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Executive functioning phenotypes in youth with epilepsy

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ABSTRACT

Objective: The objectives of this study were to identify executive functioning (EF) phenotypes in youth with epilepsy and to examine whether phenotypes differ on psychosocial and medical outcomes (i.e., absence/presence of seizures in the past three months), health-related quality of life (HRQOL), and emotional and behavioral functioning.
Methods: Youth 5–18 years with diagnosed epilepsy and caregivers completed a battery of questionnaires as part of a larger national validation of the Pediatric Quality of Life (PedsQL) Epilepsy Module. The primary measure of interest was the Behavior Rating Inventory of Executive Function—Parent Form. Medical chart reviews and demographic data were also collected. Latent class analysis was used to identify EF phenotypes. Chi-square and analyses of covariance (ANCOVA) were conducted to examine EF phenotype group differences on seizure outcomes, HRQOL, and behavioral and emotional functioning.
Results: Two-hundred and thirty-seven children with epilepsy (M_{age} = 11.2 years; 56% female; 60% White: Non-Hispanic; 55% experienced seizures in the past three months) and their caregivers participated. Four EF phenotypes were identified: Group 1 — No EF deficits (45% of sample), Group 2 — Global EF deficits (29% of sample), Group 3 — Behavioral Regulation + Working Memory deficits (8% of sample), and Group 4 — Metacognitive deficits (17% of sample). No significant EF phenotype group differences were found for seizure characteristics. The ANCOVAs indicated significant EF phenotype group differences on HRQOL (parent-reported Impact, Cognitive, Sleep, EF, and Mood/Behavior and child-reported Cognitive, Sleep, EF, and Mood/Behavior subscales; *ps* < .001) and emotional and behavioral functioning (Externalizing, Internalizing, and Behavioral Symptom Index; *ps* < .001), with the Global EF deficits (Group 2) and Behavioral Regulation + Working Memory deficits groups (Group 3) demonstrating the greatest level of impairment.
Conclusion: Phenotypic variability in EF is significantly related to patient-reported outcomes.
Interventions addressing EF deficits need to be individualized to a child's particular EF phenotype to achieve optimal outcomes.

1. Introduction

Executive functioning (EF), the skills needed to perform complex and goal-directed activities, including problem-solving, organizing and planning, self-regulation, initiating, monitoring, and working memory [1], can be compromised in youth with epilepsy. In fact, up to 50% of youth with epilepsy demonstrate executive dysfunction [2–8]. Unfortunately, executive dysfunction can persist or worsen over time [9–12] if left untreated and lead to academic [7,13] and social difficulties [14], as well as poor health-related quality of life (HRQOL) [15,16]. Youth with epilepsy can exhibit global deficits or deficits in particular areas, including inhibition, emotional control, initiation, planning/organizing, and monitoring. Additionally, youth with epilepsy appear to have significant deficits in the area of working memory [8,17,18]. While several studies have identified EF deficits in youth with epilepsy, none have examined whether particular EF phenotypes exist.

Identifying EF phenotypes in epilepsy could be beneficial for a variety of reasons. Examining the antecedents and consequences of such phenotypes could lead to the development of tailored EF interventions targeted to the subgroups for whom there would be the greatest benefit. Further, identification of EF phenotypes may also indicate the need to refine and modify existing EF interventions in pediatric epilepsy [19–22] to target a

Abbreviations: EF, executive functioning; HRQOL, health-related quality of life; ANCOVA, analyses of covariance; LCA, latent class analysis; n.s., nonsignificant; PedsQL, Pediatric Quality of Life; BASC, Behavior Assessment Schedule for Children.

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particular EF phenotype. Finally, to discover additional conferred risk, description of EF phenotypes could provide a new classification system to evaluate whether EF phenotypic variability predicts differences in key outcome variables, including seizures, HRQOL, and behavioral and emotional functioning.

