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RESEARCH ARTICLE

Long-term characterization of behavior phenotypes in children with seizures: Analytic approach matters

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Abstract

Objective: Behavioral problems in children with new onset epilepsies have been well established in the literature. More recently, the literature indicates the presence of unique behavioral patterns or phenotypes in youth with epilepsy that vary significantly in vulnerability and resilience to behavioral problems. This study contrasts the interpretation of behavioral risk as inferred from cross-sectional versus latent group analytic perspectives, as well as the presence, consistency, stability, and progression of behavioral phenotypes in youth with new onset epilepsy and sibling controls over 3 years.

Methods: Three hundred twelve participants (6–16 years old) were recruited within 6 weeks of their first recognized seizure along with 223 unaffected siblings. Each child's behavior was recorded by parents and teachers frequently over 36 months using the Child Behavior Checklist (CBCL), and each child completed self-report measures of depression symptoms over 36 months. Measures were evaluated cross-sectionally and longitudinally to identify clusters with prototypical behavioral trajectories.

Results: Cross-sectional analyses exhibited a pattern of generalized and undifferentiated behavioral problems compared to sibling controls at baseline and prospectively. In contrast, latent trajectory modeling identified three distinct behavior phenotype clusters across all raters (parents, teachers, and youth) over baseline and longitudinal assessments. CBCL Cluster 1 (~30% of youth with epilepsy) exhibited behavior similar to/better than controls, Cluster 2 (~50%) exhibited moderate behavior issues, and Cluster 3 (~20%) exhibited the most pronounced/problematic behavior, falling into Achenbach's clinically relevant behavior range. Behavior within clusters remained stable and consistent. Teachers' and children's behavior assessments corresponded to these cluster groupings consistently over 36 months. Predictors of cluster membership include seizure syndrome type and social determinants of health.

Significance: This study demonstrates the varying public health perspectives of behavioral risk in youth with epilepsy that result as a function of analytic approach

as well as the presence of distinct latent behavioral trajectory phenotypes over time in youth with new onset epilepsy.

KEYWORDS
behavior, epilepsy, latent trajectory phenotypes, pediatric, predictors

1 | INTRODUCTION

The increased risk of behavioral problems and psychiatric complications among youth with epilepsy has been documented in population- and community-based investigations as well as innumerable clinical studies.[1–15] The elevated rate of both internalizing and externalizing behavioral problems of various types has been reported in youth with established focal and idiopathic generalized epilepsies.[4,16–19] These complications can be observed not only in youth with established and chronic epilepsies but also among children with new onset and drug naïve as well as recently diagnosed and medicated epilepsy, with further evidence that these issues can antedate recognition of the first seizure and/or medical treatment.[7,16,20,21]

This accumulating evidence has proven critical in depicting the range of neurobehavioral problems that may be associated with the epilepsies and adds to the characterization of burden of the disease for youth, adults, and their families. However, this literature tends to paint an arguably dysphoric public health picture of epilepsy, as do similar investigations that present overall or average profiles of cognition, quality of life, stress, and other issues.[16,22–24] However, heterogeneity has become a key concept in epilepsy, including the neurobehavioral comorbidities—heterogeneity that is evident among individuals within discrete epilepsy syndromes. This has been demonstrated most convincingly in regard to the cognitive status of children and adults with temporal lobe epilepsy.[25–30] These investigations have applied unsupervised machine learning techniques, such as cluster analysis, wherein a more personalized picture of the cognitive comorbidities of epilepsy have resulted.

In short, these studies have shown that sizable subsets of participants with epilepsy are indistinguishable from healthy controls in regard to their cognitive profiles, with a modest subset of patients exhibiting very significant complications. It is this latter group(s) that colors the mean or average cognitive profile of the total group. This approach to the issue of cognitive comorbidities in epilepsy provides an alternative public health picture of the consequences of epilepsy.[27] Less work in this direction has been devoted to the behavioral complications of epilepsy,[31–34] but it again has been predominated by work in temporal lobe epilepsy, where the same trends have been observed.[32,33,35]

Key points

- Over 36 months, unique behavioral phenotypic patterns emerge among youth with epilepsy, indicating varying vulnerability and resilience to behavioral problems.
- Three distinct clusters were identified and remained stable over 36 months, with parent, teacher, and child (self) reports aligning consistently.
- Predictors of cluster membership include seizure syndrome type and social determinants of health.
- Employing this analytic approach to assess behavior in children with new onset epilepsy has significant implications for identifying high-risk groups.

