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Amygdala Volume and Psychopathology in Childhood Complex Partial Seizures

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Abstract

Purpose—This study compared amygdala volume in children with cryptogenic epilepsy, who had complex partial seizures (CPS), with age and gender matched normal children. It also examined the relationship of amygdala volumes with seizure variables and the presence of psychopathology in the patients.

Methods—28 children with cryptogenic epilepsy, all of whom had CPS, and gender matched normal children, aged 6–16 years had magnetic resonance imaging (MRI) at 1.5 Tesla. Tissue was segmented and total brain volume and amygdala volumes obtained from manual tracings were computed.

Results—There were no significant differences in the amygdala volume of the CPS and normal groups. Within the CPS group, the children with an affective/anxiety disorder had significantly larger left amygdala volumes compared to those with no psychopathology as well as greater amygdala asymmetry. Exploring the association of seizure variables to amygdala volumes yielded no significant predictors.

Conclusions—In pediatric CPS left amygdala involvement might reflect effects of the neuropathology underlying comorbid affective or anxiety disorders on amygdala development rather than effects of on-going seizures.

Keywords

complex partial seizure disorder; childhood; magnetic resonance imaging; amygdala; seizure variables

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1. Introduction

The amygdala plays an important role in the generation of epilepsy in animal models (1,2) and in patients with temporal lobe epilepsy (TLE) (3–6). Adult magnetic resonance imaging (MRI) studies have shown amygdala volume reduction ipsilateral to the seizure focus in TLE (7–10) associated with longer duration of epilepsy but not with other seizure variables.

The amygdala has also been implicated in both depression (11,12) and anxiety disorders (13, 14) in non-epileptic patients. Several adult studies have demonstrated amygdala volume reduction in major depressive disorder (MDD) (15–17) in keeping with neuropathologic findings of significant reduction of glial cells and glial/neuron ratio in the left amygdala of MDD patients (18). Recent childhood studies found similar amygdala volume reduction in MDD (19) and anxiety disorders (20). However, other studies have reported enlarged amygdala volumes in adults with MDD (12,21,22), adults with refractory partial epilepsy and comorbid affective disorders (23–25), as well as in children with MDD (26) and generalized anxiety disorder (27). These discrepant findings might be related to methodological factors, such as differences in anatomical boundaries used to measure the amygdala in these studies.

There are high rates of comorbid MDD and anxiety disorders in adults (28–33) and children with epilepsy (34–41). Amygdala volume findings, however, vary with two studies showing increased volumes in presurgical TLE adults with depression (42,43) and two studies showing no change in volumes in individuals with TLE (44,45). Richardson et al. (42) found a positive correlation between left and right amygdala volumes and scores on the Beck Depression Inventory (46) in individuals with TLE, including adolescents. To date, however, there have been no structural studies on amygdala volumes in children with epilepsy.

The study presented in this paper examined if amygdala volume in children with cryptogenic epilepsy who had complex partial seizures (CPS) was significantly smaller than age and gender matched normal children. Within the CPS group, we explored if those with anxiety/affective disorders would have significantly larger amygdala than those without psychopathology. In the absence of evidence regarding the relationship between seizure variables and amygdala volumes in children with CPS, we explored if in addition to duration of epilepsy, variables, such as age of onset, lateralization of EEG findings, history of prolonged and febrile seizures, as well as seizure frequency and number of antiepileptic drugs (AEDs) were associated with these volumes.

There is evidence for increased incidence of mood and anxiety disorders in families in the general population (47) and for a possible role of perinatal factors in the generation of CPS (48,49). We, therefore, also explored if a family history of mood and anxiety disorders in first-degree relatives and a history of perinatal problems were related to amygdala volume in the CPS group.

2. Methods

2.1 Subjects

The study included 28 children with cryptogenic epilepsy, all of whom had CPS, and 30 children without epilepsy, aged 6–16 years. Table 1 describes the demographic features of the study subjects. Significantly more CPS children come from lower socioeconomic status (SES) families than the normal group based on the Hollingshead 2 factor index (50), derived from parent occupational and educational status. A score of I-III was classified as high SES while a score of IV-V was classified as low SES. The CPS group also had significantly lower mean IQ scores than the normal subjects.