The aims of the current study were first, to identify EF phenotypes in youth with epilepsy and second, to evaluate EF phenotype group differences on medical and psychosocial outcomes (i.e., absence/presence of seizures in the past three months, HRQOL, and emotional and behavioral functioning). Based on the existing literature and our own pilot work, we hypothesized at least 4 EF phenotypes for youth with epilepsy: 1) global deficits across all EF domains, 2) no EF deficits, 3) behavioral regulation deficits (e.g., Inhibit, Shift, and Emotional Control), and 4) metacognitive deficits (Initiation, Working Memory, Plan/Organize, Organization of Materials, and Monitoring). For the second aim of the study, we hypothesized that the global EF deficit phenotype would exhibit more seizures, lower HRQOL, and greater emotional and behavioral problems.

2. Methods

2.1. Participants

Data for this cross-sectional investigation are part of a larger national validation study [23]. A total of 237 youth with epilepsy between the ages of 5–18 years and their caregivers were included in the current study. All participants were recruited from three different tertiary-care pediatric medical centers, including Cincinnati Children's Hospital Medical Center, Children's Hospital of Orange County, and Medical University of South Carolina. Inclusion criteria included: 1) a diagnosis of epilepsy in children between 5 and 18 years and 2) the ability to read English. Children with other chronic medical illness (e.g., diabetes) requiring daily medications were excluded from the study.

2.2. Procedures

Eligible participants were identified by a trained research assistant and provided with an overview of the study before they were invited to participate. All questions about the study were thoroughly answered prior to enrollment. Parental consent and permission, child assent (11 years and older), and **Health Insurance Portability and Accountability Act** release were obtained from all pertinent participants. Data collection was conducted in various settings, including outpatient neurology clinics, inpatient settings, and electroencephalography (EEG) monitoring units among others. Developmentally appropriate paper and pencil measures were completed by youth and their caregiver based on the patient's age. Trained research staff completed a chart review to extract relevant medical information. All participants received a gift card as compensation for the time. All study procedures received approval by the Institutional Review Board of participating institutions.

2.3. Measures

2.3.1. Sociodemographic and medical information

A brief background questionnaire was completed by caregivers to provide information on their child's age, sex, race, and caregiver employment history and marital status. Information about medical history including epilepsy type, epilepsy duration, seizure control, number of antiepileptic drugs (AEDs), and treatment regimen were collected via retrospective medical chart review.

2.3.2. Executive functioning

The Behavior Rating Inventory of Executive Function—Parent Form (BRIEF-PF) [24] is a reliable and validated 86-item caregiver-proxy report measure of children's EF. It has eight subscales including Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. These clinical subscales create two broader indexes, including the Behavioral Regulation Index and the Metacognition Index, as well as an overall score, the Global Executive Composite. T-scores are age- and gender-matched, with higher T-scores indicating greater deficits in EF abilities. T-scores ≥65 are considered clinically elevated, and T-scores ≥60 and <65 indicate at-risk elevations. This measure has strong internal consistency reliability [24]. For the purpose of the latent class analysis (LCA), we classified participants on the 8 subscales as follows: scores <60 were classified as no/low deficits (=0), and scores ≥60 were considered elevated/at risk (=1). We included the at-risk criteria as a lower benchmark to ensure that we identify patients who may need future interventions or services.

2.3.3. Health-related quality of life

The Pediatric Quality of Life (PedsQL) Epilepsy Module [23] is a 29-item epilepsy-specific HRQOL measure for youth with epilepsy between the ages of 2 and 18 years with excellent reliability and validity. A total of five different subscales comprise this measure, including Cognitive, Impact, Sleep, Executive Functioning, and Mood/Behavior. Parallel and developmentally appropriate forms exist for both youth and their caregiver, who record their answers using a 5-point Likert scale ranging from 0 = never a problem to 4 = almost always a problem. Scores range from 0 to 100, with higher scores representing better HRQOL. Internal consistency for the subscales ranges from 0.70 to 0.94 [23].

