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# The Nature and Extent of Cerebellar Atrophy in Chronic Temporal Lobe Epilepsy

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## Abstract

**Purpose—**Research indicates that patients with chronic temporal lobe epilepsy (TLE) exhibit cerebellar atrophy compared to healthy controls, but the degree to which specific regions of the cerebellum are affected remains unclear. The purpose of this study was to characterize the extent and lateralization of atrophy in individual cerebellar lobes and subregions in unilateral TLE using advanced quantitative MRI techniques.

**Methods—**Study participants were 46 persons with TLE and 31 age- and gender- matched healthy controls. All participants underwent high-resolution MRI with manual tracing of the cerebellum yielding gray and white matter volumes of the right and left anterior lobes, superior posterior lobes, inferior posterior lobes, and corpus medullare. The degree to which asymmetric versus generalized abnormalities was evident in unilateral chronic TLE was determined and related to selected clinical seizure features (age of onset, duration of disorder).

**Results—**There were no lateralized abnormalities in cerebellar gray matter or white matter in patients with right or left TLE (all p's > 0.2). Compared with controls, unilateral TLE was associated with significant bilateral reductions in the superior ($p = 0.032$) and inferior ($p = 0.023$) posterior lobes, while volume was significantly increased in the anterior lobes ($p = 0.002$), especially in patients with early onset TLE, and not significantly different in the corpus medullare ($p = 0.71$). Total superior cerebellar tissue volumes were reduced in association with increasing duration of epilepsy.

**Discussion—**Patients with unilateral TLE exhibit a pattern of bilateral cerebellar pathology characterized by atrophy of the superior and inferior posterior lobes, hypertrophy of the anterior lobe, and no effect on the corpus medullare. Cross-sectional analyses show that specific aspects of cerebellar pathology are associated with neurodevelopmental (anterior lobe) or chronicity related (superior posterior lobe) features of the disorder.

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**Keywords**

cerebellar lobes; quantitative magnetic resonance imaging; cerebellum

## Introduction

The relationship between chronic epilepsy and cerebellar atrophy has been recognized for quite some time (Bouchet & Cazauvieilh, 1825; Spielmeyer, 1930; Scholz, 1951). Margierison and Corsellis (1966) reported that 45% of 55 patients with chronic temporal lobe epilepsy (TLE) demonstrated injury to the cerebellum, ranging from gross atrophy to gliosis and loss of Purkinje and granular cells in neuropathologic specimens. The etiology of cerebellar damage in TLE and other epilepsy syndromes continues to be debated and current theories include perinatal/developmental injury (Crooks et al., 2000), hypoxic-ischemic injury during prolonged seizures (Botez et al., 1988; Dam, 1970), and the adverse effects of some anti-epileptic medications (Alioglu et al., 2000; Kuruvilla & Bharucha, 1997;Lindvall & Nilsson, 1984).

Early studies used data obtained posthumously, but cerebellar atrophy has been evaluated over the years by evolving imaging techniques including pneumoencephalography (Selhorst et al., 1972; Afifi & Van Allen, 1968; Iivanainen et al., 1977), computed tomography (CT) (McLain et al., 1980; Ballenger et al., 1982; Masur et al., 1990; Botez et al., 1998), and most recently using magnetic resonance imaging (MRI) (Kuruvilla & Bharucha, 1997; Hagemann et al., 2002; Hermann et al., 2005; Szabo et al., 2006; Riederer et al., 2008; McDonald et al., 2008). Most prior neuroimaging studies examined only total cerebellar volumes (Masur et al., 1990; Kuruvilla & Bharucha, 1997; Specht et al., 1997; Lawson et al., 2002; De Marco et al., 2003; Liu et al., 2005), or right and left cerebellar hemispheres (Sandok et al., 2000; Lawson et al., 2000; Szabo et al., 2006; Riederer et al., 2008). Very few studies have examined segmented gray and white matter volumes within each cerebellar hemisphere or specific cerebellar subregions (Hagemann et al., 2002; McDonald et al., 2008; Bonilha et al., 2004). With the advancement of MRI acquisition techniques, the intricate anatomy of the cerebellum is not only more apparent, but is also detailed enough to assess the individual lobes and segmented gray and white matter volumes of the cerebellum, facilitating detection of subtle abnormalities within the cerebellum that may have otherwise been harder to appreciate in older standard imaging procedures. A precise characterization of abnormalities in specific cerebellar lobes among patients with TLE and their relationship to clinical seizure features focusing on neurodevelopmental (age of onset) and so-called chronicity related features of epilepsy (e.g., duration of epilepsy) has yet to be undertaken. Such efforts may be of clinical relevance given reports of an association between cerebellar atrophy in TLE and poorer seizure control following anterior temporal lobectomy (Specht et al., 1997).

Cerebellar atrophy is routinely reported to occur in a subset of patients with chronic epilepsy, the rate varying across studies (Margerison & Corsellis, 1966; Ghatak et al., 1976; Specht et al., 1997; Hermann et al., 2005) which is likely due to varying definitions of pathology as well as differences in patient samples and imaging procedures. Prior work has also suggested that clinical seizure features may be related to cerebellar atrophy including duration of epilepsy, number of lifetime generalized tonic-clonic seizures, treatment factors, and other clinical considerations (Luef et al., 1996; Bohnen et al., 1998; Sandok et al., 2000; Lawson et al., 2000; Hagemann et al., 2002; Hermann et al., 2005; McDonald et al., 2008). However, there again remains considerable variation in findings across studies. Focusing more specifically on individual cerebellar lobes may provide new information regarding selective vulnerabilities associated with specific features of the disorder including its

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neurodevelopmental (age of epilepsy onset) and progressive (duration of epilepsy) characteristics.

