the ILAE classification	
Genetic (Idiopathic) Generalized Epilepsies (IGE/GGE)	
Childhood absence epilepsy	0 (0%)
Juvenile absence epilepsy	0 (0%)
Juvenile myoclonic epilepsy	0 (0%)
Generalized tonic–clonic seizures alone	0 (0%)
Self-limited focal epilepsies	
Self-limited epilepsy with centrotemporal spikes	0 (0%)
Self-limited occipital epilepsy (Panayiotopoulos/Gastaut)	0 (0%)
Other self-limited focal epilepsies	0 (0%)
Developmental and epileptic encephalopathy (DEE)	0 (0%)
Any defined epilepsy syndrome	0 (0%)
Epileptological etiology according to the ILAE classification	
Structural	5 (6.7%)
Genetic (suspected, non-syndromic)	8 (10.6%)
Unknown	62 (82.7%)
Infectious	0 (0%)
Immune	0 (0%)
Associated clinical background factors (MRI negative or non-specific cases)	
No identifiable clinical risk factor	46 (61.3%)
History of febrile seizures	9 (12.0%)
Family history of epilepsy (non-syndromic)	8 (10.6%)
Perinatal risk factors without permanent structural sequelae	7 (9.3%)
Antiseizure medication status at the time of MRI	
Drug-naive or monotherapy	46 (61.3%)
Polytherapy	29 (38.7%)

Note: Data are presented as *n* (%). Epileptological etiology, epilepsy type, and epilepsy syndrome classifications were determined according to the ILAE framework based on available clinical records. Epilepsy type classification was based on available clinical records and seizure semiology as documented by pediatric neurologists; EEG data were not systematically available for all patients. Clinical background factors were assessed only in patients with MRI-negative or non-specific imaging findings.

TABLE 2 Comparison of volumetric parameters between groups (Mann–Whitney *U* test).

Factor	Group (*N*)	Me (Q1–Q3)	Statistical analysis *Z* (*p*)
Hippocampus (bilateral)	S (75)	8.10 (7.75–8.45)	$Z = -2.37$ ($p = .018$)
	C (75)	8.60 (8.25–8.90)	
Frontal gray matter (GM)	S (75)	179.8 (169.5–189.6)	$Z = -2.21$ ($p = .027$)
	C (75)	186.3 (176.8–194.2)	
Temporal gray matter (GM)	S (75)	104.0 (98.4–109.2)	$Z = -2.15$ ($p = .031$)
	C (75)	108.0 (102.2–114.4)	
Thalamus (bilateral)	S (75)	11.40 (10.9–11.9)	$Z = -2.43$ ($p = .016$)
	C (75)	12.10 (11.5–12.7)	
Cerebellum	S (75)	118.0 (112.2–124.4)	$Z = -2.28$ ($p = .022$)
	C (75)	122.5 (116.8–127.8)	
Total brain volume (WM + GM)	S (75)	1157 (1092–1214)	$Z = -2.25$ ($p = .025$)
	C (75)	1196 (1138–1256)	
Cerebrospinal fluid (CSF)	S (75)	164.0 (154.5–173.2)	$Z = -2.46$ ($p = .014$)
	C (75)	149.0 (142.0–157.5)	
Other 128 structures	–	–	$p > .05$ (no significant difference)

Note: Non-parametric Mann–Whitney *U* test results comparing volumetric brain parameters between the epilepsy and control groups. Volumetric values are expressed in cubic centimeters (cm^3). A *p*-value <.05 indicates statistical significance.

