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Cognitive phenotypes in childhood idiopathic epilepsies

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ABSTRACT

Objective: The objective of this study was to identify cognitive phenotypes in children with new-onset focal and generalized idiopathic epilepsies and determine their relationship with epilepsy syndrome, brain structure, neurodevelopmental history, and family characteristics.
Methods: One hundred thirty-eight children with new-onset epilepsy and 95 controls (age: 8–18) underwent neuropsychological, clinical, and quantitative MR evaluations. Control participants' neuropsychological data were subjected to confirmatory factor analysis and then resultant factor scores were applied to participants with epilepsy and subjected to latent class analysis. Identified cognitive phenotypes were examined in relation to epilepsy syndrome, quantitative neuroimaging, and familial and neurodevelopmental variables.
Results: Confirmatory factor analysis identified five cognitive factors (verbal, perceptual, speed, attention, executive), and latent class analysis identified three clusters of participants with epilepsy: 1) average and similar to controls, 2) mild impairment across multiple cognitive domains, and 3) impairment across all domains with severe attentional impairment, representing 44%, 44%, and 12% of the epilepsy sample, respectively. Cognitive phenotype membership was not associated with epilepsy syndrome but was associated with increasing abnormalities in brain structure, parental IQ, and features of early developmental history.
Significance: Cognitive phenotypes are present in idiopathic childhood epilepsies that are unassociated with traditional epilepsy syndromes but are associated with measures of brain structure, family history, and neurodevelopmental features.

1. Introduction

Cognitive impairment is a major comorbidity of the epilepsies [1]. A longstanding tradition in neuropsychological research has been to examine relationships between cognition and a range of factors that reflect core features of the epilepsies (epilepsy syndrome, EEG pathophysiology), medication treatment (type, dose, number), or clinical features that characterize epilepsy course and severity (age of onset, seizure frequency, duration of epilepsy) [2,3]. This work has led to a better understanding of the correlates of cognitive morbidity across the epilepsies with characterization of syndrome-specific *modal cognitive profiles* which inform the cognitive consequences associated with a particular epilepsy as well as the cognitive similarities and differences across discrete epilepsy syndromes (e.g., Nolan et al. [4], Jackson et al. [5]).

Considerably less work has been devoted to the identification of cognitive phenotypes that may exist within and across epilepsy syndromes. Here, the issue is whether individuals with similar cognitive profiles can be identified, profiles that may range from indistinguishable from controls to focal impairment in specific cognitive domains to generally impaired cognition. This approach may not only yield a different view of the cognitive consequences of epilepsy but may also encourage the search for biomarkers and the broader meaning of identified phenotypic membership. We took this approach previously with a cohort of patients with chronic temporal lobe epilepsy (TLE) whose modal cognitive profile was characterized by impaired performance across all cognitive domains compared with that of controls [6]. However, latent class analysis deconstructed this modal profile into three subgroups including a group with TLE whose neuropsychological status was comparable with that of controls, a group primarily with memory/executive function impairment, and a group with global impairment with especially severe impairments in executive function and speed [7]. These cognitive phenotypes were associated with unique quantitative MRI findings and prospective cognitive courses [7,8].

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In this investigation, we applied a similar research philosophy and approach to children with diverse idiopathic epilepsies—many of which fall under the rubric of so-called "benign epilepsies". The goal was to determine whether cognitive phenotypes could be identified and to ascertain their relationship to clinical epilepsy (epilepsy syndrome), neuroimaging (volumes of cortical and subcortical structures and cerebellum), family variables (parental IQ and education), and neurodevelopmental characteristics (pregnancy complications, birth weight). The hypotheses were as follows: a) discrete cognitive phenotypes exist and will range from unaffected and comparable with controls to varying degrees and types of cognitive compromise and b) phenotype membership will be independent of epilepsy syndrome but c) will be associated with brain structure and familial and neurodevelopmental characteristics.

2. Methods

2.1. Participants

Research participants consisted of 233 youths aged 8–18 years, including 138 with new-onset and recent-onset epilepsy and 95 healthy first-degree cousin controls (see Table 1). Children with epilepsy were recruited from pediatric neurology clinics at three Midwestern medical centers (University of Wisconsin—Madison, Marshfield Clinic, Dean Clinic) who met the following inclusion criteria: (i) diagnosis of epilepsy within the past 12 months, (ii) no other developmental disabilities (e.g., intellectual impairment, autism), (iii) no other neurological disorders, and (iv) normal clinical MRI. All children entered the study with active epilepsy diagnosed by their treating pediatric neurologists and confirmed by medical record review of the research study pediatric neurologist. We did not exclude children on the basis of psychiatric comorbidities (including ADHD) or learning disabilities. However, children with intellectual disability, autism, and/or other neurological disorders were excluded (see [9] for details). In general, we tried to stay true to the concept of "epilepsy only" as defined broadly in the literature: normal neurological exam, intelligence, and attendance at regular schools [10,11]. Each child's epilepsy syndrome (genetic generalized epilepsy [GGE] or focal epilepsy [FE]) was defined in a research consensus meeting that included a research pediatric neurologist who reviewed all available clinical data (e.g., seizure description and phenomenology, EEG, clinical imaging, neurodevelopmental history) while blinded to all research data.