Here, we directly compare and contrast these two methodological approaches, the first examining overall or mean neurobehavioral status in epilepsy versus control groups using a cross-sectional group comparison approach and the second focused on identifying latent behavioral groups. These tasks are undertaken using a unique data set involving children with new onset seizures who were followed and assessed longitudinally over a 36-month period. Furthermore, behavioral ratings were provided by parents, teachers, and the children themselves to characterize the consistency of ratings and behavioral trends over time. For behavioral phenotyping, the methodological approach of latent trajectory modeling was used to characterize progressive patterns of behavioral status and the nature of diverse phenotype trajectories over a 36-month period. Understanding the degree to which these clusters may remain stable, recover, or worsen over time is a clinically meaningful task and may inform the optimal timing of behavioral intervention.

2 | MATERIALS AND METHODS

2.1 | Participants

Study participants included children with newly diagnosed seizures, their siblings as controls, and their primary caregivers in each household.[6,19] The core investigation was conducted at Indiana University and Cincinnati Children's Hospital at the University of Cincinnati. Children were recruited through electroencephalographic (EEG) laboratories, emergency departments, and pediatric neurologists in two large children's hospitals (Indianapolis and Cincinnati) and from practices of private pediatric neurologists in Indianapolis. When children met the criteria, refusals were <10%. All children in this sample met the International League Against Epilepsy criteria for epilepsy.[36]

A total of 312 children with epilepsy were recruited within 6 weeks of their first recognized seizure (mean = 35 days). The sibling control sample was a comparison group of 223 healthy siblings of the children with epilepsy. Only one sibling was recruited per family. For each child in the seizure group, we attempted to recruit a healthy sibling aged 2–18 years (preferring aged 6+ years for cognitive testing). If there were multiple siblings, the sibling that was closest in age to the child with the seizure was included in the study. When the sibling was too young (<6 years), had another chronic condition (e.g., asthma), or was too old (>18 years), he/she was not included in the study. There was minimal difficulty recruiting siblings when siblings were available.

Exclusion criteria for both children with epilepsy and siblings were a comorbid chronic physical disorder, intellectual disability (based on either clinic records or parent report), or seizures precipitated by an acute event (e.g., intracranial infection, metabolic derangement, recent head injury). Children who had had two or more febrile but no afebrile seizures or who were placed on daily antiseizure medication (ASM) after a febrile seizure were also excluded. Siblings did not have epilepsy and were not on medication that could affect mental status. Parental informed consent and child assent were obtained prior to data collection. The study was approved by the institutional review boards at Indiana University and Cincinnati Children's Hospital Medical Center.

2.2 | Measures

2.2.1 | Child Behavior Checklist: Completed by parent

The Child Behavior Checklist (CBCL) was completed by a caregiver/parent to measure each child's behavior problems during the past 6 months. The test was administered at baseline (B), 9 months from B (M09), 18 months from B (M18), 27 months from B (M27), and finally at 36 months from B (M36). Details of this instrument are provided elsewhere.[37] Briefly, the CBCL has 118 items describing behaviors that are rated using 3-point scales of 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true). For further information in regard to the validity and reliability of the CBCL, see https://aseba.org/reliability-validity-information/. Summary scores from the CBCL were used in this study—specifically, *T*-scores for total internalizing problems and total externalizing problems, all normed for age and sex. These two summary scores were used for the phenotyping analyses discussed below. For the children with seizures, parents were specifically instructed to exclude any behaviors that might have represented actual seizure activity or any behaviors that occurred immediately prior to, or after, a seizure.