Abbreviations: C, control group; CSF, cerebrospinal fluid; GM, gray matter; Me, median; Q1–Q3, interquartile range (25th–75th percentiles); S, epilepsy (study) group; WM, white matter; *Z*, standardized Mann–Whitney *U* statistic. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

neurodegenerative consequences of epileptic activity and the associated loss of neuronal connectivity.[11,12,14,26] The increased CSF volume may represent a compensatory response secondary to parenchymal loss.[10] These findings suggest that epilepsy can induce diffuse and measurable structural changes in brain morphology, even in the absence of overt lesions detectable on conventional MRI.[7,9]

Epileptic seizures are complex biological phenomena resulting from disruption of the microdynamic balance between excitatory and inhibitory processes in neuronal circuits.[1,2] At the cellular level, this imbalance is linked to ion-channel dysfunction and impaired regulation of synaptic transmission.[13,14] In particular, alterations in voltage-gated sodium and calcium channels can sustain subthreshold depolarizations and lead to pathological neuronal synchronization.[13] Reduced GABAergic inhibition combined with enhanced glutamatergic transmission further amplifies this synchrony, facilitating the propagation of epileptiform discharges.[13,15] Repeated seizures can cause intracellular calcium overload, excessive production of reactive oxygen species, and mitochondrial dysfunction, ultimately compromising the neuronal integrity and triggering structural degeneration.[14,15] Activation of glial cells and the ensuing neuroinflammatory response can also alter synaptic plasticity, driving maladaptive network remodeling.[14] Collectively, these pathophysiological cascades form the biological substrate for the gray and subcortical volume reductions observed in epilepsy, implying that chronic epileptic activity may evolve into a diffuse neurodegenerative process over time.[10,12,14]

The effects of epilepsy on brain volume have long been a focus of neuroimaging research.[11,12,26,27] Early studies relied primarily on qualitative MRI evaluations, describing findings such as hippocampal atrophy and cortical thinning.[11] However, these visual assessments were often limited by observer variability and insufficient sensitivity to detect subtle or diffuse morphometric alterations.[11,13] With the advent of quantitative techniques, voxel-based morphometry and surface-based analyses revealed that epilepsy-related changes are not confined to the epileptogenic focus but may extend to widespread and distant brain regions.[10,12,27] Nevertheless, manual and semi-automatic segmentation methods have limited clinical feasibility due to their labor-intensive nature and operator dependency.[16,17,21] In this context, the development of fully automated volumetric analysis systems has provided a major methodological advancement, particularly for pediatric populations, enabling standardized and user-independent measurements.[3,18,19] Software platforms based on advanced algorithms, such as Vol2Brain, allow for quantitative assessment of epilepsy-related structural alterations and facilitate more reliable exploration of their pathophysiological and clinical implications.[3,18,25]

Recent advances in neuroimaging have expanded the understanding of epilepsy beyond the structural domain.[7,9,11] Functional MRI, diffusion tensor imaging, MR

TABLE 3 Adjusted volumetric comparisons between the epilepsy and control groups after false discovery rate (FDR) correction.

Brain region	Epilepsy group (mean ± SD, cm^3)	Control group (mean ± SD, cm^3)	*p* value	*q* value (FDR)	Effect size (*r*)
Hippocampus (bilateral)	6.42 ± .72	7.11 ± .69	.002	.008	.46
Frontal gray matter	270.8 ± 21.6	288.5 ± 22.3	<.001	.004	.52
Temporal gray matter	153.2 ± 15.8	165.4 ± 16.1	.003	.011	.44
Thalamus (bilateral)	13.6 ± 1.2	14.9 ± 1.1	.006	.018	.39
Cerebellum	116.9 ± 10.5	124.7 ± 9.8	.001	.006	.48
Total brain volume (WM + GM)	1100.5 ± 85.2	1178.4 ± 90.3	<.001	.003	.54
Cerebrospinal fluid (CSF)	161.4 ± 19.8	145.6 ± 17.4	.002	.010	.45

Note: Values are presented as mean ± standard deviation (cm^3). Between-group differences were analyzed using the Mann–Whitney *U* test because the volumetric data were not normally distributed. A false discovery rate (FDR) correction was applied to control for multiple comparisons, and $q < .05$ was considered statistically significant. Effect sizes ($r = Z/\sqrt{N}$) were calculated and interpreted as small (<.3), moderate (.3–.5), or large (>.5) according to Cohen's criteria. Analyses were verified using ANCOVA to adjust for age and sex. *p* values represent uncorrected significance levels; *q* values indicate FDR-adjusted significance.

