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Thought disorder and frontotemporal volumes in pediatric epilepsy

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ABSTRACT

The aim of this study was to determine if volumes of frontotemporal regions associated with language were related to thought disorder in 42 children, aged 5–16 years, with cryptogenic epilepsy, all of whom had complex partial seizures (CPS). The children with CPS and 41 age- and gender-matched healthy children underwent brain MRI scans at 1.5 T. Tissue was segmented, and total brain, frontal lobe, and temporal lobe volumes were computed. Thought disorder measures, IQ, and seizure information were collected for each patient. The subjects with CPS had more thought disorder, smaller total gray matter and orbital frontal gray matter volumes, as well as larger temporal lobe white matter volumes than the control group. In the CPS group, thought disorder was significantly related to smaller orbital frontal and inferior frontal gray matter volumes, increased Heschl's gyrus gray matter volumes, and smaller superior temporal gyrus white matter volumes. However, significantly larger orbital frontal gyrus, superior temporal gyrus, and temporal lobe gray matter volumes and decreased Heschl's gyrus white matter volumes were associated with thought disorder in the control group. These findings suggest that thought disorder might represent a developmental disability involving frontotemporal regions associated with language in pediatric CPS.

1. Introduction

Children with a broad range of neurobehavioral disorders including epilepsy [1–3], schizophrenia [4], attention-deficit hyperactivity disorder (ADHD) [5], and high-functioning autism [6], as well as young otherwise healthy children [4], have thought disorder. Compared with their peers, these children have difficulty using language to formulate and organize their thoughts. When speaking, they present their ideas with impaired reasoning (i.e., illogical thinking) and unpredictable change the topic of conversation (i.e., loose associations). They also use few linguistic (i.e., cohesive) devices to connect ideas (e.g., conjunctions) and to refer to people, objects, or events (e.g.., pronouns, the article, demonstratives) within and across sentences. In addition, while they speak, they infrequently monitor and self-repair communication breakdowns or errors in how they organize their thoughts and use syntax, word choice, and reference to express their ideas. These discourse deficits make it difficult for the listener to follow whom and what they are talking about.

Given the importance of social communication in our daily lives, these social communication deficits have functional correlates. Thus, studies in children with epilepsy have demonstrated an association between thought disorder and disruptive disorder diagnoses (i.e., ADHD, oppositional defiant disorder, conduct disorder), high Child Behavior Checklist externalizing factor scores, decreased academic achievement, school problems, and poor peer interaction [1–3]. In children with ADHD, thought disorder is related to cognitive and attentional deficits [5], and in children with high-functioning autism, it is related to impaired cognition [6].

From the developmental perspective, in children with cryptogenic epilepsy with complex partial seizures (CPS) and focal involvement in the temporal and frontal lobes, the severity of thought disorder is related to increased seizure frequency, early age at onset, history of prolonged seizures, and type of antiepileptic drug (AED), as well as younger age, male gender, and lower Verbal IQ scores [3]. These cross-sectional findings, together with significantly more thought disorder in younger compared with older children with CPS, imply that thought disorder might reflect a developmental delay or disability involving the normal maturation of social communication skills in pediatric CPS [3].

Age at onset of CPS, a history of prolonged or febrile seizures, as well as localization and lateralization of epileptic activity, are, however, also associated with frontotemporal volumes in these children [7]. More specifically, earlier onset of CPS is related to smaller gray and white matter orbital frontal gyrus (OFG) volumes and temporal lobe white matter volumes, a history of prolonged seizures is related to increased inferior frontal gyrus (IFG) gray

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and white matter volumes, and left focal EEG activity is related to reduced total white matter volumes [7].

Recent structural imaging studies describe protracted maturation of frontotemporal regions associated with the integration of language and thought in normal children, with a decrease in gray matter density, but increase in white matter volumes, that continues through adolescence [8,9]. Functional imaging studies demonstrate involvement of Broca's (i.e., IFG) and Wernicke's (i.e., STG) areas, their right hemisphere homologs, and the dorsolateral prefrontal cortex (DLPFC) in how typically developing children make sense of the logic and topic of conversation [10].