2.2.2 | Teacher Report Form: Completed by teacher

The Teacher Report Form (TRF) was completed by each child's teacher based on the child's current behavior at B, M18, and M36 following the child's first seizure to assess baseline neuropsychological functioning and temperament and changes over time. Details of this instrument are also provided elsewhere.[38] The TRF was completed by one teacher only (primary teacher) per time period, who usually was a different primary teacher at each time period.

Both the CBCL and TRF have been used extensively in children with epilepsy and have been found to be reliable and valid in the pediatric epilepsy population.[5,17,19,31,39] Many past studies have relied primarily upon parents to rate their child's behavior problems. Making use of both the CBCL and TRF provides insight into informant consistency and lends credence to the reliability of the behavior problems of the child as seen in multiple different settings (school and home primarily).

2.2.3 | Children's Depression Inventory 2: Completed by child

The Children's Depression Inventory (CDI) is a self-report questionnaire for children and adolescents designed to identify symptoms of depression at each developmental age.[40] The children with seizures completed this measure at B, M18, and M36.

All testing was administered by psychometrists who were trained, observed, and certified on the test battery

and its scoring by a pediatric neuropsychologist. Seizure characteristics and sociodemographic data (e.g., caregiver's highest education level, caregiver's household income, child's age, child's sex, child's education) were also collected via structured interviews by trained research coordinators as well as psychometrists. Clinical seizure variables including seizure classification, results of EEG, and imaging were collected from the electronic medical record and were coded independently by study physicians blinded to the cognitive and behavioral data. The sociodemographic data, collected at the B visit only, included highest level of maternal education, household income, parental marital status, and self-identified race.

Data were first collected within 6 weeks of the first recognized seizure (B) from both children with newly diagnosed epilepsy and siblings. For children with epilepsy, the attrition rate over the first 18 months of the investigation was 10% and another 5% over the second 18 months. All data were included in the analysis regardless of the number of visits completed.

2.3 | Statistical analysis

2.3.1 | Cross-sectional group comparisons

Statistical Package for Social Sciences software (version 29.0, IBM) was used to conduct one-way analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA) tests to compare behavior and risk factors (clinical epilepsy characteristics) in children with new onset seizures with sibling controls at each timepoint. When the F statistic was significant (level of significance $\alpha = .05$), Tukey honest significant post hoc comparisons were conducted among the groups.

2.3.2 | Longitudinal group comparisons: Latent group trajectory modeling

To identify distinct patterns of behavioral performance change over a 36-month period, an analysis of latent group-based trajectory modeling (LGBM) of longitudinal data was carried out by SAS *Proc Traj*.[41] LGBM data analyses were all conducted using SAS version 9.4. LGBM captures the heterogeneity of subgroups among a specific population by simultaneously estimating several trajectories as opposed to fitting an overall population mean. Internalizing, externalizing, and total behavior summary T-scores for each CBCL visit (B, M09, M18, M27, and M36) and each TRF visit (B, M18, and M36), along with Depression symptom summary scores for each CDI visit (B, M18, and M36) were utilized for this modeling trajectory analysis. To find the optimal number of trajectories, Bayesian information criterion was used to compare the fitness of models between trajectories with a differing number of groups or between different shapes of a trajectory. At baseline, we ensured a minimum of 10% for each of the trajectory groups. Multivariate logistic regression was utilized to compare behavioral phenotype groups and to identify the significant predictors (risk factors) of behavioral phenotype class membership. The level of significance $\alpha = .05$ was used for the multivariate logistic regression.

Risk factors assessed for both cross-sectional and longitudinal analyses included clinical seizure characteristics (age, sex, years of education, epilepsy syndrome [0 = idiopathic generalized, 1 = localization-related]), age at onset of first recognized seizure, seizure frequency (number of seizures/year), and percent on first ASM at baseline as well as the Sociodemographic Disadvantage Score. The Sociodemographic Disadvantage Score is an index based on four sociodemographic variables: mother's education level, race (self-identified), household income, and marital status. Details are provided elsewhere.[42,43] Briefly, families were assigned a rating based on disadvantage level. For caregiver education level and household income, those families below the mean were assigned a score of 0, whereas those families at or above the mean were assigned a score of 1. For race and caregiver marital status, non-White race and nonmarried status were each assigned a score of 0, whereas white race and married status received a score of 1. Scores ranged from 0 to 4, with lower scores indicating higher disadvantage.