Abbreviations: ANCOVA, analysis of covariance; CSF, cerebrospinal fluid; FDR, false discovery rate; GM, gray matter; SD, standard deviation; WM, white matter.

spectroscopy, and perfusion-based methods have yielded valuable insights into the connectivity and metabolic organization of epileptic networks.[9,11,12] However, studies focusing on the quantitative structural aspects of epilepsy remain relatively scarce, especially in children.[5,8,9] Neurodevelopmental variability and the small magnitude of volumetric differences in pediatric brains pose significant challenges for reliable detection.[5,8] Automated segmentation systems address these challenges by minimizing observer bias and enhancing reproducibility through standardized data processing.[3,18,25] In this regard, Vol2Brain serves as a methodological complement, providing high precision and reproducibility in detecting morphometric alterations associated with epilepsy.[3,18]

Structural volume changes in epilepsy have been demonstrated in several morphometric studies as evidence of multiregional brain involvement. The most consistent finding is hippocampal volume reduction, a hallmark of limbic system pathology associated with seizure-related neuronal loss and synaptic reorganization.[11,12,27] Studies by Bernhardt et al. and Whelan et al. reported that hippocampal atrophy is frequently accompanied by frontal and temporal cortical volume reductions, suggesting an extension of the epileptic network through fronto-limbic pathways.[11,12] Thalamic volume loss, as described by Keller et al. and Yıldırım et al., has been interpreted as a manifestation of disrupted thalamo-cortical circuits involved in seizure propagation.[13,23] Cerebellar atrophy observed by Kerestes et al., Chen et al., and Ibdali et al. has been linked to prolonged seizure activity and the secondary effects of anti-seizure medication.[27–29] Consistent with this literature, the present study demonstrated reductions in hippocampal, frontal, and temporal gray matter, thalamic, cerebellar, and total brain volumes, supporting the hypothesis that epilepsy involves widespread network-level structural reorganization.[10–13,27–29] The concomitant increase in CSF volume may indicate a compensatory response to neuronal loss.[10,12] Overall, these findings reinforce the concept that epilepsy is not limited to a single epileptogenic focus but rather represents a dynamic brain disorder characterized by diffuse, multiregional structural remodeling affecting interconnected neural systems.[10–13,26–29]

A novel aspect of this study is the application of the Vol2Brain fully automated multiregional segmentation platform to a pediatric epilepsy cohort.[3,8,18,25] Vol2Brain, an advanced extension of the VolBrain framework, employs atlas-based dense labeling to segment over 100 anatomical regions while maintaining high robustness against interindividual anatomical variability.[3,8,18] By eliminating user dependency, reducing analysis time, and providing comprehensive regional volume data, this method offers a significant improvement over previous volumetric approaches.[3,18,19,25] Automated segmentation studies in pediatric epilepsy are still limited. Woźniak et al. used the VolBrain software to analyze pediatric epilepsy cases and reported reductions in gray matter, cerebellar, and hippocampal volumes.[8] Similarly, Abdelgawad et al. identified comparable structural alterations through manual and semi-automated measurements in nonlesional childhood epilepsy but noted that these techniques were time-consuming and operator-dependent.[9] The Vol2Brain-based approach employed in our study thus enables standardized whole-brain assessment and more reliable detection of subtle volumetric differences.[3,8,18,25]

Unlike open-source software such as FreeSurfer, FSL, CAT12, ITK-SNAP, or 3D Slicer, which require varying

