



Seizure-related variables are predictive of attention and memory in children with epilepsy



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ABSTRACT

Children with epilepsy (CWE) are at greater risk for cognitive deficits and behavioral difficulties than are typically developing healthy children, and particular epileptic symptoms and treatments may contribute to this risk. The current study examined the relationships between four seizure-related variables and attention and memory functioning in a sample of 207 CWE (ages 6–16) using both neurocognitive and parent/teacher-report measures. Sociodemographic, medical, and neuropsychological data were collected from patients' medical charts in a retrospective fashion. Hierarchical multiple regressions were performed with sociodemographic variables (age, gender, race) entered as step one and seizure-related variables (number of anti-epileptic drugs [AEDs], EEG laterality, EEG lobe of focus, lifetime seizure duration) entered as step two. Results indicated that seizure-related variables were consistently predictive of poor cognitive performances above and beyond sociodemographic variables, although only minimally predictive of parent/teacher-reports. A longer duration of seizure burden and greater number of AEDs were robust predictors of performances on most cognitive measures. These findings indicate that CWE with long lifetime seizure durations and multiple AEDs are at risk for inefficiencies in attention and memory. Knowledge of this risk will allow treating providers greater accuracy and precision when planning medical treatment and making recommendations to families.

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1. Introduction

Pediatric epilepsy has widespread negative impact on children's development and functional status, including both cognition and behavior. As a group, children with epilepsy (CWE) tend to display compromised cognitive abilities when compared with non-epileptic matched controls [1,2]. A broad range of neurocognitive deficits has been documented in CWE, including language [3–6], perception, concept formation, problem solving and executive function [7–9], processing speed and attention [10–14], and memory and learning [15–20].

Difficulties with attention are among the most common problems reported by parents of CWE [11], and results of several studies indicate that CWE are at increased risk for inattention [10,13,21,22], hyperactivity [11], and impulsivity [14]. Importantly, investigations examining the comorbidity of epilepsy and Attention-Deficit/Hyperactivity Disorder (ADHD) have suggested that clinically significant ADHD symptoms are present in 37.7% of CWE, with the inattentive subtype being most commonly diagnosed [11,14,23]. Building upon the attention literature, memory and learning difficulties are also common in CWE across a

variety of seizure etiologies, including those with both established foci and generalized onset [12,17,19] and encompassing both visual and verbal domains [3,19,24,25]. Although memory deficits are most commonly documented in temporal lobe epilepsy (TLE; [19,26–30]), several studies have shown that amnesic syndromes are also present in other epilepsy subtypes such as frontal lobe epilepsy [7,19,31,32] and idiopathic generalized variants including childhood absence epilepsy (CAE; [19,33,34]) and benign epilepsy with centrotemporal spikes [35–37].

Several factors have been identified as likely upstream causes of neurocognitive deficits in CWE, including but not limited to a) seizure frequency, b) laterality and lobe of seizure activity, and c) number of prescribed anti-epileptic drugs (AEDs). First, significant attention has been paid to the potential impact of recurrent seizures on a developing brain. Studies of cognition in children with continuous and/or frequent spike-wave discharges during sleep have suggested that excessive electroencephalography (EEG) spike discharges have a deleterious impact on several areas of cognition, including language and memory [38]. Additionally, Riva and colleagues [39] indicated that, although IQ remained intact, frequent seizures correlated with difficulties in attention and weaknesses in inhibition of impulsive responses. In support of these findings, a cross-sectional neurodevelopmental study of 50 CWE ages 5–12 showed that cognition, communication, social-emotional functioning, adaptive behavior, and general development were significantly delayed in patients who experienced three or more seizures per

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month [40]. Importantly, attention problems, aggression, thought problems, and behavioral somatic symptoms were rated in the clinically significant range by parents of patients with higher seizure frequencies.

Second, in addition to frequency/duration, seizure location has also been thoroughly investigated, with some variability in findings. Specifically, some studies have documented greater decrements in full scale IQ and memory for patients with generalized rather than focal seizures [1,19,40,41]. Interestingly, given high degrees of brain plasticity in children, some researchers have posited that localization of focal epilepsies in children has less relevance with respect to the specificity of cognitive impairment than in adults [42,43]. In contrast to this notion, temporal lobe epilepsy has widely documented specific impairments in memory, learning, and emotion recognition in children as well as in adults [19,26–30,41,44–47]. Moreover, executive function and attention deficits have been associated with frontal lobe epilepsy [7,48], further arguing for the power of localization in determining cognitive outcome.