Examining individual cerebellar lobe volumes and focusing on segmented (gray and white matter) tissue in patients with chronic unilateral TLE compared to healthy controls, we report here that chronic unilateral TLE is associated with a differential impact across cerebellar lobes with evidence of atrophy in some regions, no differences in others, and hypertrophy in selected regions. Further, the patterns of abnormality are bilateral in nature despite the unilateral nature of the epilepsy, and clinical seizure factors including age of onset and duration of disorder appears to be selectively associated with specific regions of the cerebellum.

## Methods

### Subjects

Subjects were patients with temporal lobe epilepsy (n = 46) and healthy controls (n = 31), aged 14-60. Epilepsy subjects had complex partial seizures of temporal lobe origin as determined by consensus diagnosis, an absence of MRI abnormalities other than atrophy on clinical reading, and no other neurological disorder. Healthy controls were either a friend, relative, or spouse of an epilepsy participant, had no current substance abuse or medical or psychiatric condition that could affect cognitive functioning, no episode of loss of consciousness greater than five minutes, identified developmental learning disorder, or repetition of a grade in school.

The majority (n=35) of the temporal lobe epilepsy patients had undergone continuous video-EEG monitoring of spontaneous seizures and 17 had unilateral left and 18 had unilateral right temporal lobe onsets. The remaining subjects did not undergo ictal monitoring. Ictally confirmed unilateral temporal lobe epilepsy patients provided the opportunity to determine whether there were lateralized or bilateral cerebellar effects. Table 1 provides demographic and clinical seizure characteristics of the study participants.

There were no significant group differences in sociodemographic features, although TLE subjects were slightly older (p=0.06). Subjects with temporal lobe epilepsy suffered from seizures of adolescent onset (mean = 12.7 yrs) and long duration (mean = 21.7 yrs). Regarding treatment, the majority of patients (64%) were treated with polytherapy (48 subjects on two medications, 11 subjects on three medications, and 2 subjects on four medications). The minority of patients (36%) were treated with monotherapy including carbamazepine [n=20], phenytoin [n=4], sodium valproate [n=1], gabapentine [n=3], lamotrigine [n=4], phenobarbital [n=1], and topiramate [n=2].

Patient medication history was documented while blinded to cerebellar volumes. Through patient and family interview followed by subsequent confirmation by review of current and all obtainable prior medical records, the presence of phenytoin use and years of phenytoin therapy were obtained in order to relate to the presence and nature of cerebellum abnormalities.

### MRI Procedures

**MR acquisition—**Images were obtained on a 1.5 Tesla GE Signa MR scanner. Sequences acquired for each participant included: 1) T1-weighted, three-dimensional SPGR acquired with the following parameters: TE = 5, TR = 24, flip angle = 40, NEX = 2, FOV =26, slice thickness = 1.5 mm, slice plane = coronal, matrix = 256×192; 2) Proton Density (PD), and 3) T2-weighted images acquired with the following parameters: TE = 36 msec (for PD) or

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96 msec (for T2), TR = 3000 msec, NEX = 1, FOV = 26, slice thickness = 3.0 mm, slice plane = coronal, matrix = 256×192, and an echo train length = 8.

**MR Processing—**MRIs were processed using a semi-automated software package, i.e., Brain Research: Analysis of Images, Networks, and Systems (BRAINS) (Andreasen et al., 1992; Andreasen et al., 1993; Andreasen et al., 1996; Harris et al., 1999; Magnotta et al., 1999; Magnotta et al., 2002). MR processing staff was blinded to the clinical, sociodemographic, and neuropsychological characteristics of the participants. The T1 weighted images were spatially normalized so the anterior-posterior axis of the brain was realigned to the ACPC line and the interhemispheric fissure was aligned relative to the other two axes. A piecewise linear transformation was defined providing the ability to warp the standard Talairach atlas space (Talairach & Tournoux, 1988) onto the re-sampled image. Images from the three pulse sequences were then co-registered using a local adaptation of automated image registration software (Woods et al., 1998). Following alignment of the image sets, the PD and T2 images were re-sampled into 1mm cubic voxels following which an automated algorithm classified each voxel into gray matter, white matter, CSF, blood, or unclassified (Harris et al., 1999). All measurements were obtained in the image space of the subject and not normalized. Age, gender and height were used as covariates in the analysis. All tracing to be described was conducted while blinded to group status and all other subject characteristics.

**Cerebellar Tracing—**The tracing of the cerebellum was based on published guidelines developed by Pierson et al. (2002) (see Figure 1). Figure 2 provides a 3-D representation of the resulting cerebellar lobes. Guide traces along two major fissures were used to assist in subdividing the cortex. The primary fissure, which extends from the cerebellar surface to the white matter center just posterior to lobule V, was identified on the midline sagittal slice and traced on several slices in the axial plane. The horizontal fissure, which is bordered by crus I of VIIA superiorly and crus II of VIIA inferiorly, was traced on several slices in the coronal plane. Guide traces were used to establish the limits of the corpus medullare in the coronal view, starting at its most posterior point and continuing anteriorly on every third slice until the peduncles emerged from the cerebellum. Guide traces were also used to provide a "cutoff point" for the cerebellar peduncles. A guide trace was placed to connect the points where the gray matter ends on the lateral borders of the peduncles to the most anterior point of cerebellar gray matter at the midline, excluding any matter that extends past the gray matter in the axial view.

