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Developmental stage affects cognition in children with recently-diagnosed symptomatic focal epilepsy

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ABSTRACT

This study explored the impact of developmental stage on cognitive function in children with recently-diagnosed epilepsy. In keeping with a neurodevelopmental framework, skills in a critical developmental period were expected to be more vulnerable than those stable at the time of seizure onset. We studied children with early-onset (EO) symptomatic focal epilepsy (onset: 3–5 years; $n = 18$) and compared their performance with that of the group with late-onset (LO) epilepsy (onset: 6–8 years performance of; $n = 8$) on a range of cognitive tasks. Performance of both groups was compared with normative standards. 'Critical' and 'stable' classifications were based on developmental research. Nonparametric analyses revealed that skills in a critical developmental period for the group with EO epilepsy fell below normative standards (Phonological Processing: $p = .007$, Design Copying: $p = .01$, Visuomotor Precision:, $p = .02$) and fell below the performance of the group with LO epilepsy (Design Copying: $p = .03$, Visuomotor Precision: $p = .03$). There were no differences between the group with EO epilepsy and the group with LO epilepsy on measures of receptive vocabulary and memory, which were proposed to be in a stable developmental period across both groups. Auditory span, as measured by Word Order, was reduced for both the group with EO epilepsy ($p = .02$) and the group with LO epilepsy ($p = .02$) relative to normative standards, but the groups did not differ from each other. These results are consistent with a prolonged period of critical development for this skill. These findings support the notion that skills in a critical phase of development are particularly vulnerable following the onset of symptomatic focal epilepsy in childhood.

1. Introduction

Seizure activity during critical periods of brain development has the potential to cause significant cognitive problems for the child, which may have lifelong consequences. Infants are particularly prone to seizures, with events having the propensity to be frequent and/or prolonged [1]. Furthermore, seizures produce distinct maladaptive anatomical and physiological changes in the developing brain [2,3]. The resultant disruption to neural networks has been correlated with adverse behavioral outcomes [3]. It follows that there may also be a lasting impact of early-onset seizures on cognitive development.

Adult and child studies across a range of epilepsy syndromes consistently suggest that intellectual and cognitive impairment is greater when seizures begin early rather than later in life [4–12]. In support of this view, intellectual outcome is particularly poor if seizures begin prior to the age of five [5,13–17], with the poorest outcomes associated with seizure onset in the first year of life [11,18]. The effect of age at onset persists once factors such as seizure control [14,19], number of antiepileptic drugs (AEDs) [19], etiology [20], duration of epilepsy [14,19,21], and extent of pathology are controlled [22], implying that developmental processes have an independent effect on cognitive outcome.

Some recent studies have explored the relationship between age at seizure onset and specific cognitive functions across childhood. These studies have yielded mixed results, with age at seizure onset found to predict motor function [23], attention [6], language [8], nonverbal reasoning [16], memory [24], and executive functions [25,26]. However, several studies have reported the absence of such effects across these cognitive domains [27–31]. These inconsistencies not only may reflect differences in methodology and sample characteristics but also may be due to limitations of utilizing age at seizure onset as a marker of

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development, a variable enmeshed with illness duration, medication, and cumulative burden of seizures [32].

One approach, to separate developmental effects from illness variables, has been to study cognition in children with new-onset epilepsy. Studies utilizing such methodologies have identified difficulties across a range of cognitive skills [30,33], with attention and information processing being most consistently impaired [34,35]. These studies highlight the cognitive burden experienced by children with new-onset epilepsy; however, they do not account for developmental factors. That is, previous research has largely overlooked the impact of the timing of seizure-onset occurrence and the possibility of different outcomes for specific skills at different developmental stages.

A handful of studies have considered developmental stage, but this approach is yet to be applied to a cohort with new-onset epilepsy. Upton and Thompson [36] stratified their sample of adults with frontal lobe epilepsy (FLE) according to three groups with different ages at seizure onset that correspond to stages of executive development. The two measures of executive function employed yielded inconsistent results but did not suggest a lasting effect of age at seizure onset. Of note, their design may have overlooked a delay in development. Consistent with that possibility, Hernandez et al. [37] studied a sample of children with FLE and found that these children had specific deficits in aspects of executive function that were more apparent in younger as opposed to older children, suggesting a delay in these abilities rather than a discrete impairment.

Developmental effects may be particularly apparent in executive functions because of the prolonged developmental trajectory of the neural architecture supporting this aspect of cognition. This concept can be applied to other cognitive domains that emerge earlier in childhood. Dennis [38] provided a useful heuristic to examine developmental delays and deficits by recognizing potentially different outcomes for skills in an emerging, developing, or established phase at the time of insult. Empirical studies testing this framework suggest that skills in an emerging phase of development are associated with poorer outcome than more established skills in generalized brain insults [39,40]. While Dennis' original model does not easily accommodate nonlinear patterns of development which have been, she and colleagues [41] have recently suggested an update to accommodate periods of relative stability and critical bursts of change resulting in a wider range of potential developmental outcomes following early childhood brain insult.