2.3.4. Behavioral and psychosocial Functioning

The Behavior Assessment Schedule for Children—2nd edition (BASC-2) [25] is a reliable and widely used measure of behavioral and emotional difficulties in children and adolescents that includes nine different clinical subscales (e.g., hyperactivity, aggression, depression, somatization, attention problems). These subscales form three different composite scores: Externalizing Symptoms, Internalizing Symptoms, and Behavioral Symptom Index. Individual raw scores for each of the subscales are calculated and compared to age-matched normative data to obtain standardized T-scores, with higher T-scores indicating greater difficulties. T-scores ≥65 and <70 are considered in the at-risk range and indicate symptomatology that may warrant clinical attention and evaluation. T-scores ≥70 are considered in the clinically significant range and indicate high levels of maladjustment.

2.4. Data analytic approach

Descriptive statistics including mean, standard deviation, and ranges were used for all study variables to characterize the sample. The LCA is a special case of mixture modeling [26] used to classify individuals into homogenous subgroups, where individual differences in observed response patterns on categorical variables are explained by differences in latent class membership [27,28]; LCA is well-suited to many health applications, for example, to identify disease subtypes or diagnostic subcategories. In the current paper, we sought to classify participants into different phenotypes based on their EF profile. Mplus version 8 was used for the LCA [29]. We tested models estimating 3 classes, 4 classes (as hypothesized), and 5 classes. To determine the optimal number of classes, we considered several criteria: 1) interpretability of the classes, 2) high entropy (values near 1.0), 3) no less than 1% of total count in a class, 4) high posterior probabilities (near 1.0), and 5) good model fit, evaluated as the smallest Bayesian information criterion, a significant Lo-Mental-Rubin Likelihood Ratio Test, and a significant parametric bootstrapped likelihood ratio test [30]. We then used χ^2 tests of independence to evaluate differences between the EF groups identified by the LCA on categorical seizure characteristic variables (e.g., type, chronicity) and ANCOVAs with Tukey's posthoc comparisons to examine differences among the EF phenotype groups on HRQOL scores and emotional/behavioral outcomes of interest. For these analyses, Stata version 14 was employed.

3. Results

3.1. Description of sample

Participants included 237 youth with epilepsy between 5 and 18 years of age. Thirty-eight percent of the sample was from Cincinnati Children's Hospital Medical Center, 31% from Children's Hospital of Orange County, and 31% from the Medical University of South Carolina. Participant demographic and medical data are provided in Table 1.

3.2. Identification of EF phenotypes

Latent class analysis revealed that 4 distinct EF phenotypes best explained the pattern of responses on the BRIEF subscales for youth with epilepsy. The first phenotype (Group 1 — No EF deficits), accounting for 45% of the sample, exhibited no significant elevations on any of the BRIEF subscales. The second phenotype (Group 2 — Global EF deficits), accounting for 29% of the sample, exhibited clinical elevations in all EF domains. The third phenotype (Group 3 — Behavioral Regulation + Working Memory deficits), which represented 8% of the sample, exhibited elevations in Inhibition, Shifting, Emotional Control, as well as Working Memory. The final phenotype (Group 4 — Metacognitive deficits) represented the remaining 17% of the sample with clinical elevations in some of the Metacognitive subscales of the BRIEF (i.e., Initiation, Working Memory, and Plan/Organize). The pattern of EF deficits can be seen in Fig. 1.

3.3. Differences in outcome variables by EF phenotypes

3.3.1. Seizures

χ^2 tests suggest no significant differences among the EF phenotype group for the absence (=0) or presence (=1) of seizures in the prior three months (No seizures: 50%—Group 1; 37%—Group 2; 30%—Group 3; 45%—Group 4; χ^2 (3, n = 234) = 4.64, p = n.s.). Similarly, no significant differences were found by epilepsy type (Localization-related epilepsy: 52%—Group 1; 41%—Group 2; 60%—Group 3; 48%—Group 4; χ^2 (6, n = 237) = 4.30, p = n.s.), etiology (Idiopathic epilepsy: 75%—Group 1; 66%—Group 2; 53%—Group 3; 65%—Group 4; χ^2 (3, n = 189) = 4.4, p = n.s.), or chronicity (new onset: 42%—Group 1; 22%—Group 2; 35%—Group 3; 54%—Group 4; χ^2 (3, n = 237) = 7.45, p = n.s.) based on EF phenotype group.