As a convention for all measured regions, CSF that could be viewed on a single slice as continuous with regions external to the cerebellum was excluded from the measured traces. Internal CSF not extending outside the cerebellum was included in the traces. The discrete classified image was referred to in defining an indistinct or blurry gray-matter CSF border, with reference to the other images for review of validity.

The cerebellum was parcellated into right and left anterior lobes, superior posterior lobes, inferior posterior lobes, and corpus medullare. Left and right hemispheres were designated prior to tracing, with the midline slice designated as part of the right hemisphere.

The *corpus medullare* includes the entire central white matter structure and the output nuclei; however, white matter that branches off into the folia was defined as a part of the neighboring regions. The guide traces were used to assist in identification of the points where the white matter extends into the folia. Beginning on the midline slice, the right corpus medullare was traced on every slice where it appeared, and the left corpus medullare was traced starting on the first slice to the left of the midline. The corpus medullare was

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defined not to extend laterally past the point at which the horizontal fissure extends uninterrupted from the anterior to the posterior border of the cerebellum.

The *anterior lobe* is composed of lobules I-V. Starting at the midline of the right side, the trace began at the most posterior point of the fourth ventricle, proceeding anteriorly and superiorly following the gray matter-CSF border. At the most superior point, near the peak of lobule IV, the trace followed posteriorly the border between gray matter and the tentorium. At the primary fissure, the trace proceeded into the cerebellum to the base of the primary fissure. The trace followed the darkest portion of the primary fissure, and closed to the point of origin at the fourth ventricle.

The *superior posterior lobe* was defined to include lobules VI and VIIAf (folium) in the vermis regions and lobule VI and crus I of VIIA in the hemispheres. Starting at the base of the primary fissure, the trace followed the posterior border of the anterior lobe to the surface of the cerebellum, turning posteriorly at the surface to reach the horizontal fissure. The trace continued through the horizontal fissure, and continued along the superior border of the corpus medullare back to its point of origin. Near the midline, this trace did not extend all the way to the corpus medullare, but reached the base of the horizontal fissure in the vermian lobules VI, VIIAf, and VIIAt and followed the white matter center of the folia to the corpus medullare and back to the origin.

The *inferior posterior lobe* is composed of lobules VIIAt (tuber) through X in the vermian regions, and crus II of VIIA through lobule X in the hemispheres. The trace started at the anterior inferior border of the corpus medullare, continuing along the inferior border of the superior posterior lobe to the posterior end of the horizontal fissure. The trace followed the edge of the cerebellar gray matter inferiorly and anteriorly to the fourth ventricle and then closed at its point of origin.

## Results

### Cerebellar volumes in lateralized left versus right TLE

In order to determine whether there were any differences between the left and right TLE groups in cerebellar volumes, the lateralized groups were compared in regard to segmented volumes of left and right cerebellum gray and white matter using MANCOVA with age, gender, and height as covariates. There was a significant group difference in total ICV, a more traditional covariate. Adjusting for ICV in this circumstance would lead to an underestimation of the effect of epilepsy on brain structure. Comparisons of results using age and ICV versus age, height and gender as covariates are identical in outcome except for the fact that significant differences are modestly attenuated as predicted with ICV as the covariate (comparative results available from authors). The results to be presented control for variation in brain size are using height and gender.

There were no significant left versus right TLE effects for total cerebellar tissue volume ($p = .61$), total cerebellar gray volume ($p = .95$) or total cerebellar white volume ($p = .66$). There were no significant left versus right TLE effects for total tissue volumes of the anterior lobe ($p = .42$), superior posterior lobe ($p = .99$), inferior lobe ($p = .28$) or corpus medullare ($p = .42$). There were also no significant differences between left and right TLE groups in segmented tissue volumes of gray (all p's $> .41$) or white matter (all p's $> .33$) for any of the cerebellar lobes. There were no significant left versus right TLE effects for volumes of total tissue in the left ($p = .66$) or right ($p = .50$) cerebellum, total gray matter in the left ($p = .98$) or right ($p = .94$) cerebellum, or total white matter in the left ($p = .64$) or right ($p = .47$) cerebellum. There were also no differences between the left and right TLE groups in the volumes of total tissue or segmented gray or white matter for the left or right anterior lobe,

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superior or inferior lobe, or corpus medullare (all p's > 0.37). The left and right TLE groups were therefore combined and compared to healthy controls in all subsequent analyses. In summary, lateralized left and right TLE were not associated with any indication of lateralized cerebellar pathology.

### Differences between TLE subjects and controls across cerebellar regions

Patients with TLE were first compared to controls in total cerebellar tissue volume and segmented volumes of gray and white matter using MANCOVA with age, gender and height as covariates. TLE patients showed a significant reduction in total cerebellar gray (p=.033) and for total cerebellum volume (p=.048), but not white matter (p=.91). Overall, there was an 8.8% reduction in total gray matter and 7.3% reduction in total tissue volume.