To be included in the study, the patients had to have a diagnosis of cryptogenic epilepsy with CPS, as defined by the International Classification of Epilepsy (51) and at least one seizure during the year prior to the child's participation in the study. As described in this classification, children with a clinical history of CPS with or without EEG evidence for focal epileptic activity were included in the study sample. None of the children in the study had an underlying brain lesion or MRI evidence for hippocampal sclerosis.

We recruited 36% CPS subjects 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 of America). The primary pediatric neurologist at each site reviewed the clinical history, EEG records, and diagnosis of potential CPS subjects and referred them for the study. We excluded patients with a mixed seizure disorder, an MRI abnormality, an underlying neurological disorder, a metabolic disorder, a hearing disorder, and past epilepsy surgery. Of note, none of the CPS subjects in the study had hippocampal sclerosis.

A UCLA pediatric neurology investigator (W.D.S.) reviewed the history, EEG records performed at about the time of the child's diagnosis, and diagnosis of each epileptic subject from the different recruitment sites. If he did not concur with the diagnosis or EEG findings, the child was not included in the study.

Table 2 presents information on seizure frequency during the past year, current AEDs, age of onset of seizures, duration of illness, as well as the number of febrile convulsions and number of prolonged seizures (i.e., > 5 minutes) from the parent's and the child's medical records. With the exception of one CPS child who was left handed, all the other patients in the study were right handed.

Of the 28 CPS patients, 4 had non-lateralized EEG findings, 9 had a left focus, 5 a right focus, and 8 bilateral foci. EEGs were unavailable for two CPS patients. Regarding focal EEG findings, 1 child had no focal findings, 8 had interictal spikes in the temporal lobe, 11 in the frontal and temporal lobe (4 frontal and 7 frontotemporal), and 6 in other areas. 1 CPS subject had secondary generalization and 2 had background slowing. Perinatal data on the number of pregnancy and delivery complications was collected from the children's mothers using a questionnaire modified from the Yale Neuropsycho-educational Assessment Scales (52). Of the 28 CPS subjects, 36 % had a history of delivery problems and 57 % had pregnancy problems.

We recruited the non-epileptic control subjects 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 non-epileptic children manifesting 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.

Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)—The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Present and Lifetime Version (K-SADS-PL) (53) was administered to each child (those with CPS and without epilepsy) and parent by R.C. or a trained research assistant. Because the child or parent often talks about the child's seizures during the interview, these interviewers were not blind with regards to the child's seizure disorder (i.e., presence or

absence, type). A consensus DSM-IV (American Psychiatric Association, 1994) diagnosis was reached after reviewing videotapes of the child interviews and audiotapes of the parent interviews. A child was excluded from the study if a diagnostic consensus was not reached.

Given the large number of psychiatric 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 including those with separation anxiety disorder, generalized anxiety disorder, specific phobia, and obsessive compulsive disorder. “Disruptive” disorders included attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder. Children with a “combined” diagnosis had both “affective/anxiety” and “disruptive” disorders.

A family history of psychopathology in relatives was obtained directly from the parents who filled out a questionnaire. Forty-three percent of the CPS subjects had a first-degree relative with a mood or anxiety disorder.

Cognition—The Wechsler Intelligence Scale for Children-III (54) administered to the children generated Full Scale, Verbal, and Performance IQ scores.

MRI Procedures

MRI Acquisition: All subjects completed MRI scanning on a 1.5 Tesla GE Signa magnetic resonance imaging scanner (GE Medical Systems, Milwaukee, WI). The imaging acquisition protocol used to obtain high resolution three-dimensional (3D) T-1 weighted spoiled grass (SPGR) sequences included a sagittal plane acquisition with slice thickness of 1.2 mm, repetition time of 14.6, echo time of 3.3, flip angle of 35, acquisition matrix of 256 × 192, FOV 24 and two excitations.

Image Preprocessing: Each scan was processed with 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 radio frequency correction (55). Next an automated brain extraction program (BET) was used to create a brain mask that separates brain tissue from non-brain tissue (skull and meninges) (56). This mask was manually modified to assure accurate separation of tissues. The automated tissue classification method of Shattuck et al. (56) 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 including cerebellar tissue.