Table 1
Demographic data (n = 237).

	N (%) or M ± SD
Age	11.2 ± 3.9 years
Sex	
• Females	132 (56%)
• Males	105 (44%)
Race/Ethnicity	
• White: Non-Hispanic	143 (60%)
• White: Hispanic	30 (13%)
• Black: Non-Hispanic	38 (16%)
• Black: Hispanic	1 (0.4%)
• Asian/Pacific Islander	12 (5%)
• Bi/multiracial or other	13 (6%)
Seizures in the past three months*	
• Yes	131 (55%)
• No	103 (44%)
Seizure type	
• Localization-related	115 (49%)
• Generalized	88 (37%)
• Unclassified	34 (14%)
Seizure etiology*	
• Idiopathic	129 (54%)
• Symptomatic	44 (19%)
• Cryptogenic	16 (7%)
Years since diagnosis	4.4 ± 3.8 years; range: 0–18 years
• New onset (≤2 years)	81 (34%)
• Chronic (>2 years)	156 (66%)
Number of AEDs*	1.28 ± 0.62 AEDs; range: 0–4
• Monotherapy	176 (74%)
• Polytherapy	54 (23%)
Participating caregiver	
• Mothers	206 (87%)
• Fathers	25 (11.5%)
• Other	6 (2.5%)

Note: *Data were missing for these variables: n = 3 for seizure control, n = 48 for etiology; n = 7 for Mono- versus Polytherapy. Notably, the old ILAE classification was used for seizure etiology as this study was conducted prior to implementation of the new 2017 ILAE guidelines.

3.3.2. HRQOL

Analyses of covariance were conducted with each PedsQL Epilepsy Module subscale by respondent (parent, child) as the outcome variable. Based on the larger HRQOL literature, covariates included child age, seizure control, years since diagnosis, and total AED side effects. After controlling for these variables, the ANCOVAs indicated significant EF phenotype group differences on parent-reported Impact [F(7, 215) = 30.5, p < .0001], Cognitive [F(7, 215) = 30.6, p < .0001], Sleep [F(7, 215) = 10.9, p < .0001], EF [F(7, 215) = 40.7, p < .0001], and Mood/Behavior [F(7, 215) = 13.8, p < .0001] subscales. Similarly, group differences were noted on child-reported Cognitive [F(7, 169) = 15.4, p < .0001], Sleep [F(7, 167) = 4.8, p < .0001], EF [F(7, 169) = 15.2, p < .0001], and Mood/Behavior [F(7, 167) = 5.1, p < .0001] subscales (See Fig. 2). Pairwise comparisons are represented in Table 2.

3.3.3. Emotional and behavioral functioning

Similarly, ANCOVAs were conducted with BASC subscales as outcome measures (Externalizing, Internalizing, and Behavioral Symptom Index) with the same covariates as listed above. Significant EF phenotype group differences were found for all three BASC subscales (Externalizing: [F(3, 207) = 35.9, p < .001]; Internalizing: [F(3, 207) = 15.1, p < .001]; Behavioral Symptom Index: [F(3, 167) = 69.8, p < .001]; See Fig. 3). Pairwise comparisons are represented in Table 2.

