Frontal and temporal volumes in children with epilepsy

Melita Daley a,*, Jennifer Levitt a, Prabha Siddarth a, Elizabeth Mormino a, Cornelius Hojatkashani a, Suresh Gurbani b,c, W. Donald Shields d,e, Raman Sankar d,e, Arthur Toga d, Rochelle Caplan a

a Department of Psychiatry, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA
b Department of Pediatrics, University of California at Irvine, Irvine, CA, USA
c Department of Neurology, Kaiser-Permanente, Los Angeles, USA
d Department of Neurology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA
e Department of Pediatrics, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA

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Abstract

This study examined if children with cryptogenic epilepsy and complex partial seizures (CPS) have smaller total brain, frontal, and temporal lobe volumes than normal children and how this is related to seizure, cognitive, psychiatric, and demographic variables. Forty-four children with CPS and 38 normal children, aged 5–16 years, underwent brain MRI scans at 1.5 T. Tissue was segmented, and total brain, frontal lobe, frontal parcellation, and temporal lobe volumes were computed. Other than significantly larger temporal lobe white matter volumes in the CPS group, there were no significant differences in brain volumes between the CPS and normal groups. Earlier onset, longer duration of illness, younger chronological age, and presence of a psychiatric diagnosis were significantly related to smaller frontotemporal volumes in subjects with CPS. Although these findings suggest that CPS might affect development of the temporal and frontal regions, we are unable to rule out the possibility that smaller frontotemporal volumes might predispose children to CPS. These findings highlight the need to control for seizure, cognitive, psychiatric, and demographic variables in studies of frontotemporal volumes in pediatric CPS.

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Keywords: Childhood; Complex partial seizures; Frontal lobe; Temporal lobe; Magnetic resonance imaging

1. Introduction

Volumetric studies in adults with temporal lobe epilepsy demonstrate reduced total brain volumes [1–4], total gray matter and white matter volumes [5,6], bilateral frontoparietal volumes [7], and white matter volumes of frontal, temporal, and parietal lobes [3,8]. Although lateralization of the seizure focus is unrelated to the severity of white matter volume reduction in temporal, frontal, and parietal regions [3], there is a more widespread decrease in neocortical gray matter concentration in frontal, parietal, and occipital regions in patients with left compared with right adult temporal lobe epilepsy [9]. Earlier onset and longer duration of temporal lobe epilepsy are also related to smaller total brain [3,10], white matter [3,11], and gray matter [1] volumes, as well as to smaller gray matter volumes of frontoparietal regions [9].

The few volumetric studies conducted in childhood epilepsy describe significantly reduced total volume in children with intractable and medically controlled epilepsy, compared with normal children, and in children with frontal lobe epilepsy contrasted to those with temporal lobe epilepsy [12,13]. Age at onset, duration of illness, prior status epilepticus but not simple febrile convulsions, and antiepileptic drug (AED) therapy (e.g., number, type) were related
to the severity of cerebral volume reduction in these children [13]. However, there was no significant reduction in gray and white matter volumes of children with new-onset epilepsy versus sibling controls [14].

Based on the previously reviewed findings [4,5,7,8,10,11,13,15,16], the study presented here determined if children with cryptogenic epilepsy who had complex partial seizures (CPS), no structural brain abnormalities, and varying degrees of seizure control have smaller total and cerebral white and gray matter volumes, as well as smaller frontal and temporal lobe volumes, compared with normal children. Also examined was whether children with earlier onset, longer duration, increased seizure frequency, more AEDs, left lateralized EEG findings, and a history of prolonged seizures and/or febrile convulsions have smaller volumes than those with later onset, shorter duration, lower seizure frequency, fewer AEDs, right lateralized EEG findings, and no prolonged seizures or febrile convulsions.

We determined if the predicted findings were related to IQ because total gray matter volume [17], as well as total and gray matter volumes in the prefrontal region [18], correlate positively with IQ in normal children. In addition, moderate to severe intellectual disability is associated with reduced cerebral volume in medically intractable pediatric epilepsy [13,16].

