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Language and Brain Volumes in Children with Epilepsy

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Abstract

This study compared the relationship of language skill with fronto-temporal volumes in 69 medically treated epilepsy subjects and 34 healthy children, aged 6.1–16.6 years. It also determined if the patients with linguistic deficits had abnormal volumes and atypical associations between volumes and language skills in these brain regions. The children underwent language testing and magnetic resonance imaging scans at 1.5 Tesla. Brain tissue was segmented and fronto-temporal volumes were computed. Higher mean language scores were significantly associated with larger inferior frontal gyrus, temporal lobe, and posterior superior temporal gyrus gray matter volumes in the epilepsy group and in the children with epilepsy with average language scores. Increased total brain and dorsolateral prefrontal gray and white matter volumes, however, were associated with higher language scores in the healthy controls. Within the epilepsy group, linguistic deficits were related to smaller anterior superior temporal gyrus gray matter volumes and a negative association between language scores and dorsolateral prefrontal gray matter volumes. These findings demonstrate abnormal development of language related brain regions, and imply differential reorganization of brain regions subserving language in children with epilepsy with normal linguistic skills and in those with impaired language.

Keywords

Language; epilepsy; development; MRI; frontal lobe; temporal lobe

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Introduction

Recent studies on large samples of children with epilepsy with average intelligence with both new onset (1) and chronic epilepsy (2) demonstrate linguistic difficulties and their association with seizure variables. There is an increase in the rate of language impairment from 25% in children, aged 6 - 8 years, to 33% in 8 -12-year-old subjects, and to more than 50% in those aged 12 -15 years (2). In addition, different seizure variables are related to the presence of linguistic deficits in each age group (2). These findings suggest dissimilar age-related effects of epilepsy on language development.

Although typically developing children acquire language during the toddler period, their linguistic skills continue to mature during childhood, and undergo acceleration during adolescence with an increase in syntactic complexity, advanced use of grammar and vocabulary, as well as abstraction (3-5). In parallel, language-related brain regions, such as the frontal lobe and superior temporal gyrus, particularly the posterior superior temporal gyrus, mature by the end of adolescence through antero-posterior dynamic changes in gray matter volume, thickness, and concentration (6-8). Myelination also progresses in these brain regions, albeit simultaneously (9).

Prior neuroimaging studies of children with epilepsy report abnormal lateralization of language (10-14), as well as a relationship of syntactic impairments with reduced cortical activity in the inferior frontal gyrus (13), linguistic impairment with neuroradiological abnormalities (15), and social communication deficits with volumetric abnormalities in language-related regions (16). However, there have been no prior studies on the association of language impairment with volumes in brain regions typically associated with language.

Therefore, the study presented in this paper examined if children with epilepsy with average intelligence and age matched controls would have disparate associations of basic linguistic skill with gray and white matter volumes of language-related regions including Broca's area (i.e., inferior frontal gyrus), Wernicke's area (i.e., superior temporal gyrus and its anterior and posterior divisions), as well as the dorsolateral prefrontal cortex and orbital frontal gyrus. We also determined if compared to children with epilepsy without linguistic deficits, those with language impairment had reduced gray and white matter volumes, as well as different associations of overall language function with volumes in these brain regions. In addition, we explored if the patients with and without impaired language differed on seizure variables (i.e., seizure frequency, age of onset, duration of illness, number of antiepileptic drugs, EEG lateralization and localization, febrile convulsions, and prolonged seizures).

Methods

Subjects

The study included 103 children, 69 with and 34 without epilepsy, aged 6.1 – 16.6 years. Table 1 describes the study groups in terms of demographic variables, IQ, and psychopathology. We determined socioeconomic status using the Hollingshead 2 factor index (17), based on parental occupational and educational status, Performance IQ with the Wechsler Intelligence Scale for Children-3rd edition (WISC-III) (18), and psychiatric diagnosis with the Schedule for Affective Disorders and Schizophrenia for School-Age Children, the Present and Lifetime Version (K-SADS-PL) (19), as described in detail in (20). Other than significantly lower Performance IQ scores (18) and higher rate of psychiatric diagnoses in the epilepsy groups, there were no significant differences between the groups in age, gender, ethnicity, and socioeconomic status.