Ninety-five first-degree cousins were used as controls; exclusion criteria were as follows: (i) history of initial precipitating insult (e.g., simple or complex febrile seizures, cerebral infections, perinatal stroke); (ii) any seizure or seizure-like episode; (iii) diagnosed neurological disease; (iv) loss of consciousness for greater than 5 min; and (v) history of a first-degree relative with epilepsy or febrile convulsions. We used cousin controls rather than siblings or other potential control groups for the following reasons: (i) first-degree cousins are more genetically distant from the participants with epilepsy and thus less predisposed than siblings to shared genetic factors that may contribute to anomalies in brain structure and cognition; (ii) a greater number of first-degree cousins are available than siblings in the target age range; and (iii) the family link was anticipated to facilitate participant recruitment and especially retention over time (which was our intent) compared with more general control populations (e.g., unrelated schoolmates). The study protocol was reviewed and approved by the institutional review board of the University of Wisconsin School of Medicine and Public Health. Families and children gave written informed consent and assent, respectively, on the day of the study.

Parents participated in a structured clinical interview and completed questionnaires to provide information about gestation, delivery, neurodevelopment, and seizure history. All pertinent medical records were obtained after signed release of information was obtained from the parent. Parents were questioned through structured interview about their child's school progress and, in particular, any specific educational services provided to address academic problems [8]. The parent interview was blinded to cognitive and behavioral results of the children's assessments. Finally, at baseline, the participating parent (primary caregiver) of each child was administered the two-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI) [12]. We recognize that it would have been preferable to test both parents, but practical limitations (e.g., parent employment, staff limitations) prevented this from occurring.

Children with intellectual disability were not included in the sample. As defined by DSM-V, intellectual disability involves impairments in general mental abilities that impact adaptive functioning in three domains or areas: a) the conceptual domain which includes skills in language, reading, writing, math, reasoning, knowledge, and memory; b) the social domain which refers to empathy, social judgment, interpersonal communication skills, ability to make and retain friendships, and similar capacities; and c) the practical domain which centers on self-management in areas such as personal care, job responsibilities, money management, recreation, and organizing school and work tasks. Intellectual disability does not have a specific age requirement, and an individual's symptoms must begin during the developmental period and are diagnosed based on the severity of deficits in adaptive functioning. Children with specific learning disabilities were not excluded. As defined by DSM-V, learning disability is characterized by persistent difficulties in reading, writing, arithmetic, or mathematical reasoning skills during formal years of schooling with current academic skills well below the average range of scores in culturally and linguistically appropriate tests of reading, writing, or mathematics, the individual's difficulties not better explained by developmental, neurological, sensory (vision or hearing), or motor disorders, and must significantly interfere with academic achievement, occupational performance, or activities of daily living.

Participants with epilepsy and controls did not differ in age, sex, or grade level (Table 1). Compared with controls, children with epilepsy had lower though still average full-scale IQ (FSIQ) and exhibited more academic problems (e.g., need for school or parent-based interventions to address academic performance problems).

Table 1
Study participant demographic and clinical characteristics.

Variable	Group with epilepsy (n = 138)	Controls (n = 95)
Age in years: M (SD)	12.5 (3.1)	12.5 (2.99)
Gender: Female: n (%)	70 (50.7%)	49 (51.6%)
Academic grade: M (SD)	6.5 (3.1)	6.3 (2.8)
Full scale IQ*: M (SD)	102.8 (13.5)	108.8 (10.9)
Academic services: n (%)*	66 (48.5%)	17 (18.7%)
Epilepsy syndrome: LRE[a]/IGE[b]	69/69	–
Epilepsy onset age in years: M (SD)	11.7 (3.2)	–
Antiepileptic drugs: 0/1/2+	20/110/8	–

* $p < 0.05$.
[a] LRE: Localization-related epilepsy.
[b] IGE: Idiopathic generalized epilepsy.

2.2. Neuropsychological assessment

All participants were administered a comprehensive test battery that included measures of intelligence, academic achievement, language, immediate and delayed verbal memory, executive function, and speeded fine motor dexterity (see Table 2, left column). Tests were selected for pertinence to the cognitive domains of interest and their applicability across the study's age range (8–18), ensuring identical test items/task demands, thereby providing a uniform test protocol. Fifteen of the 17 measurements were age-adjusted norm-referenced scores provided by the instruments, and 2 were raw scores (WISC-III Digit Symbol-Coding and Grooved Pegboard-dominant hand). The 2 raw scores were regressed on age, and the residuals were used in place of the raw scores. Z-scores were calculated using the healthy control mean and standard deviation for all 17 measurements.