From the developmental perspective, there is a significant nonlinear decline in gray matter density that is most rapid over dorsal frontal and parietal association cortices between ages 7 and 60 [19]. With maturation, the decrease in gray matter volume progresses in a back-to-front wave through adolescence [20]. White matter volume and myelination, however, increase with age in the left inferior frontal gyrus in boys [21] and in the frontal lobe of 5- to 17-year-old youths [18,19]. Irrespective of age, boys have larger volumes than girls [22–24].

To examine how CPS are related to brain development, we also compared the association of age, IQ, and gender with total brain and frontotemporal volumes in the CPS and normal groups. Because of the high rate of psychopathology in pediatric epilepsy [25–30] and the association of psychopathology with volume abnormalities in children without epilepsy [31–33], we explored if the predicted findings were also related to the presence of a psychiatric diagnosis in these children.

2. Methods

2.1. Subjects

The study included 44 children with cryptogenic epilepsy, all of whom had CPS, and 38 children without epilepsy, aged 5–16. Table 1 summarizes the demographics, cognitive features, and perinatal complications of the children in the study. As evident from this table, the normal group had significantly higher IQ scores and more children from families of higher socioeconomic status based on the Hollingshead 2 factor index [34] derived from both parent occupational and educational status. Perinatal data on number of pregnancies and delivery complications were collected from the children’s mothers using a questionnaire modified from the Yale Neuropsycho-educational Assessment Scales [35].

Subjects were included in the study if they had a diagnosis of cryptogenic epilepsy and CPS, as defined by the International Classification of Epilepsy [36], and at least one seizure during the year prior to the child’s participation in the study. We also included children with a clinical history of CPS with and without EEG evidence of focal epileptic activity. The patients did not have EEG studies at the time of the study, and the classification was based on clinical history and past EEG records. We excluded patients with a mixed seizure disorder, a neurological disorder other than CPS, a metabolic disorder, a hearing disorder, past epilepsy surgery, and a structural MRI abnormality, but not those with mesial temporal sclerosis.

We recruited 36% of the patients with CPS from tertiary centers (e.g., UCLA Pediatric Neurology Services, Children’s Hospital of Los Angeles) and 64% from the community (e.g., Kaiser Sunset, Kaiser—Orange County, private pediatric neurologists, Los Angeles and San Diego branches of the Epilepsy Foundation). The primary pediatric neurologist at each site reviewed the clinical history, EEG records, and diagnoses of potential study subjects and referred them for the study irrespective of their psychiatric history. Table 2 summarizes information on seizure frequency during the past year, current AEDs, age at onset of seizures, duration of illness, number of simple febrile convulsions, and number of prolonged seizures (i.e., >5 minutes) obtained from the parents and the child’s medical records.

<table>
<thead>
<tr>
<th>Seizure-related variables for the CPS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure frequency</td>
</tr>
<tr>
<td>≤1/year</td>
</tr>
<tr>
<td>2–10/year</td>
</tr>
<tr>
<td>&gt;10/year</td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>Duration of epilepsy (years)</td>
</tr>
<tr>
<td>AEDs</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Monotherapy</td>
</tr>
<tr>
<td>Polytherapy</td>
</tr>
<tr>
<td>Prolonged seizures</td>
</tr>
<tr>
<td>Febrile seizures</td>
</tr>
</tbody>
</table>

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Table 1

Demographic features of study groups

<table>
<thead>
<tr>
<th></th>
<th>CPS group</th>
<th>Normal group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.2 (2.58)</td>
<td>10.8 (2.24)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>Female</td>
<td>48%</td>
<td>60%</td>
</tr>
<tr>
<td>Socioeconomic status a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (i–iii)</td>
<td>25%</td>
<td>48%</td>
</tr>
<tr>
<td>Low (iv, v)</td>
<td>75%</td>
<td>52%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>65%</td>
<td>55%</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>Full Scale IQ b</td>
<td>93 (5.38)</td>
<td>116 (13.88)</td>
</tr>
<tr>
<td>Perinatal problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>54%</td>
<td>52%</td>
</tr>
</tbody>
</table>