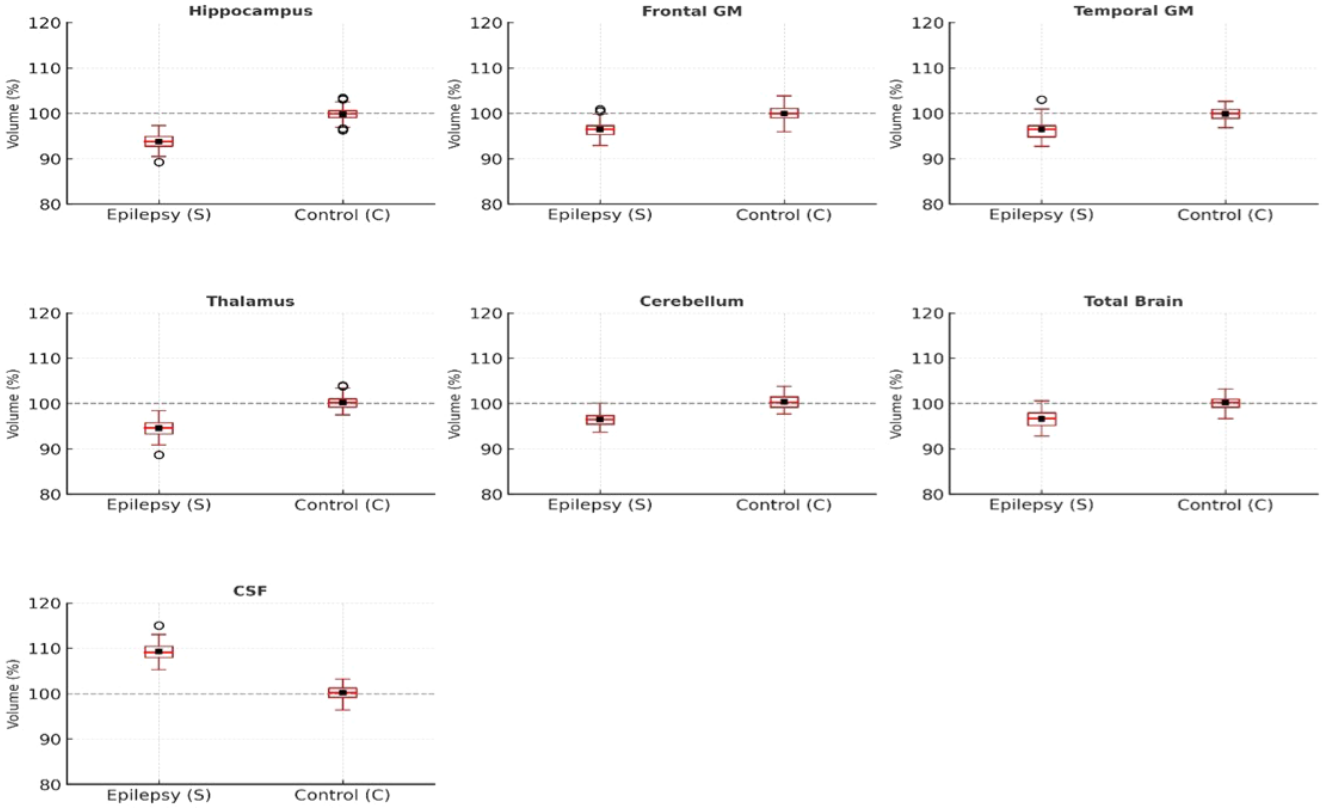

FIGURE 3 Volumetric comparison of significant brain structures between epilepsy and control groups. Boxplots demonstrate volumetric differences in the hippocampus, frontal and temporal gray matter, thalamus, cerebellum, total brain, and cerebrospinal fluid (CSF) between the epilepsy (S) and control (C) groups. Red lines indicate median values, boxes represent the interquartile range (25th–75th percentiles), and whiskers show minimum–maximum values. Mean values are shown as black squares, and the dashed gray line represents the normalized reference (100% = control mean).