4. Discussion

This is the first study to identify four unique EF phenotypes in youth with epilepsy. Consistent with the broader literature, approximately 50% of our sample exhibited some degree of EF impairment [16,31], with the other half demonstrating typical EF skills (Group 1). About 30% of participants exhibited global deficits across all subscales of the BRIEF (Group 2), indicating pervasive problems in several areas of EF. A smaller subset of patients (8%) demonstrated difficulties in inhibition, shifting, emotional control, and working memory, suggesting broad behavioral regulation, as well as working memory deficits (Group 3). The final phenotype represented 17% of the sample and exhibited deficits in metacognitive domains, including initiation, planning/organization, and working memory (Group 4). Working memory was a significant problem across all phenotypes (i.e., Groups 2–4), which is consistent with the larger literature showing that working memory problems are frequently identified in youth with epilepsy [8] and a key aspect of their cognitive functioning difficulties. While working memory difficulties must be addressed as part of EF interventions, exclusive focus on working memory is unlikely to satisfactorily address broader EF difficulties in youth with epilepsy. Consideration of these working memory difficulties is also important in other non-EF focused psychosocial interventions, which require cognitive abilities for skill development (e.g., cognitive-behavioral interventions).

Surprisingly, EF phenotypes did not differ by seizure type, control, epilepsy duration, or etiology. Past literature on EF deficits and seizure-related variables has been mixed. Some studies have demonstrated that children with generalized epilepsy exhibit more EF deficits than children with localization-related epilepsy [32,33], while others found no differences by seizure type [34]. Similarly, there is equivocal data regarding seizure control and EF [6,31,35]. Unlike other studies, we found no significant association between EF phenotypes and seizure etiology [36]

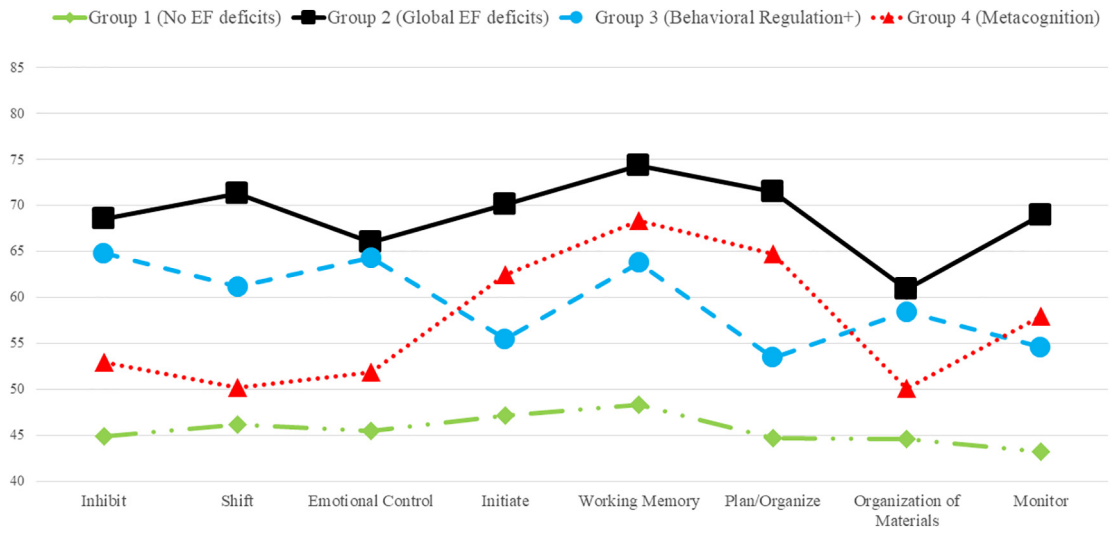

Fig. 1. Executive functioning phenotypes in youth with epilepsy.

or epilepsy duration [37,38]. Overall, our data suggest that seizure characteristics do not appear to confer additional risk for EF deficits nor do they serve as antecedents of specific EF phenotypes. More importantly, our data highlights the importance of neurocognitive screening and the need for clinical interventions that target EF vulnerabilities regardless of seizure semiology and clinical outcomes.