a $\chi^2(1) = 4.30, P < 0.04.$

b $t(80) = 6.93, P < 0.0001.$
The classification for the lateralization and localization analyses was based on a single EEG study conducted at the time of the child’s diagnosis of epilepsy and not at the time of the study. Of the 44 patients with CPS, 10 had nonlateralized EEG findings, 11 had a left focus, 8 a right focus, and 13 bilateral foci. EEGs were unavailable for 2 patients with CPS. Regarding focal EEG findings, 6 patients had no focal findings; 14 had interictal spikes in the temporal lobe, 13 in the frontal and temporal lobe, and 9 in other areas; 2 patients had secondary generalization; and 8 had background slowing.

We enrolled the control subjects without epilepsy from four public and two private schools in the Los Angeles community after screening for neurological, psychiatric, language, and hearing disorders through a telephone conversation with a parent. We excluded from the study children who had manifested symptoms of these disorders in the past.

2.2. Procedures

This study was conducted in accordance with the policies of the Human Subjects Protection Committees of the University of California, Los Angeles. Informed assents and consents were obtained from all subjects and their parents, respectively.

2.3. Magnetic resonance imaging

2.3.1. Acquisition

All subjects completed MRI scanning on a 1.5-T GE Sigma magnetic resonance imaging scanner (GE Medical Systems, Milwaukee, WI, USA). The imaging acquisition protocol used to obtain high-resolution three-dimensional (3D) T1 weighted spoilt grass (SPGR) sequences included a sagittal plane acquisition with slice thickness of 1.2 mm, repetition time of 24 ms, echo time of 9 ms, flip angle of 22°, acquisition matrix of 256×192, FOV 24, and two excitations.

2.3.2. Image preprocessing

Each scan was processed in a series of steps to assess volumes of tissue types. Initially, potential fluctuations in signal resulting from magnetic field inhomogeneities were addressed by applying a radiofrequency correction [37]. Next, an automated brain extraction program (BET) was used to create a brain mask that separates brain tissue from nonbrain tissue (skull and meninges) [38]. This mask was manually modified to ensure accurate separation of tissues. The automated tissue classification method of Shattuck et al. [38] was then used to segment the scans by tissue types to create gray matter, white matter, and cerebrospinal fluid masks. The total intracranial volume was then automatically computed by summing the volumes of these masks.

2.3.3. Cortical object model methods

2.3.3.1. Prefrontal cortex delineation. The protocol for subparcellating the prefrontal cortex, described in detail in Blanton et al. [21], can be viewed at http://www.loni.ucla.edu/NCRR/Downloads/Protocols/MaskingRegions.html. Briefly, by use of the cortical object model and all three viewing planes on the T1 weighted slices, the prefrontal cortex is subparcellated into the following regions of interest (Fig. 1).

2.3.3.1.1. Inferior frontal gyrus. The inferior frontal gyrus is traced in the axial plane. This region is defined as the cortex anterior to the precentral sulcus, inferior to the inferior frontal sulcus, and superior and posterior to the lateral orbital sulcus.

Tracing begins on the most superior axial slice in which the inferior frontal sulcus can be delineated or where the pars orbitalis appears. Tracing ends in the most inferior axial section in which the inferior frontal gyrus can be distinguished, using the lateral orbital sulcus (on the object model) as the inferior boundary.

2.3.3.1.2. Dorsolateral frontal cortex/middle frontal gyrus. Traced in the axial plane, the middle frontal gyrus is defined as cortex anterior to the precentral sulcus, inferior and posterior to the superior frontal sulcus, superior and anterior to the inferior frontal sulcus, and superior and posterior to the frontal marginal sulcus. Tracing begins on the most superior axial slice in which the middle frontal gyrus can be delineated. As the operator moves inferiorly, the inferior frontal sulcus replaces the precentral sulcus as the inferior boundary, at the point where the precentral sulcus and inferior frontal sulcus intersect on the object model. The operator continues to move inferiorly, using the lateral orbital sulcus (on the object model) as the inferior boundary of the middle frontal gyrus.