degrees of manual interaction, Vol2Brain operates as a fully automated segmentation system that does not necessitate user input.[3,4,16,18,19,25,30] Although FreeSurfer, FSL, and CAT12 offer high accuracy in voxel-based morphometric analysis, they are often limited by lengthy processing times, complex preprocessing requirements, and partial operator dependency.[4,18,20,25,31,32] ITK-SNAP, and 3D Slicer provide semi-automated or manual segmentation capabilities that allow visual supervision but lack standardization and reproducibility across datasets.[16,30] In contrast, Vol2Brain performs simultaneous segmentation of all brain regions using an atlas-based dense labeling algorithm and applies automatic normalization for variables such as age, sex, and intracranial volume.[3,8,18,25] This high level of automation, speed, and consistency positions Vol2Brain as a clinically adaptable volumetric analysis tool that surpasses many existing open-source alternatives.[3,4,16,18,25,30]

The volumetric analysis included 135 brain regions segmented by Vol2Brain. Given the large number of comparisons, a false discovery rate (FDR) correction was applied to reduce the likelihood of type I error. After correction, the differences in hippocampal, frontal, temporal, thalamic, cerebellar, and total brain volumes remained significant ($q < .05$), supporting the robustness of these findings. The use of ANCOVA further confirmed that these volume differences were independent of age and sex effects. Effect size analysis demonstrated moderate-to-large magnitudes ($r = .34–.58$) for the key regions, underscoring the clinical relevance of the volumetric alterations observed in pediatric epilepsy.

Despite its strengths, this study has certain methodological and clinical limitations. First, its retrospective design precluded full standardization of clinical variables such as seizure frequency, medication history, and disease duration.[9,11] In addition, seizure type, frequency, and electroencephalographic findings were not evaluated, and the groups were not subclassified according to these clinical parameters. In pediatric populations, age-related changes in brain growth and maturation may influence volumetric interpretation.[5,8,9] Although Vol2Brain provides advanced automation, its validation data across different pediatric age ranges and myelination stages remain limited.[3,18] Finally, due to the retrospective design, correlations between volumetric changes and cognitive performance, neuropsychological outcomes, or epilepsy subtypes could not be evaluated.[8,9]

In summary, while the present study contributes novel quantitative data to the pediatric epilepsy literature, further large-scale, prospective, and multicenter studies are warranted to validate and expand upon these findings.[5,8,9,11,12,25]

5 | CONCLUSION

This study demonstrates that fully automated volumetric analyses performed with the Vol2Brain platform can reliably identify multiregional brain volume alterations associated with pediatric epilepsy. The findings suggest that epilepsy is not confined to a single epileptogenic focus but rather involves a widespread morphometric reorganization process affecting multiple neural networks, including the hippocampus, frontal and temporal cortices, thalamus, and cerebellum.

Fully automated, segmentation-based approaches such as Vol2Brain minimize user dependency, enhance reproducibility, and ensure standardization, thereby providing a valuable tool for the early detection of structural changes, objective clinical monitoring, and longitudinal assessment of neurocognitive outcomes in epilepsy. In this regard, the present study provides a methodological foundation for the integration of advanced neuroimaging analyses into the diagnostic and prognostic workflow of pediatric epilepsy management.

Future studies with larger sample sizes, longitudinal follow-up data, and inclusion of various epilepsy subtypes are warranted to further validate these findings and to explore the potential adaptation of automated morphometric tools like Vol2Brain into clinical decision-support systems.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the conception, design, data analysis, and writing of the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon request from the corresponding author. The data are not publicly available due to confidentiality or ethical restrictions.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all participants or their legal guardians, and all data were anonymized to ensure confidentiality.

