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Research report

Mapping the landscape of cognitive development in children with epilepsy

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ABSTRACT

Objective: Normal childhood development is defined by age-dependent improvement across cognitive abilities, including language, memory, psychomotor speed and executive function. Epilepsy is often associated with a global disruption in cognitive development, however, it is still largely unknown how epilepsy affects the overall organization of overlapping cognitive domains. The aim of the study was to evaluate how childhood epilepsy affects the developmental interrelationships between cognitive domains.

Methods: We performed a comprehensive assessment of neuropsychological function in 127 children with new onset epilepsy and 80 typically developing children matched for age, gender, and socio-demographic status. A cross-correlation matrix between the performances across multiple cognitive tests was used to assess the interrelationship between cognitive modalities for each group (patients and controls). A weighted network composed by the cognitive domains as nodes, and pair-wise domain correlation as links, was assessed using graph theory analyses, with focus on global network structure, network hubs and community structure.

Results: Normally developing children exhibited a cognitive network with well-defined modules, with verbal intelligence, reading and spelling skills occupying a central position in the developing network. Conversely, children with epilepsy demonstrated a less well-organized network with less clear separation between modules, and relative isolation of measures of attention and executive function.

Conclusion: Our findings demonstrate that childhood-onset epilepsy, even within its early course, is associated with an extensive disruption of cognitive neurodevelopmental organization. The approach used in this study may be useful to assess the effectiveness of future interventions aimed at mitigating the cognitive consequences of epilepsy.

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1. Introduction

Normal cognitive development is characterized by the age dependent harmonious improvement across multiple cognitive abilities. There is now considerable agreement that childhood onset epilepsy disrupts this systematic developmental process with adverse impact on executive function (Bell, Lin, Seidenberg, & Hermann, 2011; D'Agati, Cerminara, Casarelli, Pitzianti, & Curatolo, 2012; Seidenberg et al., 1986), academic skills (Berg et al., 2005; Seidenberg et al., 1986), linguistic abilities (Caplan et al., 2008, 2009) and emotional/behavioral status and quality of life (Berg et al., 2008; C. Camfield, Breau, & Camfield, 2003; P. Camfield & Camfield, 2003). However, cognitive domains do not operate in isolation and it remains undefined how epilepsy influences the interactions among different neuropsychological domains.

Recent cognitive training studies support the notion that the interrelationship among domains is crucial for academic success in school-aged children. First, fluid intelligence and problem solving skills can be improved when children engage in working memory exercises (Jaeggi, Buschkuehl, Jonides, & Shah, 2011). Second, training in executive function enhances other domains including language and mathematical skills (Goldin et al., 2014). Therefore, the understanding of the interrelationship among cognitive domains can provide crucial insight on how childhood-onset epilepsy interferes with the global structure of cognitive development. It may also aid in the identification of strategies for future targeted intervention.

In this study, we employed graph theory to investigate the impact of epilepsy on the global cognitive landscape. Graph theory is a mathematical method that has recently been applied to examine brain network structure in epilepsy, revealing global disruption in brain architecture (Bonilha et al., 2013, 2012; Vaessen et al., 2014, 2012). Large-scale structural morphometrical brain changes have been correlated with specific cognitive deficits in epilepsy (Alexander, Concha, Snyder, Beaulieu, & Gross, 2014; Bonilha, Tabesh, et al., 2014). However, to date, there has not been a comprehensive examination of neuropsychological measures, as a cognitive network per se, using graph theory. To our knowledge, this study is the first to use graph theory measures to investigate the cognitive network in children with epilepsy.

We investigated the global cognitive network in a large cohort of children with new-onset epilepsy and healthy controls by examining the inter-correlations of 23 neuropsychological measures. The neuropsychological tests were selected to provide a broad profile of cognitive function, indexing abilities in six discrete cognitive domains: intelligence, academic performance, language, memory, executive function, and psychomotor speed.

We hypothesized that epilepsy may disrupt age-related cognitive development, which is manifested in altered interactions among different cognitive domains. We therefore expected to find a different arrangement of the cognitive network in children with epilepsy compared with healthy controls.

2. Methods

2.1. Subjects

We assessed data from 127 children with epilepsy (mean age: 12.31 years; s.d. = 3.17; girls = 67, boys = 60) and 80 healthy controls (mean age: 12.69 years; s.d. = 3.17; girls = 39, boys = 41) (Table 1). There were no significant differences between the epilepsy and control families in terms of parent intelligence quotient (IQ; Wechsler Abbreviated Scale of Intelligence (WASI), controls: 109.7 ± 12.22, patients: 110.82 ± 15.41, $p = .80$), or parental employment status (full-time, part-time, unemployed; mother's, chi-square = 4.72, $p = .19$; father's, chi-square = 2.68, $p = .44$), indicating similar socioeconomic status between the groups. The educational background was also similar between patients and controls (patient mean grade = 6.2, control mean grade = 6.4, $p = .69$). About 53% of patients with epilepsy and 20% of controls received educational services in the past. All subjects included in this study were enrolled in regular schools.

Inclusion criteria for the patient group were: 1) diagnosis of epilepsy within the past 12 months, 2) no other neurological disorders, 3) normal neurological examinations, and 4) normal clinical imaging results. A board-certified pediatric neurologist (blinded to neuropsychological and interview data) confirmed that all patients had idiopathic epilepsies and provided independent confirmation of syndrome diagnosis. All patients were diagnosed according to the criteria defined by the International League Against Epilepsy (ILAE) (Blume et al., 2001; Engel, 2006). We excluded children with intellectual disability (IQ < 70), autism, and/or other neurological disorders. Specifics regarding the participant selection process have been described in detail in a previous publication (Hermann et al., 2006). In general, we tried to stay true to the concept of "epilepsy only" as defined broadly in the literature: normal neurological exams, average intelligence, and attendance at regular schools.

Healthy controls were age- and gender-comparable first-degree cousins of the epilepsy participants. All controls had no history of seizures, early initial precipitating injuries (e.g., febrile convulsions), other developmental or neurologic disease, or episodes of loss of consciousness. Research approval was obtained from the Institutional Review Board at the University of Wisconsin Medical School. Written informed consent was obtained for all subjects from legal guardians. Parents underwent a clinical interview and completed questionnaires to characterize gestation, delivery, neurodevelopment, and seizure history. All pertinent medical records were obtained after signed release of information was obtained from the parent. Parents were also interviewed through a structured questionnaire about their child's school progress and any specific educational services provided to address academic problems (AP). These services included the traditional individualized educational plan (IEP) as well as early childhood interventions (e.g., speech, physical or occupational therapy), mandatory summer school, grade retention, special tutoring services, and other related services. This interview was conducted blinded to cognitive and behavioral results.