Consistent with our hypothesis, youth with global EF deficits demonstrated lower levels of HRQOL compared with youth without deficits and youth with metacognitive deficits. Specifically, aspects of HRQOL that appeared most negatively related to EF impairment in this group included Mood/Behavior, EF, and the impact of epilepsy on daily life. The lack of significant differences between the global EF deficits phenotype and the behavioral regulation + Working Memory deficits phenotype (i.e., Groups 2–3) suggests that youth with broad executive dysfunction or behavioral regulation difficulties are at particularly high risk for poor HRQOL. Lastly, youth with metacognitive deficits demonstrated worse HRQOL in only 2 domains (e.g., cognitive and EF) compared with youth with no EF deficits. These results suggest that the influence of metacognitive difficulties on HRQOL may be limited to cognitive aspects of HRQOL only. In general, our results are consistent with prior studies indicating that EF deficits are strongly associated with and strongly predict HRQOL [16].

In contrast, phenotypic variability was not as strongly related to child-reported outcomes. While the HRQOL domain of EF was consistently lower across phenotypes 2–4 compared to youth with no EF deficits (Group 1), only youth in the global EF deficit phenotype perceived the pervasive impact that EF difficulties have on their HRQOL. It is possible that children in this age range do not have the cognitive insight required to recognize their own EF deficits. It is possible that this lack of awareness extends beyond EF skills and affects more general aspects of functioning and HRQOL. Taken together, our results on EF phenotypes and their relation to HRQOL underscore the importance of considering

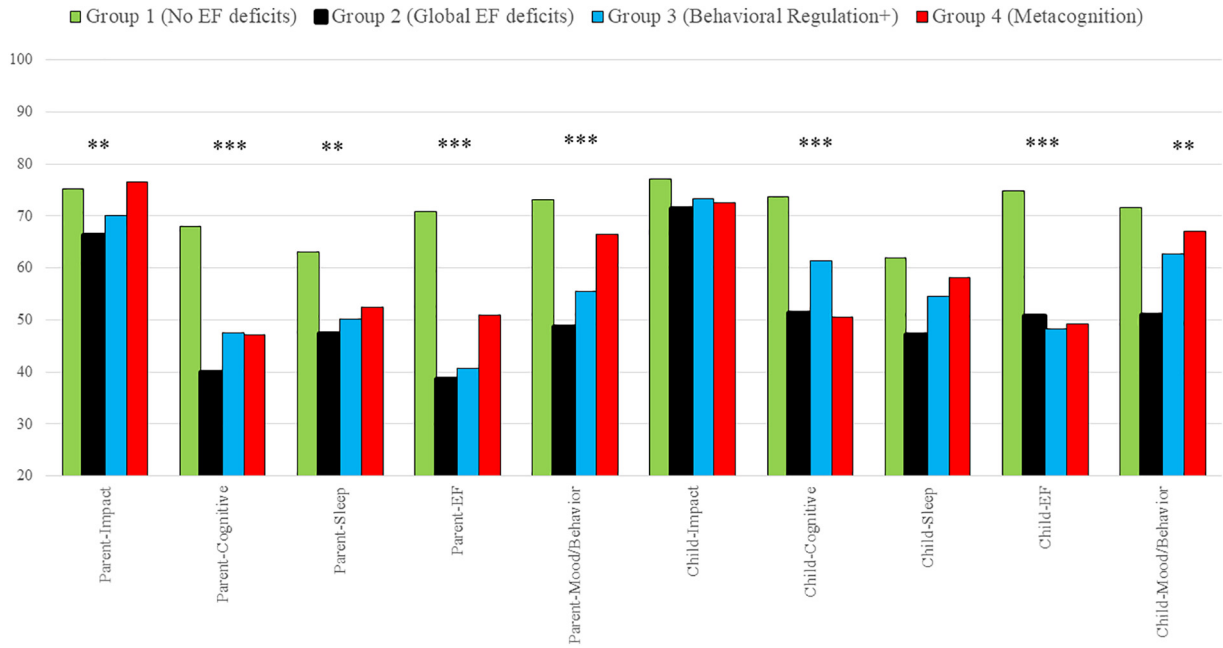

Fig. 2. HRQOL differences based on EF phenotypes in youth with epilepsy. Significance is represented as follows: $^{**}p < .01$, $^{***}p < .001$.