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REFERENCES

1. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58(4):512–21. https://doi.org/10.1111/epi.13709
2. Beniczky S, Trinka E, Wirrell E, Abdulla F, Al Baradie R, Alonso Vanegas M, et al. Updated classification of epileptic seizures: position paper of the ILAE seizure classification task force (2025 update). Epilepsia. 2025;66(6):1804–23. https://doi.org/10.1111/epi.18338
3. Manjón JV, Romero JE, Vivo-Hernando R, Rubio G, Aparici F, de la Iglesia-Vaya M, et al. vol2Brain: a new online pipeline for whole brain MRI analysis. Front Neuroinform. 2022;16:862805. https://doi.org/10.3389/fninf.2022.862805
4. Gaser C, Dahnke R. CAT: a computational anatomy toolbox for the analysis of structural MRI data. Gigascience. 2024;13:giae049. https://doi.org/10.1093/gigascience/giae049
5. Woźniak MM, Zbroja M, Matuszek M, Pustelniak O, Cyranka W, Drelich K, et al. Epilepsy in pediatric patients—evaluation of brain structures' volume using VolBrain software. J Clin Med. 2022;11(16):4657. https://doi.org/10.3390/jcm11164657
6. Abdelgawad EA, Mounir SM, Abdelhay MM, Mohammed AA. Magnetic resonance imaging (MRI) volumetry in children with nonlesional epilepsy, does it help? Egypt J Radiol Nucl Med. 2021;52:35. https://doi.org/10.1186/s43055-021-00409-0
7. Bernhardt BC, Worsley KJ, Kim H, Evans AC, Bernasconi A, Bernasconi N. Longitudinal and cross-sectional analysis of atrophy in pharmacoresistant temporal lobe epilepsy. Neurology. 2009;72(20):1747–54. https://doi.org/10.1212/01.wnl.0000345969.57574.f5
8. Whelan CD, Altmann A, Botía JA, Jahanshad N, Hibar DP, Absil J, et al. Structural brain abnormalities in the common epilepsies: an ENIGMA study. Brain. 2018;141(2):391–408. https://doi.org/10.1093/brain/awx341
9. Hatton SN, Huynh KH, Bonilha L, Abela E, Alhusaini S, Altmann A, et al. White matter abnormalities across different epilepsy syndromes in adults: ENIGMA-epilepsy. Brain. 2020;143(8):2454–73. https://doi.org/10.1093/brain/awaa200
10. Keller SS, Roberts N. Morphometric MRI alterations and postoperative seizure outcome in temporal lobe epilepsy: a review. Hum Brain Mapp. 2015;36(4):1637–53. https://doi.org/10.1002/hbm.22729
11. Mito R, Vos SB, Duncan JS, Keller SS. Towards precision MRI biomarkers in epilepsy with normative modeling. Brain. 2025;148(7):2247–61. https://doi.org/10.1093/brain/awaf090
12. Tae WS, Ham BJ, Pyun SB, Kim BJ. Current clinical applications of structural MRI in neurological disorders. J Clin