The epilepsy group included 45 children with cryptogenic epilepsy who had complex partial seizures (CPS) and 24 children with childhood absence epilepsy (CAE). A pediatric neurologist at each recruitment site made a diagnosis of CPS or CAE according to the International Classification of Epilepsy (21). The study inclusionary criteria for the epilepsy subjects included a diagnosis of CPS or CAE and at least one seizure during the year prior to participation in the study. A CPS subject had to have cryptogenic epilepsy and clinical manifestations of CPS with or without focal EEG findings. All CAE patients had EEG evidence of 3 Hz spike and wave in addition to absence seizures induced by hyperventilation.

We excluded patients with a mixed seizure disorder, previous epilepsy surgery, atypical spike and wave complexes, juvenile myoclonic epilepsy, a structural MRI abnormality other than mesial temporal sclerosis, a neurological illness other than epilepsy, chronic medical illness, a metabolic disorder, a hearing disorder, mental retardation based on school/classroom placement or $IQ < 70$, and bilingual speakers of American English who did not attend English speaking schools or speak English at home. None of the epilepsy subjects had MRI evidence of mesial temporal sclerosis.

We recruited 37% subjects from tertiary centers (i.e., UCLA and USC based clinics) and 63% from community services (i.e., Los Angeles and Anaheim Kaiser Permanente, the Los Angeles and San Diego Chapters of the Epilepsy Foundation of America, private practices). UCLA IRB approved recruitment flyers were available for parents of the epilepsy children at each recruitment site. Parents who decided to enter their children into the study contacted the study coordinator who provided information about the study and used a UCLA IRB approved telephone script to determine if the children met the study's inclusionary but none of the exclusionary criteria. The study coordinator also contacted the child's pediatric neurologist to confirm that the child's diagnosis and rule out exclusionary criteria. One UCLA pediatric neurology investigator (W.D.S.) reviewed the history, EEG records, and diagnosis of each epilepsy 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.

Based on information obtained from the parents and the children's medical records, 21% of the patients had one seizure, 21% had 2-10, and 58% had more than 10 seizures during the year prior to participation in the study. Regarding antiepileptic drugs (AEDs), 72% of the children were on polytherapy, 24% on monotherapy, and 14% received no AEDs. The mean age of onset and duration of illness were 6.85 (SD 2.14) and 3.02 (SD 2.41) years, respectively. Twelve percent of the epilepsy subjects had a past history of febrile convulsions and 34% of seizures that lasted more than five minutes.

Reports of EEGs conducted at the time of the children's initial epilepsy diagnosis were available for 42 of the 45 CPS subjects with the following localization findings: non focal in 6, fronto-temporal in 13, temporal in 14, and other localization in 9. Regarding lateralization of EEG findings, 12 patients had left, 8 had right, 12 had bilateral, and 10 had no lateralized epileptic activity. All CAE subjects had 3Hz spike and wave, and none had generalized tonic clonic seizures. One CPS patient had secondarily generalized seizures. There was background slowing in 8 CPS patients and 1 CAE child. Based on the laterality index described in Soper et al. (22), 62 epilepsy subjects were right handed, 1 was left handed, and handedness information was unavailable for three subjects.

To include control children from a wide range of ethnic and socioeconomic status backgrounds similar to that of the epilepsy group, we recruited 34 control subjects, aged 6.1 – 15.8 years, from four public and two private schools in the Los Angeles community. The study coordinator screened potential participants for neurological, psychiatric, language, and hearing disorders through a telephone conversation with a parent. Given volumetric abnormalities in children

without epilepsy who have attention-deficit-hyperactivity disorder (ADHD) (23), depression (24,25), and anxiety disorders (26,27), we excluded children with these diagnoses in the past or who met criteria for these disorders once enrolled in the study from the control group. All the subjects in the control group were right handed.

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.