The left and right cerebellar lobes were then compared between epilepsy and control groups via MANCOVA with age, gender and height as covariates (Figure 3). The overall MANCOVA was significant ($F(16,58) = 3.11$, $p = 0.02$). There was no difference between epilepsy and control groups in the volume of the corpus medullare (p=.61). Anterior lobe tissue volume was significantly *increased* in epilepsy patients (p=.001), while volumes were significantly *reduced* in the inferior (p=.013) and superior (p=.02) posterior lobes. The findings were attributable primarily but not exclusively to differences in gray matter volumes with increased gray matter volume in the anterior lobe in TLE patients (p=.002) and reduction in gray matter in the inferior (p=.041) and superior (p=.008) posterior lobes (Figure 4). Differences in white matter were limited with increased volume in the anterior lobe (p=.014), but no significant differences in the inferior (p=.89) or superior posterior (p=.42) lobes.

The changes in gray matter volume were symmetric and evident bilaterally. The inferior posterior lobe reductions in gray matter were evident in both the left (p=.02) and right sides (p=.05), the superior posterior lobe reductions in gray matter were evident in both the left (p=.01) and right (p=.006) lobes, and the increase in the anterior lobe occurred in both the left (p=.01) and right (p=.002) lobes (Figure 5).

### Phenytoin Effects

The potential effects of phenytoin use were examined in three ways. First, TLE patients with versus without history of lifetime use of phenytoin were contrasted. There were no significant effects of a history of phenytoin use across all left and right gray and white matter cerebellum measures (all p's > 0.8). Secondly, among those patients with a history of phenytoin use, the duration of phenytoin therapy was correlated with the volumes of cerebellum lobe gray and white matter. Again there were no significant correlations detected ($r^2$ from 0.003 to 0.15, all p's > 0.80). Finally, cerebellar volumes were compared for current phenytoin users (yes vs. no) across the cerebellar measures and again no significant effects were found (all p's > 0.9).

### Relationship of onset and duration of epilepsy to cerebellar volumes

The relationship between epilepsy chronicity (duration of epilepsy) and cerebellar volume was examined across lobes. A potential confounding factor when examining duration effects is the subjects' chronological age as increasing duration of epilepsy is highly associated with older age ($r^2 = 0.665$, $p < 0.001$). As cerebellar volume decreases with age (Liu et al., 2003) this becomes an important confound. Partial correlations were performed with age, gender and height as covariates. A significant negative correlation was found such that longer duration of epilepsy was associated with smaller total cerebellar tissue volumes ($r^2 = -0.344$, $p = 0.033$) (Figure 6). Patients with epilepsy were also examined by determining the median duration (20 years) and, using age, gender and height as covariates in the MANCOVA, a

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significant overall effect of duration was noted ($F(2,40) = 2.92$, $p = 0.047$). Duration effects were evident for the total cerebellar tissue ($p = 0.036$) and total cerebellar gray matter ($p = 0.031$) volumes. However, when individual lobes are examined duration effects were associated only with the volume of the superior posterior lobe. The right ($p = 0.022$) and left ($p = 0.017$) superior posterior lobe cerebellar tissue and right ($p = 0.01$) and left ($p = 0.012$) cerebellar gray matter volume reductions in particular were significantly associated with increasing duration of epilepsy. White matter volumes were not significantly affected by duration of epilepsy ($p > 0.1$).

Neurodevelopmental effects (age of onset of recurrent seizures) of epilepsy were examined by determining the median age of onset (12 years) and, using gender and height as covariates, a significant overall effect of age of onset was identified ($F(2,41) = 2.87$, $p = 0.044$). Epilepsy patients with early age of onset (<12 years of age) had significantly larger right ($p = 0.008$) and left ($p = 0.02$) anterior cerebellar gray matter compared to controls. The anterior cerebellar lobe volumes of epilepsy patients with later age of onset (>12 years of age) were not significantly different from controls ($p > 0.3$).

## Discussion

This study investigated the presence and extent of volumetric abnormalities in specific cerebellar lobes among patients with chronic TLE and healthy controls, ages 14-60. Three core findings resulted from this investigation: 1) When comparing left versus right TLE groups there were no *lateralized* abnormalities in total or segmented gray or white matter tissue volumes across any region of the cerebellum. When cerebellar abnormalities are present in unilateral TLE, the abnormalities are bilateral in nature. 2) Identified abnormalities vary across cerebellar lobes and tissue types in that patients with TLE exhibit significant volume reduction in the inferior and superior posterior lobes due to atrophy of gray but not white matter, and significant hypertrophy of the anterior lobes affecting both gray and white matter, with no difference in the volume of the corpus medullare; and 3) Clinical seizure features have differential relationships with various regions of the cerebellum. Increasing chronicity of epilepsy was associated with total cerebellar tissue volumes, but when examined more specifically by cerebellar lobe there was a selective association of duration with volume reduction in the gray matter of the posterior cerebellar lobe. In contrast, earlier age of onset of epilepsy was associated with increased volume of white and gray matter in the anterior lobes. These findings are discussed in more detail below.

### Bilateral cerebellar abnormalities in unilateral temporal lobe epilepsy

Comparing patients with left and right TLE, there were no lateralized differences in the presence or degree of cerebellar pathology across volumes of left versus right cerebellum (total tissue and segmented gray and white matter volumes). These findings corroborate the small number of previous reports of lack of asymmetric cerebellar pathology in unilateral TLE and the absence of lateralized differences in segmented cerebellar gray or white matter in particular (Szabo et al., 2006; McDonald et al., 2008). Further, our data indicated that there were no lateralized differences in the individual left or right cerebellar lobes (anterior, inferior posterior, superior posterior lobes) or the corpus medullare in left versus right TLE. Despite the presence of chronic unilateral TLE, the impact on the structure of the cerebellum is symmetric in nature.