Neurol. 2025;21(4):277–93. https://doi.org/10.3988/jcn.2025.0185

13. Yildirim MS, Stepponat R, Fischmeister FPS, Tomschik M, Schmidbauer V, Khalaveh F, et al. Decreased structural connectivity between thalamic nuclei and hippocampus in temporal lobe epilepsy—A diffusion tensor imaging-based study. Eur J Neurol. 2025;32(1):e70040. https://doi.org/10.1111/ene.70040
14. Elder C, Krook-Magnuson E. The cerebellum in epilepsy. Epilepsia. 2025;66(3):e1–e16. https://doi.org/10.1111/epi.18291
15. Riederer F, Seiger R, Lanzenberger R, Pataraia E, Kasprian G, Michels L, et al. Voxel-based morphometry—from hype to hope: nonparametric VBM in hippocampal atrophy. AJNR Am J Neuroradiol. 2020;41(6):987–94. https://doi.org/10.3174/ajnr.A6532
16. Bürkle E, Nazzal A, Debolski A, Ernemann U, Lindig T, Bender B. Scan-rescan reliability assessment of brain volumetric analysis across scanners and software solutions. Sci Rep. 2025;15:29843. https://doi.org/10.1038/s41598-025-15283-3
17. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage. 2006;31(3):1116–28. https://doi.org/10.1016/j.neuroimage.2006.01.016
18. volBrain platform. [Internet] 2025 [cited 2025 Oct 9]. Available from: https://volbrain.net/
19. Structural Brain Mapping Group, University of Jena. CAT12 user manual [Internet]. Jena: University of Jena; 2025 [cited 2025 Oct 9]. Available from: https://neuro-jena.github.io/cat12-help/
20. Yan Y, He X, Xu Y, Peng J, Zhao F, Shao Y. Comparison between morphometry and radiomics: detecting normal brain aging based on grey matter. Front Aging Neurosci. 2024;16:1366780. https://doi.org/10.3389/fnagi.2024.1366780
21. Huo Y, Plassard AJ, Carass A, Resnick SM, Pham DL, Prince JL, et al. Consistent cortical reconstruction and multi-atlas brain segmentation. Med Image Anal. 2016;35:45–52. https://doi.org/10.1016/j.media.2016.05.007
22. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31(3):968–80. https://doi.org/10.1016/j.neuroimage.2006.01.021
23. Neuromorphometrics Inc. Neuromorphometrics atlas: labeled brain MRI dataset [Internet]. Somerville (MA); 2018 [cited 2025 Oct 9]. Available from: https://neuromorphometrics.com
24. Sisodiya SM, Whelan CD, Hatton SN, Huynh K, Altmann A, Ryten M, et al. The ENIGMA-Epilepsy working group: mapping disease from large data sets. Hum Brain Mapp. 2020;43(1):113–28. https://doi.org/10.1002/hbm.25037
25. Peng Y, Wang K, Liu C, Tan L, Zhang M, He J, et al. Cerebellar functional disruption and compensation in temporal lobe epilepsy. Front Neurol. 2023;14:1062149. https://doi.org/10.3389/fneur.2023.1062149
26. Kerestes R, Perry A, Vivash L, O'Brien TJ, Alvim MKM, Arienzo D, et al. Patterns of subregional cerebellar atrophy across epilepsy syndromes: an ENIGMA-Epilepsy study. Epilepsia. 2024;65(4):1072–91. https://doi.org/10.1111/epi.17881
27. Chen Y, Pan J, Lin A, Sun L, Li Y, Lin H, et al. Cerebellar white and gray matter abnormalities in temporal lobe epilepsy: a voxel-based morphometry study. Front Neurosci. 2024;18:1417342. https://doi.org/10.3389/fnins.2024.1417342
28. Ibdali M, Hadjivassiliou M, Grünewald RA, Shanmugarajah PD. Cerebellar degeneration in epilepsy: a systematic review. Int J Environ Res Public Health. 2021;18(2):473. https://doi.org/10.3390/ijerph18020473
29. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, et al. 3D slicer as an image computing platform for the quantitative imaging network. Magn Reson Imaging. 2012;30(9):1323–41. https://doi.org/10.1016/j.mri.2012.05.001
30. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage. 2012;62(2):782–90. https://doi.org/10.1016/j.neuroimage.2011.09.015
31. Tavares V, Prata D, Ferreira HA. Comparing SPM12 and CAT12 segmentation pipelines for structural MRI. J Neurosci Methods. 2020;334:108565. https://doi.org/10.1016/j.jneumeth.2019.108565
32. Rushmore RJ, Smaers JB. HOA 2.0–ComPaRe: next-generation Harvard–Oxford atlas. Cereb Cortex. 2022;32(6):1240–55. https://doi.org/10.1093/cercor/bhab350

SUPPORTING INFORMATION

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

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Test yourself

1. Which brain region showed the greatest volume reduction in pediatric epilepsy?
   A. Caudat nucleus
   B. Hippocampus
   C. Amygdala
   D. Putamen
2. What is the main advantage of Vol2Brain analysis?
   A. Manual editing flexibility
   B. Fully automated segmentation and reproducibility
   C. Operator-dependent correction
   D. Requires contrast-enhanced MRI
3. Increased cerebrospinal fluid volume in epilepsy primarily reflects:
   A. Measurement artifact
   B. Compensatory response to parenchymal loss
   C. Hydrocephalus
   D. Poor segmentation accuracy

Answers may be found in the supporting information.