Language

All subjects underwent testing with the Test of Language Development (TOLD)-2 (28). This test has 3 forms: the TOLD - 2 Primary normed for children aged 4 - 8 years; the TOLD - 2 Intermediate normed for children aged 8 - 12 years; and the TOAL normed for adolescents 12 - 18 years (28). Each form of the TOLD-2 consists of a series of subtests through which it assesses both vocabulary and grammar. The TOLD manual provides normative data and findings of studies indicating reliability and validity of the instruments (28). Thirty-four subjects (25 epilepsy, 9 control) did the TOLD Primary, fifty-one the TOLD Intermediate (33 epilepsy, 18 normal), and eighteen (11 epilepsy, 7 control) the TOAL. The Spoken Language Quotient (SLQ), derived from each of these tests, was the independent variable for the study's data analyses.

Magnetic Resonance Imaging (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 24 ms, echo time of 9 ms, flip angle of 22, acquisition matrix of 256×192 , FOV 24, and two excitations. A detailed description of the MRI procedures, image preprocessing, delineation of the prefrontal cortex, dorsolateral frontal cortex/middle frontal gyrus, dorsolateral frontal cortex/superior frontal gyrus, orbital frontal cortex, temporal lobe, and intra- as well as inter-rater reliability can be found in Daley et al. (29) and for the superior temporal lobe and its parcellations, the anterior and posterior superior temporal lobe, in Taylor et al. (30).

Data Analysis

We compared SLQ scores as well as total brain, gray and white matter volumes between the children with and without epilepsy using analysis of covariance (ANCOVA). Frontal and temporal volumes were compared across groups using repeated measures ANCOVAs with hemisphere (left, right) as the within-subject variable and group as the between-subject variable. Separate analyses were conducted for each of the frontal and temporal volumes. Demographic (i.e., age, gender, and ethnicity) variables and Performance IQ were used as covariates in all these analyses since both brain development (31) and the maturation of language (32) are related to these variables.

For the within group analyses of the relationship of SLQ with fronto-temporal volumes, we estimated general linear mixed models with the volumes as the dependent variables, SLQ as the predictor and age, gender, and ethnicity as covariates. We did not control for Performance IQ because SLQ and Performance IQ are highly correlated with each other in both subject groups (control: $r = .57$, $p < .0005$; epilepsy: $r = .47$, $p < .0001$). Retaining highly correlated predictors in the models leads to multicollinearity, and this can invalidate the results by skewing the individual coefficients as well as the associated tests of significance.

Given the previously described relationship of psychiatric diagnosis with fronto-temporal volumetric abnormalities (23-27) and the exclusion of control subjects with a psychiatric diagnosis, within the epilepsy group, we conducted secondary analyses to determine whether the associations between SLQ scores and the fronto-temporal volumes were moderated by the presence/type of psychiatric diagnosis. To determine this, we included psychiatric diagnosis and its interaction with SLQ scores as additional predictors in the regression. A significant interaction term would indicate a differential association between fronto-temporal volumes and SLQ scores in the groups of subjects (presence vs. absence of a psychiatric diagnosis).

Within the epilepsy group, we classified subjects as having linguistic deficits if they had average language scores 1SD below the population mean of 100 and standard deviation of 15. These two subgroups of epilepsy subjects were compared on their seizure variables, including type of seizure (CPS vs. CAE), EEG lateralization and localization, age of onset, seizure frequency, and number of AEDs. We then compared those subjects with average language scores to those with linguistic deficits on their regional gray and white matter volumes using repeated measures ANCOVAs. Hemisphere (left, right) was used as the within-subject variable and group was used as the between-subject variable. Separate models were estimated for each of the frontal and temporal volumes. We also examined the association of SLQ with fronto-temporal volumes within each of these two subgroups of epilepsy subjects using general linear models as described before for the within-normal and within-epilepsy groups. All tests were two-tailed and a significance level of 0.05 was adopted.

Results

Mean Language Scores and Volumes

ANCOVA controlling for age, gender, ethnicity, and Performance IQ scores demonstrated that the SLQ scores of the epilepsy subjects (Mean: 95, SD: 16.77) were significantly lower ($F(1,97) = 7.78, p < .006$) than those of the control group (Mean: 105, SD: 15.96). Repeated measures ANCOVAs of fronto-temporal volumes controlling for age, gender, ethnicity, and Performance IQ demonstrated significantly smaller orbital frontal gyrus gray matter volumes in the epilepsy group compared to the control group (Table 2).