### Abnormalities in specific cerebellar lobes and tissue types

We demonstrated that the impact of chronic TLE on the cerebellum varied as a function of the specific cerebellar lobe and tissue type (Bonilha et al., 2004; McDonald et al., 2008). In

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comparison to healthy controls, patients with TLE exhibited significantly smaller *total* cerebellar volumes (Sandok et al., 2000; De Marco et al., 2003; Hermann et al., 2005; Riederer et al., 2008), which was due primarily to gray matter volume reduction (McDonald et al., 2008). However, the major finding was the variable impact of chronic TLE across cerebellar lobes and tissue types. Compared to healthy controls, patients with TLE had significantly smaller volumes of both the right and left inferior and superior posterior lobes due to significantly affected gray but not white matter. In contrast, volumes of the right and left anterior lobes were increased in TLE patients compared to controls due to affected gray and white matter. Finally, there was no difference in the volume of the corpus medullare. To our knowledge, this is the first MRI report of differential effects of TLE on specific regions and tissue types within the cerebellum.

The literature in this regard has been quite limited. In neuropathologial studies, Corsellis (55) characterized cerebellar atrophy in TLE and suggested that the inferior and superior posterior lobes were more severely affected than the anterior lobes. Crooks et al. (2000) also found a varying impact of chronic epilepsy on cerebellar lobes depending on the etiology of previous cerebral damage. Using MRI techniques, Hagemann et al. (2002) evaluated cerebellar lobe volumes in patients with chronic epilepsy, regardless of epilepsy type or syndrome, and found a variable impact as well with significant volume reduction only in the inferior posterior lobes. Conceivably, as our well characterized TLE patients had very chronic epilepsy of largely childhood/adolescent onset, both neurodevelopmental and chronicity processes could play a role in the obtained findings.

### Neurodevelopmental and chronicity effects on the cerebellum

The effects of the clinical seizure features examined here appeared to have selective relationships to cerebellar pathology. Increasing chronicity of epilepsy (longer duration) was associated with total cerebellar volume loss and further analysis identified region-specific chronicity effects with significantly smaller superior posterior cerebellar lobe volumes compared to patients with a shorter duration of epilepsy. Cerebellar gray matter within these lobes was most impacted by duration of epilepsy. Several studies have reported a significant effect of duration of temporal lobe epilepsy on cerebellar atrophy as a whole (Sandok et al., 2000; Hermann et al., 2005; McDonald et al., 2008; De Marco et al., 2003); however, this is the first report of the effects of duration on a specific cerebellar lobe. Interestingly, this effect is primarily seen after the first 10 years of epilepsy duration and then levels off over subsequent years as examined here. Similarly, the neurodevelopmental consequences of epilepsy appeared to be selective in nature in that patients with early-onset TLE had significantly enlarged anterior lobe volumes.

The potential mechanisms underlying these differential effects in TLE are necessarily speculative. Abnormalities in the foliation and fissuration of the cerebellum during development may lead to cerebellar dysplasias resulting in anterior lobe hypertrophy (Damaerel, 2002; Patel & Barkovich 2002). The anterior lobe also appears to have a different neurodevelopmental origin from that of the posterior lobe (Hallonet et al., 1990; Tiemeier et al., 2010). Studies using quail-chick chimera have demonstrated that the cells of the anterior lobe originate from the metencephalon while the posterior lobe cells come from the mesencephalon. Furthermore, a recent human study on developmental trajectories indicates that the inferior and superior posterior lobes show a much stronger relationship to each other than to the anterior lobe, which may also reflect their different neurodevelopmental origins (Tiemeier et al., 2010).

Connectivity also differs across the cerebellar lobes in interesting ways. Projections from the motor and premotor areas (frontal lobe) terminate mainly in the anterior cerebellar lobes, whereas, the posterior cerebellar lobes mainly receive input from the parietal, temporal, and

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frontal lobes, as well as the cingulate neocortex (Brodal & Bjaalie, 1979; Ito, 1984; Middleton & Strick, 1998; Savic & Thorell, 1996; Schmahmann & Sherman, 1998).

Cerebro-cerebellar connections are bi-directional and there is experimental evidence of the inhibitory role of the cerebellum on the cortex in seizures, particularly, the anterior lobes (Cooper & Upton, 1978; Hori et al., 1987; Davis & Emmonds, 1992; Middleton & Strick, 1998; Lawson et al., 2000). The inhibitory output nuclei of the anterior lobe serve as a gatekeeper of cerebellar output. This inhibitory effect was the basis for Cooper's protocol for electrical stimulation of the anterior cerebellar lobe to reduce seizure frequency (Cooper et al., 1997), positing that the inhibitory cerebellar input to the thalamus resulted in diminished excitatory output to the cortex, thus reducing seizures. Could a larger anterior lobe function similarly, resulting from increasing inhibitory cerebellar input to the thalamus? On the other hand, the larger anterior lobe could also be a result of less apoptosis during development. It is also possible that epilepsy patients who are more severely affected may start with more neurons as a result of abnormal development. These questions may be better answered with longitudinal studies.