Amygdala Volumes: For amygdala volume analysis, the data were aligned into the Talairach co-ordinate system using the anterior commissure as the center of origin, and then reformatted into an oblique coronal plane to assure that the images were oriented in space with the long axis of the anterior hippocampus perpendicular to the coronal plane (57). These reformatting methods, described briefly here, are detailed in Bartzokis et al. (58). While viewing the image data in all three planes, the most anterior section containing the anterior commissure was marked in the coronal plane, and then located in the axial plane. Using these landmarks, the images were then rotated so that the interhemispheric fissure was perpendicular to a horizontal line at 0 degrees. Next, the sagittal image containing the most lateral slice of the anterior hippocampus was marked with a line dropped perpendicular to the anterior third of the left hippocampus. This angle was then used to obtain the oblique coronal sections used for volumetric analysis of the anterior and posterior hippocampi.

Volumes of the amygdala were then obtained on each subject by manually tracing these regions as outlined below in Figure 1. These methods have been described in detail in previously published papers (58,59) and will be summarized briefly here. An MRI atlas was used to

confirm identification of all structures (60). The most anterior slice of the amygdala was traced at the level where the thickness of the amygdala is 2.5 times the thickness of the surrounding cortex. The alveus represented the inferior boundary of the amygdala in the posterior sections, and the temporal lobe white matter represented this boundary in more anterior slices. Medially, the border included the medial temporal lobe cortex. Therefore, a small amount of medial temporal structures such as gyrus ambiens was included in the amygdala measure (57). The amygdala was traced posteriorly to the last slice where a pyramidal shape above the ventricle could easily be visualized.

Reliability of Measurements: The drawings were performed by one rater (27) and checked by a second rater (37), 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. Ten re-drawings of the medial temporal lobe regions in this study population showed intra-rater reliability > 0.9 and an inter-rater reliability of 0.95.

Data Analysis: We compared amygdala volumes (total, left and right) and amygdala asymmetries (left-right amygdala volumes) between the CPS and normal groups using ANCOVAs, controlling for total brain volume. In investigating the association of amygdala volumes with psychopathology within the CPS group, we conducted ANCOVAs with amygdala volumes as the dependent variables and presence of psychiatric diagnosis as the predictor, controlling for total brain volume. Of the 28 CPS subjects, 18 had no psychopathology. Of the other 10 CPS subjects with a psychiatric diagnosis, 6 had affective/anxiety disorder diagnoses, 2 had both anxiety disorder and disruptive disorder diagnoses and 2 had other types of diagnoses. Therefore, in the within CPS ANCOVAs looking at psychopathology, we compared only those CPS subjects with an affective/anxiety disorder (n=8) *vs* those without any psychopathology (n=18). Similarly, ANCOVAs were used to explore the association of amygdala volumes with family history variables, namely family history of mood and anxiety disorders and a history of perinatal problems, controlling for total brain volume.

In exploring the association of amygdala volumes with seizure variables within the CPS group, general linear models were used, with amygdala volumes as the dependent variables and age of seizure onset, duration of illness, seizure frequency, AED use (monotherapy ors polytherapy), prolonged seizures (yes or no), febrile seizures (yes or no) were used as predictors. We first included all these variables as predictors in a stepwise regression model and determined a subset of predictors which contributed significantly ($p<0.1$) to the variance. We then computed ANCOVAs with this subset of predictors. Total brain volume was used as a covariate in these analyses. All tests were two-tailed and an alpha level of 0.05 was adopted for all inferences.

3. Results

Between Group Differences

Table 3 presents mean amygdala volumes of the CPS and normal groups. ANCOVAs of amygdala volumes controlling for total brain volume demonstrated no significant differences between amygdala volumes in the children with CPS compared to the normal children. There were also no significant differences between the CPS and normal groups in amygdala asymmetry (left-right volumes).