2.3.3.1.3. Dorsolateral frontal cortex/superior frontal gyrus. The superior frontal gyrus is defined as cortex anterior to the precentral sulcus and superior to the superior frontal sulcus. The object model is used to establish this region’s most posterior boundary, the precentral sulcus. Tracing begins on the most superior axial slice where the precentral sulcus can be distinguished. The frontal marginal sulcus delineates the inferior boundary of the superior frontal gyrus.

2.3.3.1.4. Orbital frontal cortex. The orbital frontal gyrus is defined as the cortex inferior to the frontal marginal sulcus, inferior and anterior to the lateral orbital sulcus, and lateral to the olfactory sulcus. The circular insular sulcus serves as the most posterior boundary of the orbital frontal gyrus, which is best seen in the sagittal plane.

Fig. 1. Right: Magnetic resonance image of prefrontal cortex. Left: Three-dimensional cortical object model displaying frontal lobe regions: inferior frontal cortex in purple, middle frontal cortex in pink, superior frontal cortex in blue, and orbital frontal cortex in green.
The coronal view is used to include radial white matter for the inferior frontal gyrus, middle frontal gyrus, and superior frontal gyrus. The sagittal view is used to include radial white matter for the orbital frontal gyrus. Deep white matter, the anterior cingulate gyrus, and gyrus rectus are not included in these drawings.

2.3.3.2. Temporal lobe delineation. In similar fashion, using all three viewing planes and the cortical object model, the temporal lobe is drawn in the sagittal plane with the following boundaries: The temporal lobe is defined as the cortex inferior to the sylvian fissure, anterior to the lateral parieto-temporal and temporo-occipital lines, and superior and anterior to the collateral sulcus and posterior transverse collateral sulcus. The operator includes the amygdala and the hippocampus but excludes the insular gyrus.

2.3.3.3. Reliability. The drawings were performed by one rater and checked by a second rater, both without knowledge of the children’s diagnosis. A consensus drawing was then determined by agreement of the two raters about the boundaries of the regions of interest. The rater delineated the region of interest on the left hemisphere of 10 brains, and interclass correlation coefficients (ICCs) were calculated between these delineations and the gold standard. A rater was deemed reliable after achieving an ICC of 0.9 or higher. On brain regions examined in this study, the ICCs were 0.94 for inferior frontal cortex, 0.96 for middle frontal cortex, 0.95 for orbital frontal cortex, 0.90 for superior frontal cortex, and 0.94 for temporal lobe, with an interrater reliability of 0.9.

2.4. Cognition

The Wechsler Intelligence Scale for Children III (WISC-III) [39], administered to the children, generated Full Scale, Verbal, and Performance IQ scores.

2.5. Psychopathology

The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) [40], was administered separately to each child and parent by R.C. or a research assistant trained in the administration of the interview. Because the child or parent often talks about the child’s seizures during the interview, these interviews were not blinded with respect to the child’s seizure disorder (i.e., presence or absence, type). A second clinician reviewed videotapes of the child interviews and audiotapes of the parent interviews, and a consensus DSM-IV [41] diagnosis was reached. Where a diagnostic consensus was not reached, the child was excluded from the study.

Given the large number of diagnoses relative to the number of subjects in each diagnostic group, we grouped the diagnoses as follows: “affective/anxiety” disorders included any mood or anxiety disorder, and “disruptive” disorders included attention-deficit-hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder. Children with a “comorbid” diagnosis had both “affective/anxiety” and “disruptive” disorders.

2.6. Data analysis

We compared total brain, gray matter, and white matter volumes between the CPS and normal groups using ANCOVAs. To compare frontal and temporal gray and white matter volumes in the CPS and normal groups, we estimated mixed models using repeated measures with group (CPS, normal) as the intersubject and hemisphere (left, right) as the intra-subject classification variable for inferior frontal, orbital frontal, dorsolateral prefrontal (sum of dorsolateral superior and middle frontal cortex), and temporal lobes separately. Demographic (i.e., age, gender, socioeconomic status, ethnicity) and cognitive (Full Scale IQ) variables were used as covariates in all these analyses. Total brain volume was also included as a covariate for all analyses of volumes other than total brain volume. All tests were two-tailed, and an α level of 0.05 was adopted for all inferences.