Within the control group, general linear mixed models of fronto-temporal volumes revealed an association of higher mean SLQ scores with larger total brain volumes ($F(1,30) = 4.09, p < .06$), both gray ($F(1,30) = 5.07, p < .04$) and white matter volumes ($F(1,44) = 3.27, p < .08$), as well as with larger gray ($F(1,30) = 4.36, p < .05$) and white matter dorsolateral prefrontal volumes ($F(1,30) = 4.72, p < .04$). In contrast, within the epilepsy group, these analyses demonstrated a significant association of SLQ with gray matter volumes of the inferior frontal gyrus ($F(1,65) = 4.53, p < .04$), the temporal lobe ($F(1,65) = 5.23, p < .03$), and the superior temporal gyrus ($F(1,42) = 5.85, p < .02$). Post hoc testing of the superior temporal lobe gyrus findings demonstrated a significant positive association of SLQ with gray matter volumes for the posterior superior temporal gyrus ($F(1,42) = 4.27, p < .04$).

To determine if the presence of a psychiatric diagnosis in 48% of the epilepsy subjects (Table 1) was related to the SLQ/volume findings in this group, we conducted secondary analyses. Mixed models of the fronto-temporal volumes did not yield a significant interaction between the presence of a psychiatric diagnosis and SLQ/volume associations.

Epilepsy Subjects With and Without Linguistic Deficits

As evident from Table 3, the 25 (36%) epilepsy subjects with mean SLQ scores one standard deviation below the general population mean were significantly older (10.8 (3.04) vs. 9.3 (2.81) years; $t(67) 2.57, p < .02$) than the subgroup without linguistic deficits. However, there were

no significant differences in the seizure variables of the epilepsy subjects with and without impaired language.

Above and beyond the age differences, the children with linguistic deficits had significantly smaller gray matter volumes of the superior temporal gyrus ($F(1,44) = 3.93, p < .05$) than those with normal mean SLQ scores. Post hoc testing of the superior temporal gyrus findings revealed significantly smaller anterior superior temporal gyrus ($F(1,44) = 3.77, p < .05$) in the children with linguistic deficits compared to those without these impairments.

The epilepsy subjects with average language scores showed a significant positive association of SLQ with gray matter volumes of the inferior frontal gyrus ($F(1,40) = 5.01, p < .03$) and the temporal lobe ($F(1,38) = 7.22, p < .01$) in contrast to the previously described positive association with total brain and dorsolateral prefrontal gray and white matter volumes in the control group. For the epilepsy subjects with language deficits, on the other hand, higher SLQ scores were associated with smaller gray matter dorsolateral prefrontal volumes ($F(1,21) = 4.12, p < .05$).

Discussion

This first study on language and fronto-temporal volumes in children with epilepsy highlights discrepancies in brain regions associated with language skill in the children with epilepsy compared to the normal children. Thus, overall language functioning, measured by mean SLQ, was positively related to gray and white matter total brain and dorsolateral prefrontal cortex volumes in the normal group but to gray matter volumes of the inferior frontal gyrus, temporal lobe, and posterior superior temporal gyrus in the epilepsy group as a whole and in the subgroup with average linguistic skills. The presence of linguistic deficits within the epilepsy group was associated with smaller anterior superior temporal gyrus gray matter volumes and a negative association between language function and dorsolateral prefrontal gyrus gray matter volumes but not with seizure variables.

The association of SLQ with total brain volume and dorsolateral prefrontal volumes, both gray and white, in the control group supports Richardson and Price's (33) conclusion in their review of structural MRI studies of language function in the undamaged brain that "a higher quantity of the neural substrate being measured represents better performance on a given task." In addition, the linguistic competence of normal adults (34-36) and children (37) involve executive functions subserved by the dorsolateral prefrontal cortex, such as attention and working memory. Functional magnetic resonance imaging (fMRI) studies of typically developing children also demonstrate increased cortical activity in the dorsolateral prefrontal cortex during syntax, semantics, and discourse coherence tasks (38,39).