Yet, these same language-associated brain regions are involved in the thought disorder of adults and youth with schizophrenia who have smaller left superior temporal gyrus (STG) [11,12], right temporal [13], and orbital frontal [14] volumes. Evidence for involvement of the orbital frontal lobe in both semantics [15,16] and seizure propagation [17] suggests that in addition to the previously described "classical" language areas, structural abnormalities in the orbital frontal lobe might also play a role in the thought disorder of children with CPS.

To delineate the mechanism of the thought disorder of children with CPS, we examined the relationship of these deficits to volumes of the previously described language-related brain regions and compared the data with those for age- and gender-matched healthy children. Based on our earlier findings [3,7], we predicted that children with CPS would have significantly more thought disorder and larger temporal lobe white matter volumes than age- and gender-matched healthy children. We also hypothesized that both the control children and those with CPS with thought disorder would have smaller frontal (i.e., IFG, OFG, DLPFC) and temporal (i.e., STG, Heschl's gyrus (HG)) lobe volumes than those without thought disorder.

2. Methods

2.1. Subjects

The study included 42 children with cryptogenic epilepsy, all of whom had CPS, and 41 children without epilepsy aged 5–16 years (Table 1). The control group had significantly higher IQ scores and exhibited a trend toward more children from families of higher socioeconomic status based on the Hollingshead 2 factor index [18], which is derived from both parent occupational and educational status.

To be included in the study, the patients had to have cryptogenic epilepsy and CPS, as defined by the International Classification of Epilepsy [19], and at least one seizure during the year prior to participation in the study. As described in this classification, children with a clinical history of CPS but no EEG evidence of focal epileptic activity were also included in the study sample. 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 other than mesial temporal sclerosis.

We recruited 43% of the patients with CPS from tertiary centers (e.g., UCLA Pediatric Neurology Services, Children's Hospital of Los Angeles) and 57% from the community (e.g., Kaiser Sunset, Kaiser—Orange County, private pediatric neurologists, Los Angeles chapter of the Epilepsy Foundation). UCLA institutional review board (IRB)-approved recruitment flyers were available for parents of children with CPS 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 the child's diagnosis and to rule out exclusionary criteria.

Table 2 summarizes seizure frequency during the past year, current AEDs, age at onset, illness duration, as well as the numbers of febrile convulsions and prolonged seizures (i.e., >5 minutes) from the parents and the children's medical records. Of the 42 patients with CPS, 10 had nonlateralized EEG findings at the time of the initial epilepsy diagnosis, 12 had a left focus, 6 a right focus, and 12 bilateral foci. EEGs were unavailable for 2 patients with CPS. Regarding focal EEG findings, 6 patients had no focal findings, and 14 had interictal spikes in the temporal lobe, 12 in the frontal and temporal lobes, and 8 in other areas. Two patients with CPS had secondary generalization and eight had background slowing. None of the subjects had mesial temporal sclerosis.

To include children from a wide range of ethnic and socioeconomic backgrounds similar to those of the CPS group, we enrolled the nonepileptic 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 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.

2.2.1. MRI acquisition

All subjects completed MRI scanning on a 1.5-T GE Signa MRI scanner (GE Medical Systems, Milwaukee, WI, USA). The imaging

Table 1
Demographic features of the CPS and normal groups

	CPS group	Normal group
N	42	41
Age, mean (SD)	10.2 (2.55)	10.7 (2.41)
Gender		
Male	50%	44%
Female	50%	56%
Socioeconomic status[a]		
High (I–III)	26%	46%
Low (IV–V)	74%	54%
Ethnicity		
Caucasian	66%	54%
Non-Caucasian	34%	46%
Full Scale IQ, mean (SD)[b]	94.2 (15.43)	114.5 (13.20)

[a] $\chi^2(1) = 3.20$, $P < 0.09$.
[b] $t(75) = 0.46$, $P < 0.0001$.

Table 2
Epilepsy-related features of the CPS group

Seizure frequency	
1/year	28%
2–10/year	31%
>10/year	41%
Age at onset (years)	6.6 (3.10)
Duration of illness (years)	3.6 (2.51)
AEDs	
None	2.4%
Monotherapy	76.2%
Polytherapy	21.4%
Prolonged seizures	44%
Febrile convulsions	15%