### Limitations and Conclusions

There are several limitations to this study. First, this is a cross-sectional study which inevitably lends caution to the inferences, especially concerning analyses of the duration and age of onset effects. A longitudinal study would provide the most reliable information regarding duration effects.

Second, it remains conceivable that chronic medication therapy may affect cerebellar atrophy in TLE. Determination of the impact of medication on cerebellar atrophy is often confounded by the fact that patients on polytherapy or higher medication doses may also have more severe epilepsy, more prolonged seizures, or higher seizure frequency (Ney et al., 1994; Luef et al., 1996; Young et al., 1994). It is important to note here that TLE patients without exposure to phenytoin also exhibited significant cerebellar atrophy suggesting that non-medication effects must play a contributory role as has been suspected. Furthermore, the impact of chronic TLE on the cerebellum is a phenomenon that was well documented and characterized long before the development of AEDs, indicating that there is an independent adverse effect of chronic epilepsy on the cerebellum.

In conclusion, this is the first quantitative MRI study of the pattern and distribution of cerebellar atrophy in patients with TLE. Cerebellar atrophy was symmetric in nature regardless of the laterality of TLE, and the nature of the pathology varied across lobes and tissue types with atrophy in the posterior lobes and hypertrophy of the anterior lobes. These different patterns of pathology may be due to region specific neurodevelopmental (anterior lobe) or chronicity (posterior lobes) effects, although the impact of other factors remains to be determined.

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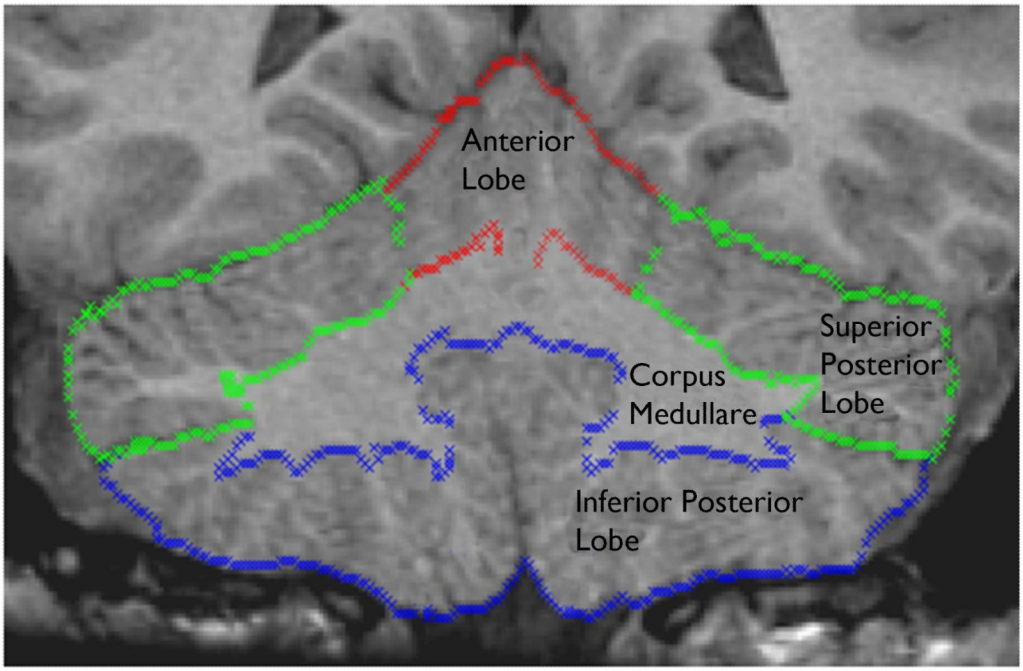


**Figure 1.**
The corpus medullare is defined as all white matter that does not extend into folia. White matter extending into the folia is considered to be part of each lobe. The anterior lobe is bordered caudally by the primary fissure and is composed of lobes I-V. The superior posterior lobe is bounded rostrally by the primary fissure and caudally by the horizontal fissure, being composed of lobe VI and crus I of VIIa. The inferior posterior lobe is bounded rostrally by the horizontal fissure and is composed of crus II of VIIA, VIIb, and lobes VIII, IX and X (numerical designations by Larsell, Schmamann).

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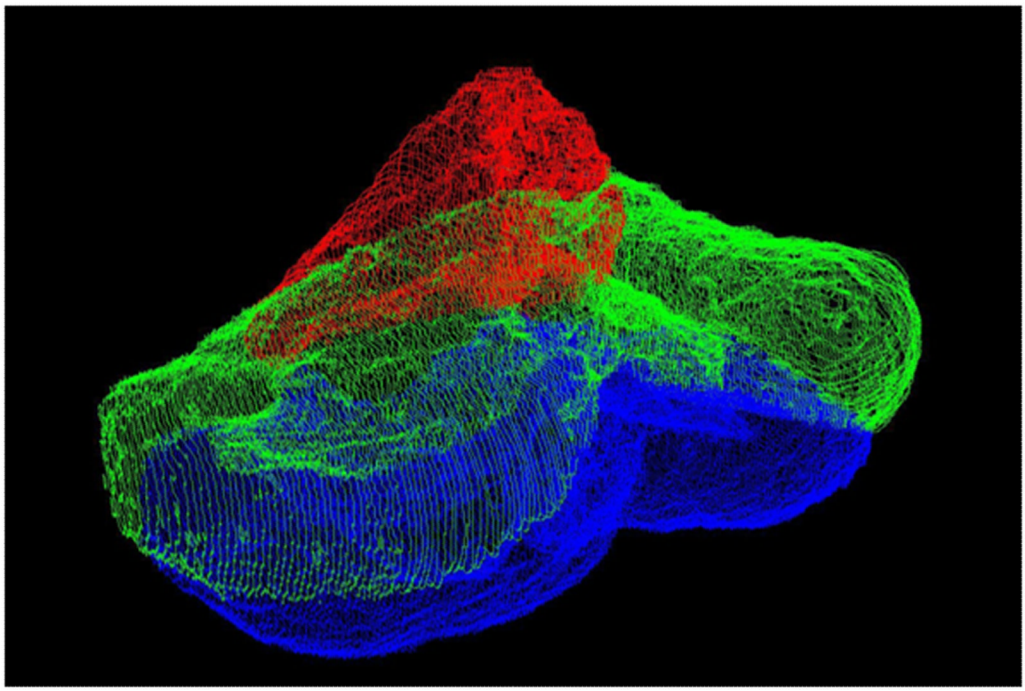