Table 2
Significant pairwise comparisons by EF Phenotype on PedsQL—Epilepsy modUle and BASC subscales.

Measure	EF phenotype			
	Group 1 (No deficits)	Group 2 (Global deficits)	Group 3 (Behavioral Regulation + Working Memory deficits)	Group 4 (Metacognitive deficits)
PedsQL Epilepsy Module; lower = worse				
Parent				
• Impact		< Group 1 and 4*		
• Cognitive		< Group 1**	< Group 1***	< Group 1***
• Sleep		< Group 1***		
• EF		< Group 1*** and 4*	< Group 1***	< Group 1***
• Mood/Behavior		< Group 1 and 4***	< Group 1**	
Child				
• Cognitive		< Group 1*		
• Sleep		< Group 1***		< Group 1***
• EF		< Group 1***	< Group 1***	< Group 1***
• Mood/Behavior		< Group 1***		
Behavior Assessment Schedule for Children (BASC); higher = worse				
• Externalizing		> Group 1*** and Group 4***	> Group 1*** and Group 4***	> Group 1*
• Internalizing		> Group 1*** and 3* and 4***		
• Behavioral Symptom Index		> Group 1*** and 3** and 4***	> Group 1*** and Group 4**	> Group 1***

* $p < .05$.
** $p < .01$.
*** $p < .001$.

the role that EF deficits may have in conferring additional risk to this vulnerable population at already heightened risk for compromised HRQOL.

As expected, youth with global EF deficits demonstrated worse psychosocial functioning across all domains compared to other phenotypes. Specifically, having compromised global EF is related to more internalizing and externalizing problems, as well as more behavioral symptoms. These robust differences indicate that youth with global EF deficits are at highest risk for poor psychosocial functioning across behavioral and emotional domains. Youth in the behavioral regulation + working memory deficits phenotype also demonstrated worse externalizing problems and behavioral symptoms compared with youth without deficits and youth with metacognitive deficits. These findings support the widely accepted notion that behavioral regulation problems confer additional risk for behavioral and emotional functioning [3]. The prevalence of EF deficits is also significantly higher in children with externalizing, internalizing, and neuropsychiatric disorders compared with those without such disorders [39]. In general, our results add to the body of empirical data supporting the role of EF deficits as an independent risk factor for psychosocial comorbidities in youth with epilepsy.

Overall, these data highlight the need to tailor, refine, and modify existing neurocognitive interventions to address EF deficits based on the phenotype that best characterizes youth with epilepsy. Existing interventions appear to either target global EF deficits or narrowly focus on only one aspect of EF, which may miss the mark for a majority of youth with epilepsy who demonstrate EF deficits. For example, Epilepsy