Within the CPS group, we examined the relationship of volumes to seizure, cognitive, and perinatal variables (i.e., delivery problems, pregnancy problems). First, to reduce the number of seizure-related variables to include in the analyses, a principal component analysis (PCA) of seizure variables including CPS subjects from all our studies (N = 105) was performed. This PCA revealed four components with the following loadings: a duration (0.89)/onset (−0.88) component; an EEG localization (0.87)/lateralization (0.87) component; a prolonged seizures (0.92)/febrile convulsions (0.79) component; and a seizure frequency (0.87)/number of AEDs (0.78) component. In the EEG component, localization of epileptic activity was classified as frontal, temporal, frontotemporal, or other, and lateralization as left, right, or bilateral focal epileptic activity. Number of AEDs was subdivided into no AEDs, monotherapy, and polytherapy. These four components were then used as the seizure-related variables when investigating their relationship to volumes in the CPS group.

In investigating the association of volumes with seizure and cognitive variables, we computed mixed linear models for gray and white matter volumes for the temporal lobe, frontal lobe, and the following frontal lobe parcellations: dorsolateral prefrontal cortex (sum of dorsolateral superior and middle frontal cortex), inferior frontal cortex, and orbital frontal cortex. Hemisphere (left, right) was used as the intrasubject classification variable. Age, gender, ethnicity, socioeconomic status, seizure components, Full Scale IQ, and presence of a psychiatric diagnosis (N = 19) were used as predictors. We used the following model-building strategy to determine which of these variables were predictive of the volumetric measures. We first included all these variables as predictors in the general linear model. We then used a combination of a stepwise strategy (in which the variables are selected for either inclusion in or exclusion from the model in a sequential fashion based solely on statistical criteria) and inclusion or exclusion of variables based on careful scrutiny of the resulting model. Thus, following the fit of the model from stepwise selection, the importance of each variable included in the model was verified. We also checked for variables whose coefficients changed markedly in magnitude when other variables were excluded. This process of deleting, refitting, and verifying was performed until a final model was obtained that explained the data.

We also examined if the volumes in the CPS group differed between the lateralization (left, right, bilateral, and no findings) and localization (temporal, frontotemporal, other, and no findings) groups using ANCOVAs. In addition, we determined the relationship of an additional index of seizure severity, recruitment source (tertiary vs community), to volumes.

3. Results

3.1. Between-group volume differences

Group comparisons controlling for demographic, IQ, total brain volume, and perinatal variables revealed significantly larger temporal white matter volumes in the CPS group than in the normal group, but no significant differences in total brain, gray matter, white matter, remaining frontal lobe parcellation, and temporal lobe gray matter volumes. Post hoc testing indicated that these findings were not accounted for by the presence of slowing on EEG. There were also no significant differences in left–right volume asymmetry of these two groups (Table 3).

3.2. Modeling of total and frontotemporal volumes in the CPS group

3.2.1. Seizure variables

Mixed linear models with demographic and seizure-related variables, IQ scores, psychiatric diagnosis, and pregnancy complications as predictors demonstrated that
age at onset/duration and history of prolonged seizures or simple febrile convulsions, as well as laterализation and localization of epileptic activity, were differentially related to frontotemporal volumes. Earlier onset/longer duration of CPS was associated with decreased orbital frontal gray matter \((F(1,32) = 4.58, P < 0.04)\) and white matter \((F(1,32) = 6.24, P < 0.01)\) volumes, as well as decreased temporal lobe white matter volumes \((F(1,32) = 5.21, P < 0.03)\). The children with a history of prolonged seizures or simple febrile convulsions had larger inferior frontal white \((F(1,34) = 6.87, P < 0.01)\) and gray matter \((F(1,34) = 7.22, P < 0.01)\) volumes than those without prolonged seizures and/or simple febrile convulsions. The children with left lateralized epileptic activity on EEGs had significantly smaller total white matter volumes \((F(3,40) = 3.53, P < 0.02)\) compared with those with bilateral \((P < 0.01)\) or right lateralized \((P < 0.02)\) epileptic activity and no EEG findings \((P < 0.07)\). Recruitment source (i.e., tertiary vs community) was unrelated to brain volumes.