**Figure 2.**
3D image of the coronal view of the cerebellum showing the anterior lobes (red), superior posterior lobes (green), and inferior posterior lobes (blue).

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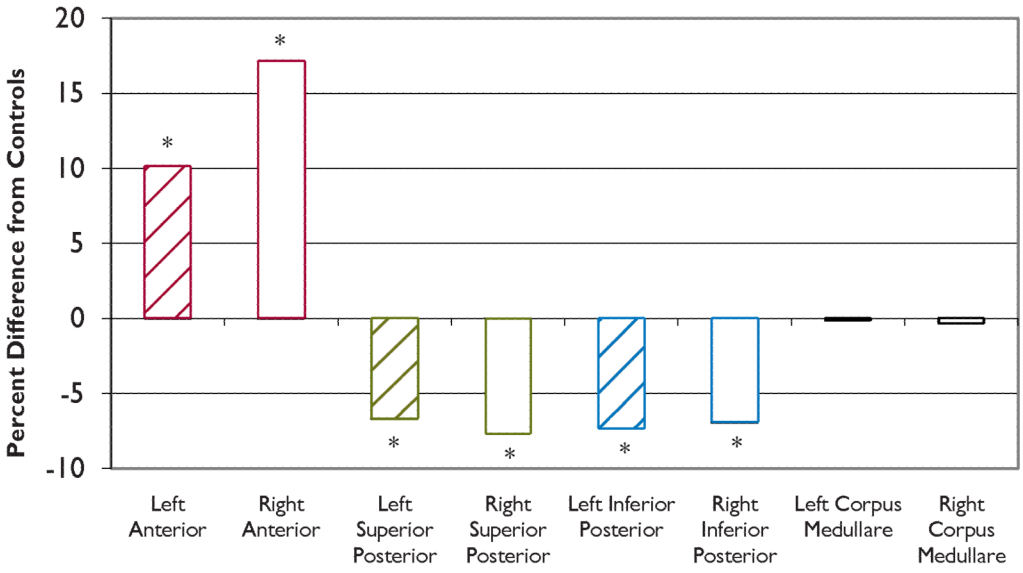


**Figure 3.**

Compared to controls, cerebellar lobe tissue volumes of epilepsy patients show hypertrophy of the anterior lobes and atrophy of the superior posterior and inferior posterior lobes. (*$p \leq 0.05$)

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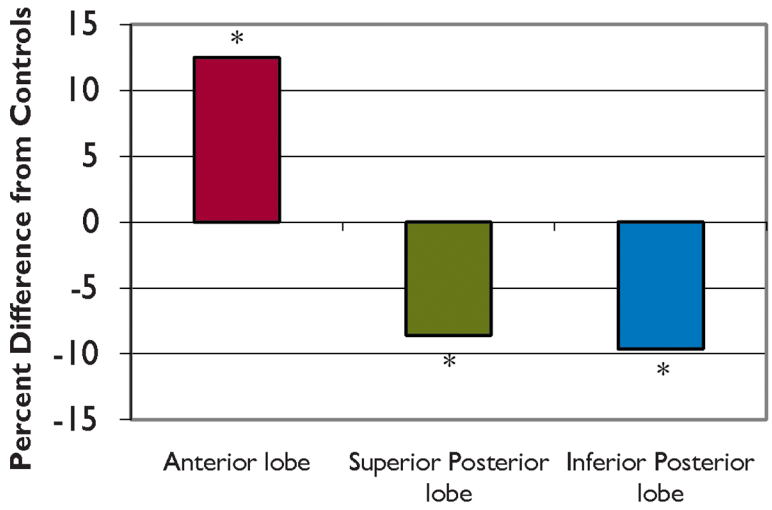


**Figure 4.**
Anterior lobe gray matter is hypertrophied compared to controls, while superior posterior and inferior posterior gray matter is atrophied compared to controls. (*$p \leq 0.05$)