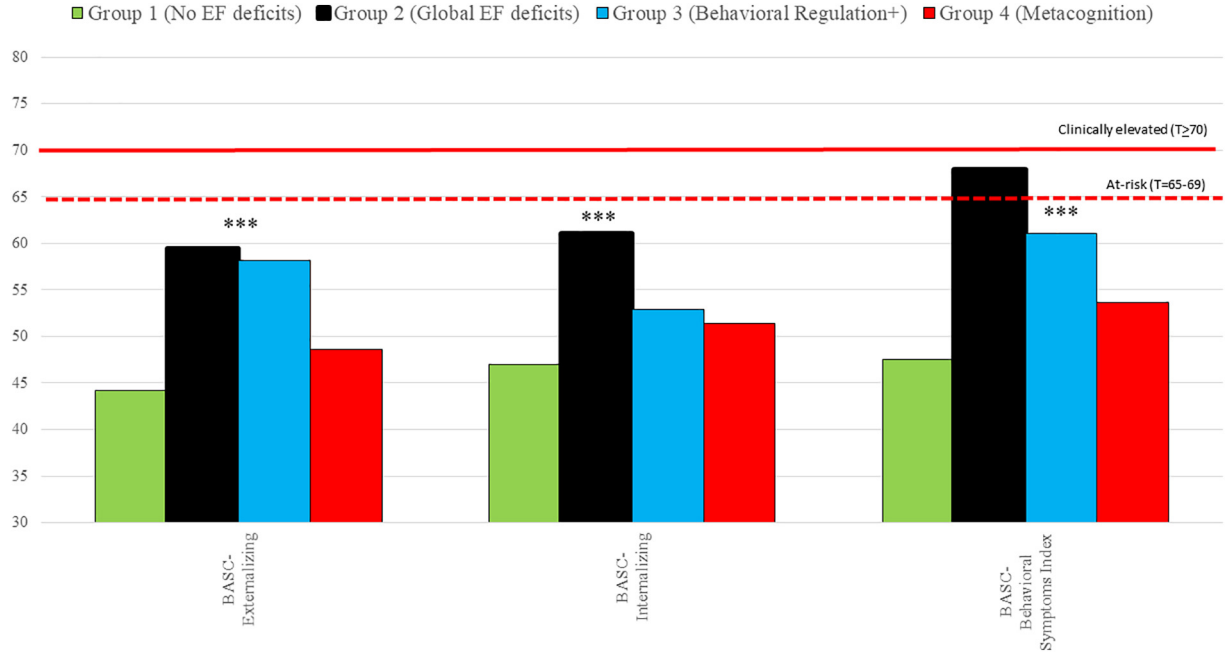

Fig. 3. Emotional/Behavioral functioning differences based on EF phenotypes in youth with epilepsy. Significance is represented as follows: ***$p < .001$.

Journey [20] addresses global EF deficits by providing 10 different modules that target all EF domains in youth with epilepsy and EF deficits. While this approach may be well-suited for 30% of youth, it is likely a broader, more intensive, and less targeted intervention than may be necessary for youth with metacognitive or behavioral regulation + working memory deficit phenotypes. In contrast, CogMed primarily focuses on working memory, which is a global deficit experienced by all youth with epilepsy who have any type of executive dysfunction. While this intervention approach can certainly be beneficial to address deficits specific to working memory, it is unlikely to effectively aid the 50% of youth who have multiple EF deficit areas (e.g., Groups 2–4). One important area for future research is the development of individualized intervention approaches that target specific EF deficits based on a patient's phenotypic characteristics. For example, use of Epilepsy Journey could be tailored to include only modules that focus on the needs of a particular patient. An important first step in providing interventions to half of the youth with epilepsy, who exhibit EF deficits, is the implementation of routine EF screening during epilepsy clinic visits, an aspect of comprehensive psychosocial care that is often neglected. Studies have demonstrated that screening is critical to address psychosocial issues that are often present prior to or around diagnosis [40,41]. Furthermore, screening for EF deficits may shed light on barriers specific to epilepsy management, including AED nonadherence caused by deficits in working, organization or planning.

While our study certainly adds to the growing body of literature on EF in youth with epilepsy, it is not without limitations. For example, only the parent-reported BRIEF was used to determine EF phenotypes, which can be influenced by the parent's own functioning and social desirability. Use of multimethod reporting to determine EF phenotypes may have gleaned different results. However, it is notable that youth tend to be poor reporters of their own EF [18,42]. Other measures of EF could have been used to determine EF phenotypes, including task-based neuropsychological measures, brain imaging, or teacher report. Our rationale for using a clinical tool, such as the parent BRIEF, was based on this tool's clinical feasibility compared to laboratory-based measures or teacher report, as well as its high ecological validity. An important future direction is to validate these EF phenotypes in the context of standard neurological assessment of EF skills and cognitive performance. Finally, our data are cross-sectional in nature, and thus, results cannot be interpreted as causal. Further, there is potential for selection bias since all participants were enrolled in a larger study of HRQOL. Future studies are needed to examine the temporal relationships between EF phenotypes and outcomes, and future replication of the phenotypes identified in the current study is critical given the somewhat small samples for LCA.

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Declarations of interest

None.

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