Association of Amygdala Volumes with Psychopathology and Seizure Variables

The CPS children with an affective/anxiety disorder had significantly larger left amygdala volumes compared to those with no psychopathology (1197.7 (119.3) *vs* 1039.1 (169.8),

$F_{1,25} = 5.11$, $p < .03$) as well as greater amygdala asymmetry (174.3 (112.1) *vs* 37.4 (121.0), $F_{1,25} = 6.63$, $p < .02$). There were no differences in the right amygdala volumes. The other analyses exploring the association of family history and seizure variables, including temporal vs extra-temporal involvement and duration of illness, to amygdala volumes did not yield any significant predictors.

4. Discussion

Controlling for total brain volume, this study found no significant difference in amygdala volumes of the CPS compared to the normal subjects. Within the CPS group, children with an affective/anxiety disorder had significantly larger left amygdala volumes compared to those with no psychopathology. Amygdala volumes, however, were unrelated to seizure variables including age of seizure onset, duration of illness, seizure frequency, and temporal involvement vs extra-temporal disease, as well as history of perinatal problems or family history of psychopathology.

Previous adult TLE studies reported amygdala volume reduction (7–10) associated with duration of epilepsy but not with other seizure variables. It is possible that our study found no significant difference between the CPS and normal subjects in amygdala volumes because of the shorter duration of illness 3.6 (2.55) in the children compared to the adults in the other studies.

Although there have been no structural MRI studies to date on amygdala volumes in children with epilepsy, supporting our findings, recent studies reported enlarged amygdala volumes in children without epilepsy who have MDD (26) and generalized anxiety disorder (27), adults with refractory partial epilepsy with comorbid affective disorders (23–25). Similar to our study, a recent study by Richardson et al. (45) showed a significant positive relationship between amygdala volumes and depression in adolescents and adults with TLE. However, unlike our study these authors (45) found a positive relationship of both right and left amygdala volumes with depression whereas our study found this association only for left amygdala volumes and in a mixed group of affective/anxiety disorders.

Despite larger left amygdala volumes in the CPS subjects with depression and anxiety disorder diagnoses, a left focus on EEG did not appear to drive this finding. In fact, as suggested by several researchers in both imaging (11–14,18) and neuropathology studies (18), these preliminary findings in children with CPS who have affective/anxiety disorder might reflect the effects of the neuropathology underlying depression and anxiety disorders on amygdala development.

Our findings, however, are unlike those of previous studies that, in keeping with neuropathologic findings of significant reduction of glial cells and glial/neuron ratio in the left amygdala of MDD patients (18), found amygdala volume reduction in children with MDD (19) and anxiety disorders (20), as well as in adults with MDD (15–17). The inclusion of children with both comorbid anxiety and depression in one group, the relatively small study sample size, and differences in amygdala anatomical boundaries across studies underscore the importance of replicating our findings on larger samples of CPS patients both with and without comorbid psychopathology.

Limitations of the present study include its exploratory nature with a retrospective analysis, the small sample size which precluded differentiating between the subgroup of children with depression and anxiety symptoms, a greater, albeit not significantly higher proportion of girls than boys, possible parental memory bias for seizure-related information, few CPS subjects with right epileptic activity, missing EEG data in 2 CPS subjects, and significant differences in the Full Scale IQ of the CPS and normal groups. Although the normal children in the study

had high mean Full Scale IQ scores, to ensure that we do not remove illness effect, we did not control for IQ differences in the group comparisons. The study limitations underscore the need for replication of our findings.

With these limitations in mind, children with CPS and comorbid affective/anxiety disorders appear to have enlarged left amygdala volumes compared to CPS children with no psychopathology. Involvement of the left amygdala and lack of association with seizure variables imply that amygdala volumes might reflect the underlying neuropathology of the comorbid affective illness rather than the epilepsy. However, these findings need to be replicated in a prospective study of a larger sample of CPS patients both with and without depression and anxiety disorder to determine the role played by epilepsy and/or the on-going depression and anxiety disorders on amygdala development in pediatric CPS.