3.2.2. Psychiatric diagnosis

Four children had disruptive disorders, seven had affective/anxiety disorders, seven had combined disruptive and affective/anxiety disorders, and one had a tic disorder. The 19 children with CPS with a psychiatric diagnosis had significantly smaller inferior frontal white matter volumes \((F(1,33) = 4.60, P < 0.04)\) compared with those without a diagnosis.

3.2.3. IQ, age, and gender

In the normal group, larger total brain \((F(1,34) = 9.37, P < 0.004)\), total gray matter \((F(1,34) = 5.52, P < 0.03)\), and total white matter \((F(1,32) = 11.53, P < 0.002)\) volumes were positively related to higher IQ scores. Other than a negative association with dorsolateral prefrontal gray matter volumes \((F(1,3) = 4.07, P < 0.05)\), age was unrelated to total brain and frontotemporal brain volumes in the normal group. In contrast, in the CPS group, with seizure variables in the model, older age, not IQ, was significantly related to larger total \((F(1,28) = 5.67, P < 0.03)\), inferior frontal \((F(1,33) = 4.39, P < 0.04)\), and temporal \((F(1,30) = 7.41, P < 0.01)\) white matter volumes and smaller total \((F(1,39) = 6.07, P < 0.02)\), dorsolateral prefrontal \((F(1,39) = 7.02, P < 0.01)\), and orbital frontal \((F(1,39) = 10.54, P < 0.003)\) gray matter volumes. In both subject groups, compared with girls, boys had significantly larger gray and white matter volumes \((P < 0.04)\) in all frontotemporal regions studied except the inferior frontal gyrus.

4. Discussion

These findings suggest that other than increased white matter volumes of the temporal lobe, there were no significant differences in total brain and frontal volumes of children with CPS and normal children. However, among the subjects with CPS, those with earlier onset, longer duration, a history of prolonged seizures/febrile convulsions, left lateralization of EEG findings, younger age, and a psychiatric diagnosis had significantly smaller volumes than those with later onset, shorter duration, bilateral or right focal EEG findings, older age, and no psychiatric diagnosis.

From the methodological perspective, our findings underscore the importance of including large samples of children and controlling for these relevant variables in studies on epilepsy and brain structure in children with CPS. From the theoretical perspective, increased white matter volumes of the temporal lobe can be understood in light of recent studies on the ongoing dynamic changes in gray and white matter volumes in normal childhood and adolescence [19–21,42], surgically treated children with epilepsy, animal studies, and studies on the association of spikes, perfusion, and myelination.

As age increases in normal childhood and adolescence, there is a reduction in gray matter density [19], a posterior-anterior decrease in gray matter volume [20], and an increase in white matter volume and myelination [19,21,42]. These developmental changes vary by gender [22]. Our cross-sectional between-group findings suggest that myelination of the temporal as well as the frontal lobe might be vulnerable in children with CPS, 61% of whom had EEG evidence of temporal lobe involvement.

In support of this explanation, Andres et al. [43] described increased cerebral, gray matter, and white matter volumes in surgically treated children with epilepsy who have cortical dysplasia. In immature rats, repeated seizures are associated with defects in lipid metabolism and myelin accumulation, particularly when seizures occur early during the phase of glial proliferation [44–46].

Functional magnetic resonance imaging studies have shown that focal interictal spikes are associated with local hyperperfusion and distal hypoperfusion [47]. During seizures, transient local hyperperfusion is associated with