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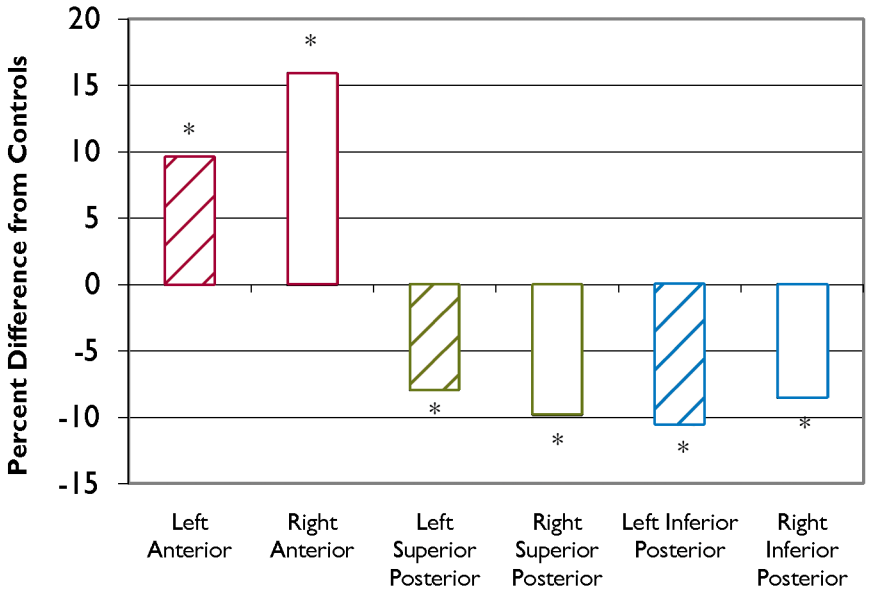


**Figure 5.**

Compared to controls, cerebellar lobe gray matter volumes of epilepsy patients reveal hypertrophy of the anterior lobes and atrophy of the superior posterior and inferior posterior lobes. (*$p \leq 0.05$)

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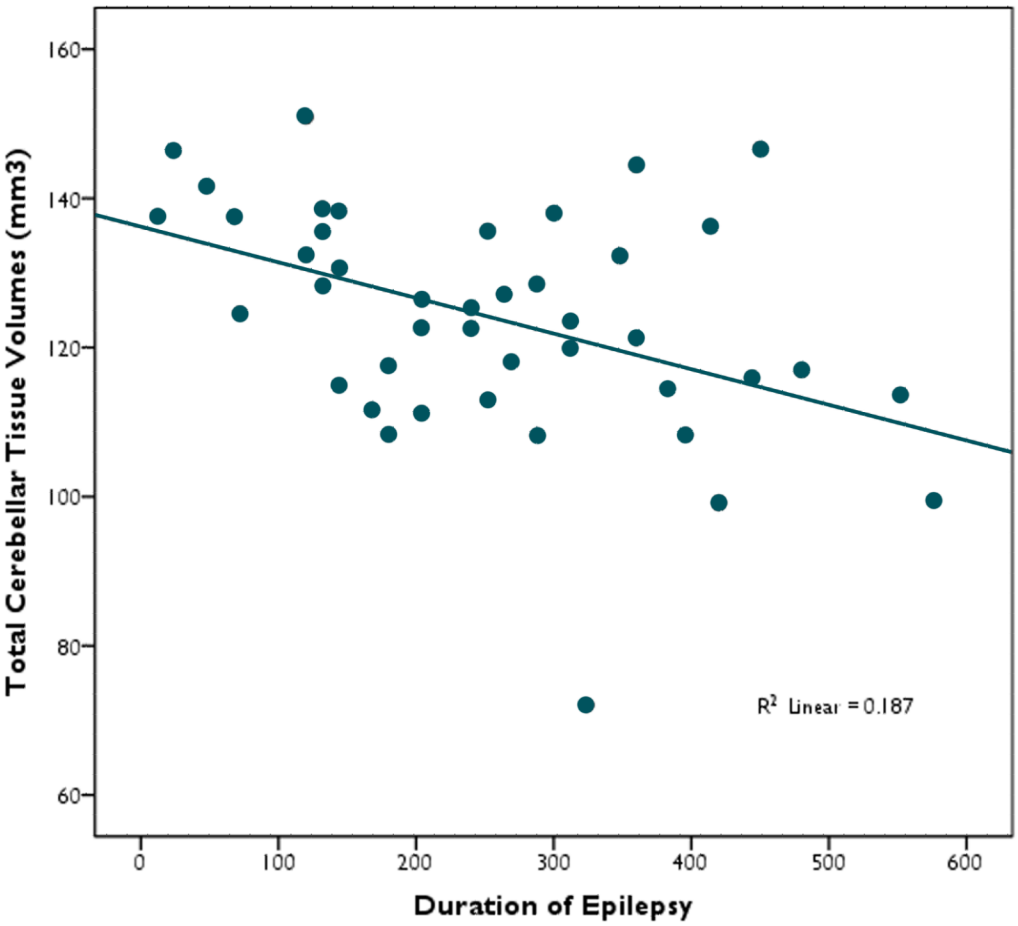


**Figure 6.**
Partial correlation (age, gender, height) shows a significant association between smaller cerebellar volumes and longer duration of epilepsy in epilepsy patients. ($r^2 = 0.334$, $p = 0.033$)

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**Table 1**

**Subject Characteristics**

| | Controls (n = 31) | Epilepsy (n = 46) |
|---|---|---|
| Age | 31.7 (10.6) | 34.5 (10.7) |
| Education (years) | 13.5 (2.4) | 12.8 (2.2) |
| Duration (years) | | 21.7 (11.6) |
| Age at onset (years | | 12.7 (9.2) |
| FSIQ | 108.3 (13.4) | 89.7 (14.9) |