In the epilepsy group as a whole and in the subgroup with average SLQ scores the a relationship of SLQ with inferior frontal gyrus, posterior superior temporal gyrus, and temporal lobe gray matter volumes rather than with dorsolateral prefrontal volumes implies structural reorganization of the brain that subserves normal language function in these children. Several lines of evidence support this explanation of the study's findings.

First, the inferior frontal gyrus, posterior superior temporal gyrus, and temporal lobe are involved in a wide range of linguistic skills (See reviews in (40) and (41)). Second, fMRI connectivity studies in typically developing children identify a normal age-related top down control of linguistic processing by the inferior frontal gyrus on posterior language-related regions of the temporal lobe, including the posterior superior temporal gyrus (8,42). Third, the association of younger age of onset with atypical language representation in an fMRI study of 45 subjects with localization related epilepsy, aged 9 - 57 years, during a word definition task suggests that intra-hemispheric and inter-hemispheric reorganization of language processing

occurs during childhood (43). Fourth, recent fMRI studies also demonstrate decreased left lateralization of cortical activity, particularly in the inferior frontal region during a silent verb generation task in children with benign rolandic epilepsy (13), as well as reduced resting connectivity in a language network that includes the left inferior frontal gyrus in adults with left temporal lobe epilepsy (44).

Unlike the epilepsy subjects with normal linguistic scores, the structural reorganization involving a negative rather than positive relationship of language function with dorsolateral prefrontal gyrus gray matter volumes and smaller anterior temporal gyrus gray matter volumes in the children with linguistic deficits was related to language impairment. What determines functional versus dysfunctional language-related structural reorganization is yet to be determined. However, Mbwana et al. (43) also identified limitations to the plasticity of language network reorganization in localization related epilepsy in their study of neural networks for processing language.

Thus, in addition to the previously reported abnormal lateralization of language in children with epilepsy (10-14), our findings suggest differential involvement of language-related brain regions in normal and impaired linguistic functioning of children with epilepsy. Similar to the dissociation between IQ and fronto-temporal volumes in children with recent onset (45) and chronic epilepsy (29,46) compared to healthy control subjects, different brain regions also appear to be involved in the linguistic skill of children with epilepsy.

Smaller anterior superior temporal gyrus gray matter volumes and SLQ scores one standard deviation below the population mean and older age in the epilepsy subjects with language impairment imply abnormal maturation of this brain region in these children. Thus, there is an age-related decrease in activation of the anterior superior temporal gyrus during auditory processing of phonological tasks as healthy children use more abstract orthographic processing and invoke the posterior superior temporal gyrus and its connections with the inferior frontal gyrus (47). Functional imaging studies of typically developing children also demonstrate participation of this brain region in the generation of verbs (48) and the comprehension of an auditory narrative task (49).

No evidence for a relationship between type of epilepsy and mean language scores for the epilepsy group as a whole and between seizure variables and the presence/absence of linguistic deficits, suggests that brain reorganization is unrelated to on-going illness effects. However, a prior study on a large sample of 182 children with epilepsy found an association of SLQ with seizure frequency, duration of illness, and history of prolonged seizures, but not with type of epilepsy and EEG findings (2). Our findings in the current study, therefore, emphasize the importance of additional studies on larger samples of children with epilepsy to determine how brain structure and seizure variables affect the development of language in these children.

Despite significantly smaller orbital frontal gray matter volumes in the epilepsy compared to the normal group, we found no association of volumes in this brain region with either language skill or deficits. Yet, the orbital frontal gyrus plays a role in the propagation of complex partial seizures (50), the onset of absence seizures (51), semantics (52,53), distinction between content and function words (54), as well as in the discourse deficits found in children with epilepsy (55). Different orbital frontal gyrus regions subserve diverse functions, including language and regulation of social behavior through the integration of factual knowledge and emotional patterns (See review in (56)). Our negative findings might, therefore, reflect measurement of total rather than regional volumes within the orbital frontal gyrus.

The findings of our study are limited by the small sample size of the normal subjects ($n = 34$) relative to the epilepsy subjects ($n = 69$), SLQ based on different age-related forms of the TOLD, higher Performance IQ scores in the control group, the exclusion of normal subjects

with a psychiatric diagnosis, and multiple statistical comparisons. Computing SLQ scores from three different age-related forms of the language instrument - the TOLD primary, the TOAL Intermediate, and the TOAL - limits generalization of the study's findings, and does not rule out undiagnosed linguistic deficits.