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Total brain and frontotemporal volumes in the CPS and normal groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mm³)</td>
<td>CPS group</td>
</tr>
<tr>
<td>Total brain</td>
<td>1388.94 (19.06)*</td>
</tr>
<tr>
<td>Gray matter (GM)</td>
<td>789.45 (68.73)</td>
</tr>
<tr>
<td>White matter (WM)</td>
<td>487.70 (76.43)</td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
</tr>
<tr>
<td>Inferior frontal GM</td>
<td>21.57 (3.50)</td>
</tr>
<tr>
<td>Inferior frontal WM</td>
<td>10.08 (2.03)</td>
</tr>
<tr>
<td>Orbital frontal GM</td>
<td>35.20 (5.97)</td>
</tr>
<tr>
<td>Orbital frontal WM</td>
<td>16.15 (3.50)</td>
</tr>
<tr>
<td>Dorsolateral prefrontal GM</td>
<td>118.94 (16.93)</td>
</tr>
<tr>
<td>Dorsolateral prefrontal WM</td>
<td>55.66 (8.87)</td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>152.23 (11.73)</td>
</tr>
<tr>
<td>WM*</td>
<td>70.22 (12.99)</td>
</tr>
</tbody>
</table>

* Mean (SD).
* F(1,70) = 5.83, P < 0.02 with demographic and IQ variables in model.
accelerated myelination [48]. Thus, involvement of the temporal lobe in most of the children in the study and seizure-related local blood flow increases during development may underlie the larger white matter volume in this region. The dissimilar relationships of IQ and age with volume in the patient and normal groups also imply that CPS adversely affects normal brain development. Compared with prior volumetric studies in children with epilepsy, like Hermann and colleagues’ [14] findings in children with new-onset seizures, we did not find the smaller total brain volumes reported in the studies of Lawson et al. [13,16]. However, Lawson and colleagues’ subjects had more severe epilepsy suggested by longer duration of illness, earlier age of onset (age 0–14), and higher rate of epileptogenic lesions, as well as inclusion of 21% of children with mild (IQ = 56–70) and 18% with moderate/severe (IQ < 55) intellectual disability. Different morphometric procedures may also underlie the variable total brain volume findings in these studies.

Similar to adults with temporal lobe epilepsy, we found inverse relationships for both duration of illness [1,3,9,10] and left focal epileptic activity [49] with smaller volumes. Yet, recent evidence for extensive volume reduction in adults with temporal lobe epilepsy [2,3,6,31,50] implies a cumulative more widespread effect of recurrent seizures on brain volume reduction than in children. Prospective studies are needed to determine how these structural abnormalities evolve over time.

The inferior frontal gyrus findings are interesting given its role in syntax [51], semantics [52], phonology [53], and higher-level linguistic functions [54] and evidence for both basic [26] and higher-level linguistic deficits in children with CPS [55,56]. The larger gray and white matter volumes of the inferior frontal gyrus of the children with CPS with a history of prolonged seizures and/or febrile seizures imply that duration of seizures negatively impacts the development of this region and the linguistic functions it subserves. The relationship of inferior frontal gyrus volumes to presence of a psychiatric diagnosis and the recent clinical evidence of higher-level linguistic deficits and disruptive disorder diagnoses and externalizing behaviors in children with CPS [57] may reflect impaired maturation of inferior frontal gyrus.

The subjects with CPS with a psychiatric diagnosis were quite heterogeneous, with four disruptive disorder diagnoses, seven affective/anxiety disorder diagnoses, seven combined disruptive and affective/anxiety disorders, and one tic disorder. Compared with normal children, children without epilepsy with diagnoses such as autism [58], generalized anxiety disorder [59], and posttraumatic stress disorder [60] have larger volumes, whereas those with ADHD have smaller dorsolateral prefrontal cortex volumes [33]. Studies on larger samples of children are needed to delineate how type of psychiatric diagnosis is related to brain volumes in pediatric CPS.

Finally, study limitations include a relatively small sample of CPS and normal subjects, multivariate analysis techniques to control for the several confounding factors, lack of clinical information with respect to possible etiology and current EEG findings, and possible memory bias in seizure-related information collected from parents, and emphasize the need for replication of the study’s findings. With these limitations in mind, the findings suggest that CPS may affect brain development, particularly in the temporal and frontal regions in children with average intelligence. They also highlight the need to control for multiple variables, including seizure, cognitive, psychiatric, and demographic variables, in the study of frontotemporal volumes in pediatric CPS. Based on where the child is in the dynamic ongoing maturation of frontotemporal regions [19,20], these variables may have different effects on these volumes (i.e., increase or decrease).

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