Third, although the impact of AEDs on cognitive performance has been investigated extensively in adults, corresponding research in children is sparse and variable. When compared with no treatment, several established AEDs have been reported to impact cognition across the lifespan [49]. However, while various AEDs have been associated with impairments in cognition and behavior, others have shown positive to no impact [8,76]. Furthermore, for several of the available AEDs, there is a lack of conclusive data [76]. Unfortunately, limitations in study designs have led to inconclusive results regarding cognitive profiles for specific AEDs in children [50] and the multi-factorial nature of emotional and behavioral problems in CWE often complicates attempts to isolate the contribution of AEDs to these difficulties [51]. Beyond the impact of individual medications, however, the overall number of AEDs ingested by children does attenuate cognitive performance. Specifically, relative to monotherapy, polytherapy has been linked to neurodevelopmental delays in cognition, communication, and socioemotional and global development [40]. Clearly, the literature on the impact of seizure-related variables on cognition and behavior in CWE is complex and multifaceted. In order to add some clarity to current conceptualizations of such relationships, we elected to examine the impact of four relevant seizure-related variables – number of current prescribed AEDs, lifetime seizure duration, EEG seizure laterality, and EEG seizure lobe of focus – on multiple neuropsychological measures of attention and memory, as well as on several informant-reported inattention and hyperactivity. We hypothesized that, holding demographic variables constant, seizure-related variables would predict a) poorer performance on measures of attention and memory and b) greater attention problems and hyperactivity via parent and teacher-report.

2. Material and methods

2.1. Participants

Participants were 207 children, aged 6 to 16 years ($M = 10.6$, $SD = 2.8$) who completed a neuropsychological evaluation in the Department of Psychology at St. Louis Children's Hospital between the years of 2004 and 2016. All participants carried a formal diagnosis of epilepsy from appropriate medical professionals. Sociodemographic, seizure-related, and neuropsychological data were obtained retrospectively from patients' archival medical records. Sample characteristics are presented in Table 1; mean intellectual level of the sample was in the Low Average range (FSIQ – $M = 84.44$, $SD = 17.31$, *Range*: 40.00–138.00). Unfortunately, variables pertaining to parents' level of education, income, and current insurance were not available in the research database and, consequently, we were unable to quantitatively document socioeconomic status for our sample.

Children were excluded from study participation if they were not within the age range of 6 to 16 years. Additionally, due to the potential extraneous influence of non-AED medications on neuropsychological functioning, children who were prescribed medication for anxiety or

Table 1
Sociodemographic and seizure-related data of the sample.

	N	Mean	SD
Age (years)	207	10.6	2.8
Lifetime seizure duration (years)	207	5.06	3.6
Number of current AEDs	207	1.7	0.86
FSIQ	207	84.88	17.31
	N	Percent	
Gender			
Male	113	54.6	
Female	94	45.4	
Race			
African American	21	10.1	
Asian	4	1.9	
White (non-Hispanic)	168	81.2	
White (Hispanic)	4	1.9	
Other	7	3.4	
ICD-9 epilepsy diagnosis			
Generalized	28	13.53	
Complex partial epilepsy	111	53.62	
Simple partial epilepsy	20	9.66	
Epilepsia partialis continua	1	0.48	
Epilepsy unspecified	45	21.74	
Unknown	2	0.97	
EEG side of focus			
Bilateral	79	38.2	
Unilateral	99	47.8	
Right	43	20.8	
Left	56	27.1	
Normal	14	6.8	
EEG lobe of focus			
Single	80	38.6	
Frontal	29	14.0	
Temporal	37	17.9	
Parietal	11	5.3	
Occipital	3	1.4	
Multifocal/generalized	75	36.2	
None	10	4.8	

Note. AEDs = antiepileptic drugs; FSIQ = full scale intellectual quotient; ICD-9 = International Classification of Diseases, Ninth Revision; EEG = electroencephalogram.

depression at the time of testing were excluded. However, in order to increase generalizability of our results, children who were prescribed medication for attention deficits were included in the sample. Specifically, 17.9% of children in the sample were on some type of medication for attention deficits. With respect to inclusionary criteria, participation was restricted to children who had not undergone epilepsy surgery due to potential confounding factors of surgical procedures. In order to increase generalizability, no exclusions were made based upon intellectual capacity. During the clinical visit, all participants were accompanied by a parent or legal guardian who provided consent for results of the evaluation to be utilized for research purposes. IRB approval was obtained prior to the initiation of the study.

2.2. Materials and procedure

Patients completed a variety of tests assessing intellectual and neuropsychological functioning. We elected to focus the current study on measures of attention, memory, and behavioral functioning, given a) previously reviewed literature suggesting strong relationships between these constructs and seizure-related variables in CWE and b) constraints in the database (e.g., missing data in measures of other constructs). The Children's Memory Scale (CMS; [52]) evaluates a variety of attention and memory dimensions in children ages 5 to 16:11 years. Scores from the CMS Numbers task were analyzed as a measure of attention and working memory. The California Verbal Learning Test – Children's Version (CVLT-C; [53]) assesses verbal learning and memory deficits in children ages 5 to 16:11 years. The total score across trials one through five reflects a child's ability to learn and recall verbal

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