Although we controlled for Performance IQ in the between group comparisons of SLQ and volumes, given the significant correlation of SLQ with Performance IQ, the different patterns of relationship between SLQ and fronto-temporal volumes might not be generalizable to epilepsy and normal subjects with similar mean PIQ scores. Exclusion of children with a psychiatric diagnosis in the normal group did not contribute to the different SLQ/fronto-temporal volume associations in the normal and epilepsy groups. Finally, although we computed multiple statistical comparisons, all statistical tests were two-tailed and a significance level of 0.05 was adopted for all inferences.

In conclusion, our findings demonstrate abnormal development of language related brain regions in medically treated children with epilepsy who have with average intelligence and no neuroradiological findings. In addition, they imply differential reorganization of brain regions subserving language in children with epilepsy with normal linguistic skills and in those with impaired language.

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Table 1

Demographic Features of Study Groups

	Epilepsy	Control
N	69	34
Age (SD) years	9.80 (2.43)	9.92 (1.98)
Gender		
Male/Female (%)	32/68	47/53
Socioeconomic Status		
High (i-iii)/Low (iv-v) (%)	26/74	33/67
Ethnicity		
Caucasian/Non-Caucasian (%)	54/46	44/56
Performance IQ (SD) ¹	99 (16.36)	112 (12.22)
Psychiatric Diagnosis ²	48%	0%

¹ $t(101)=3.19, p<0.002,$

² $\chi^2(1) = 23.93, p < .0001,$ note that children with a psychiatric diagnosis were excluded from the control group

Table 2

Fronto-Temporal Volumes in Epilepsy and Healthy Control Groups

Mean Volumes (mm ³)	Epilepsy (SD)	Control (SD)
Total Brain	1373.26 (117.74)	1408.15 (143.06)
Gray	779.35 (68.97)	810.22 (70.86)
White	479.66 (72.96)	484.13 (67.98)
Frontal		
Inferior Frontal Gray	21.94 (3.64)	23.36 (4.73)
Inferior Frontal White	10.13 (2.17)	11.18 (3.16)
Orbital Frontal Gray ^I	34.05 (6.16)	36.23 (4.47)
Orbital Frontal White	16.15 (3.64)	15.39 (2.51)
Dorsolateral Prefrontal Gray	116.57 (18.39)	122.75 (11.15)
Dorsolateral Prefrontal White	54.17 (10.20)	55.07 (8.16)
Temporal		
Gray	148.63 (14.22)	156.42 (15.68)
White	69.18 (11.98)	67.09 (11.19)
Superior Temporal Gray	37.54 (5.06)	37.84 (5.95)
Superior Temporal White	12.70 (6.14)	12.79 (2.86)
Heschl Gray	2.71 (0.73)	2.82 (0.63)
Heschl White	1.08 (0.59)	1.17 (0.33)

^IF (1,94) = 3.68, p = .05 with demographic variables and Performance IQ in the model

Table 3Seizure Variables in Epilepsy Subjects With/Without Linguistic Deficits¹

Seizure Variables	Linguistic Deficits	Average SLQ
N	25	44
Type of epilepsy		
Complex partial seizures	19	26
Left	3	9
Right	5	3
Bilateral	3	9
No focality	5	5
Not available	3	0
Childhood absence epilepsy	6	18
Seizure frequency		
< = 1/year	17%	23%
2 – 10/year	13%	26%
>10/year	70%	51%
Uncontrolled seizures ²	70%	56%
Age of onset (SD) years	7.61 (4.38)	6.40 (3.29)
Duration of illness (SD) years	3.2 (3.51)	2.90 (3.02)
Antiepileptic drugs		
None	0%	7%
Monotherapy	72%	73%
Polytherapy	28%	20%
Prolonged seizures ³	33%	34%
Febrile seizures	9%	14%

¹ SLQ 1 standard deviation < population mean,² < 5 seizures in year prior to study,³ Seizures lasting 5 or more minutes