The normal developmental trajectory of specific cognitive abilities is an important consideration in predicting cognitive impairment in clinical populations. Given that the peak incidence for the onset of focal epilepsy occurs in early childhood [42,43], skills undergoing rapid development at this time may provide an important insight into cognitive outcome for this group. Such skills include, but are not limited to, receptive vocabulary, associative memory, visuospatial function, phonological processing, deductive reasoning, and auditory span. Specifically, there is strong evidence to suggest that the first year of life represents a key period for language function, particularly receptive vocabulary [44]. Similarly, the hippocampus, which supports associative memory, undergoes a critical period of development in infancy, with maturation continuing into middle childhood [45,46]. Despite ongoing refinement, the neural foundations for receptive language and associative memory are laid down in infancy, indicating an early critical period for these skills. Although the foundations of visuospatial and phonological skills are also laid early in life, there is strong evidence to suggest that these skills undergo significant structural and functional development between the ages of 3 and 5 years, indicating a critical period for these abilities [47–49]. In terms of deductive reasoning, although rudimentary skills are apparent in preschoolers [50], the critical period for these abilities does not occur until middle–late childhood when children are better able to process complexity [51]. Auditory span has a more gradual and prolonged developmental course from the age of three through to nine years [52]. Distinct developmental spurts have not been described, with maturation characterized by a more linear progression, suggesting that the critical period for auditory span is more prolonged [52–54].

The present study aimed to examine the impact of seizure onset during early childhood and to determine whether there are differential effects for specific cognitive skills depending on developmental stage. Consistent with Dennis et al.'s [41] model, cognitive abilities were classified as 'stable' or 'critical', and performance was compared for two age groups. Three- to five-year-old children with new-onset epilepsy (group with early-onset (EO) epilepsy) were compared with a group of six- to eight-year-old children with new-onset epilepsy (group with late-onset (LO) epilepsy). It was expected that skills in a 'critical' but not 'stable' developmental phase would fall below normative standards irrespective of seizure onset. Differences between the group with EO epilepsy and the group with LO epilepsy were expected for skills, where one group was in a 'critical' developmental phase and the other was in a 'stable' developmental phase. The group in the 'critical' phase was expected to perform more poorly than that in the 'stable' phase. No between-group differences were expected for skills classified as 'critical' or 'stable' in both the group with EO epilepsy and the group with LO epilepsy.

2. Method

2.1. Participants

Twenty-eight children with symptomatic focal epilepsy participated in the study. Symptomatic focal epilepsies were defined as recurrent, unprovoked seizures with a known or presumed focal basis (including those with or without impairment of consciousness or awareness, as well as those evolving into bilateral convulsive seizures). Diagnosis, including localization, was made by the child's treating neurologist, supplemented by EEG results, MRI findings, and other clinical investigations as necessary. Any child with a current developmental or psychiatric diagnosis or a known or suspected diagnosis of intellectual disability (ID) was excluded from the study. Parent ratings of adaptive function were used to exclude children with ID, rather than IQ, given that IQ is enmeshed with the specific cognitive domains central to this study. Children with composite adaptive behavior ratings <70 on the Vineland Adaptive Behavior Scales — Second Edition (VABS-II; [55]) were excluded. Two children were excluded on this basis, resulting in a sample size of 26. Several other studies have utilized adaptive behavior to infer IQ scores in individuals with ID [56–58].

All children were assessed as close as possible to time of diagnosis but up to a maximum of two years since diagnosis. Participants were divided into two groups based on age at seizure onset: (EO: 3–5 years; $n = 18$) and (LO: 6–8 years; $n = 8$). Age at onset and age at assessment (i.e., chronological age) both fell in the same age bracket (3 years, 0 months–5 years, 11 months or 6 years, 0 months–8 years, 11 months). This was to preclude the confounding effect of children having an early age at onset but late age at assessment. Although the division between the group with EO epilepsy and the group with LO epilepsy reflects a critical point in development for many cognitive domains, change is gradual rather than associated with a fixed age or time point. Thus, the cutoff between the group with EO epilepsy and the group with LO epilepsy is somewhat arbitrary, and the distribution of the sample within the group with EO epilepsy and that with LO epilepsy becomes important, particularly for five- and six-year-old patients. The age distribution of the sample is depicted in Fig. 1. Of the seven five-year-old participants, five were between 5 years, 1 month and 5 years, 6 months of age. The six-year-old child was 6 years, 10 months of age. Thus, there was minimal clustering around the cutoff.

Current seizure frequency was classified as follows: daily, weekly, monthly–quarterly, or yearly or longer (yearly plus). Classifications were made on the basis of parent report as well as information obtained from the child's medical file. Seizure focus included the following: frontal lobe (EO: $n = 7$, LO: $n = 4$); temporal lobe (EO: $n = 8$, LO: $n = 1$); parietal lobe (EO: $n = 1$, LO: $n = 1$); occipital lobe (EO: $n = 1$, LO: $n = 1$); and hypothalamus (EO: $n = 1$, LO: $n = 1$). Chi-square revealed