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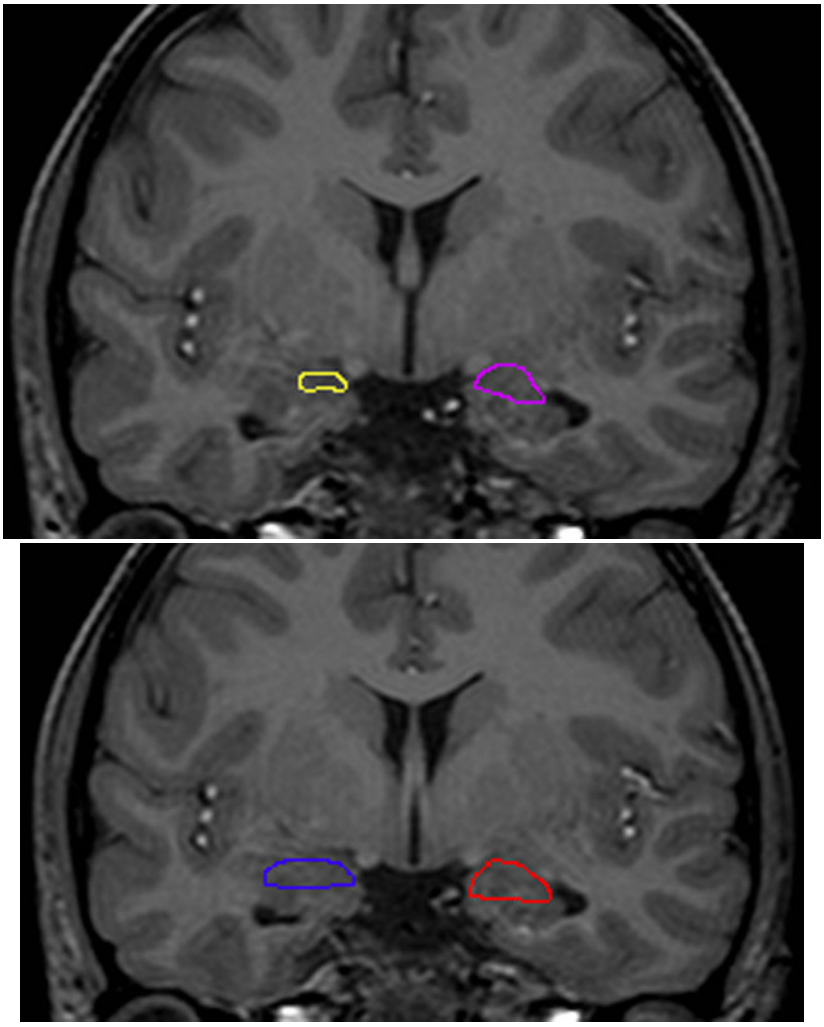

Figure 1. a) and b): Manual Tracings of Amygdala

Manual tracings in the coronal plane outlining a) left (yellow) and right (purple) amygdala in a child with complex partial seizures and no psychopathology compared to b) left (blue) and right (32) amygdala in a child with complex partial seizures and comorbid affective/anxiety disorder.

Table 1

Demographic Features of Study Groups

	CPS	Normal
N	28	30
Age (years)	9.9 (2.20)	10.2 (1.78)
Gender		
Male	43%	43%
Female	57%	57%
SES[1]		
High (i–iii)	25%	50%
Low (iv–v)	75%	50%
Ethnicity		
Caucasian	68%	53%
Non-Caucasian	32%	47%
Full Scale IQ[2]	94 (15.94)	117 (13.45)
Perinatal Problems		
Delivery	36%	23%
Pregnancy	57%	50%

[1] X^2 (1) = 3.61, $p < .05$,

[2] t (56) = 5.84, $p < 0.0001$

Table 2

Seizure-Related Variables in CPS Group

Seizure Variables	CPS
Frequency	
<=1/year	27%
2–10/year	35%
>10/year	38%
Age of onset	6.3 (2.95)
Duration of illness	3.6 (2.55)
AEDs	
None	4%
Monotherapy	75%
Polytherapy	21%
Prolonged seizures	43%
Febrile seizures	19%

Table 3

Total Brain and Amygdala Volumes in CPS and Normal Groups

Volumes (mm^3)	CPS (61)	Normal (61)
Total Brain	1379.33 (105.55)	1413.04 (150.01)
Total Amygdala	2135.44 (270.42)	2096.03 (219.86)
Left Amygdala	1110.35 (183.96)	1072.13 (132.84)
Right Amygdala	1025.09 (106.59)	1023.90 (128.32)