3 | RESULTS

3.1 | Sample characteristics

Table 1 summarizes demographic characteristics for both groups (children with seizures and siblings) and clinical seizure characteristics in the seizure group. Briefly, a total of 312 children with newly diagnosed seizures aged 6–16 years and 223 sibling controls were included in the analyses. There were no significant differences in age, biological sex at birth, global intellectual ability, and education between the children with newly diagnosed epilepsy and sibling controls (Table 1). The clinical epilepsy characteristics indicate that the children with seizures in this sample had an average age at onset of seizures of 9.48 years, and approximately 60% of the seizure group was comprised of focal epilepsy syndromes. The epilepsy syndromes were divided into two groups: idiopathic generalized epilepsies (generalized tonic–clonic, absence, and myoclonic epilepsy syndromes) and focal/localization-related (focal aware

TABLE 1 Sample characteristics for seizure and sibling control groups.

Characteristic	Children with seizures	Sibling controls
Group characteristics		
Sample size	312	223
Age, years (SD)	9.49 (2.6)	9.68 (3.7)
Sex, M/F	158/154	108/115
Global intellectual ability (SD)	100.96 (15.3)	103.58 (15.1)
Education, years (SD)	3.79 (2.45)	3.98 (2.50)
Clinical epilepsy characteristics		
Age at onset, years (SD)	9.48 (2.54)	
Seizure frequency, per year (SD)	43.32 (174.71)	
% with idiopathic generalized epilepsy	38.6%	
% with ≥2 seizure types	8.5%	

Note: No significant differences were found between groups on any demographic variable. Data are presented as mean (SD).

Abbreviation: M/F, male/female.

and focal impaired awareness epilepsy with or without secondary generalization; see Table S1). The five most frequently prescribed ASMs were lamotrigine, oxcarbazepine, carbamazepine, phenytoin, and valproic acid. Other less commonly prescribed medications included levetiracetam, ethosuximide, zonisamide, and gabapentin. In this cohort, magnetic resonance imaging abnormalities included multiple various abnormalities (e.g., bilateral or unilateral hippocampal atrophy/sclerosis, ventricular enlargement, volume loss, cortical dysplasias, heterotopias, angiomas, encephalomalacia, old hemorrhages) as described in detail elsewhere.[44] The EEG abnormalities included focal and generalized epileptiform activity (localized and generalized intermittent slowing, continuous slowing, epileptiform discharges, electrographic seizures, occipital intermittent delta activity, and frontal intermittent delta activity). In this cohort, 62% evidenced epileptiform activity, 11% slow wave activity, and 1% electrographic seizures.[45]

3.2 | Cross-sectional group comparisons

3.2.1 | Behavior over 36 months: Parent's/teacher's/child's reports

3.2.1.1 | *Parent's report*

A comparison of the CBCL summary scores—internalizing, externalizing, and total behavior—between children with new onset epilepsy and sibling controls over the five visits showed significant differences (Figure 1A, blue bars versus orange bars). There was a significant group effect (children with epilepsy vs. controls; MANOVA, Hotelling $T = .11$, $F = 20.31$, $df = 566$, $p < .001$), with significant univariate effects across both scales and timepoints (all Tukey p's $< .05$). Children with new onset seizures exhibited significantly higher levels of behavioral problems consistently in the internalizing, externalizing, and total behavior categories compared to sibling controls. This pattern remained stable and consistent over the 3-year period.

3.2.1.2 | *Teacher's report*

Over all three visits, teachers consistently reported higher levels of behavior problems in children with new onset epilepsy, similar to parent reports (Figure 1A, gray bars).

3.2.1.3 | *Child's Report*

Children with new onset seizures reported experiencing higher levels of behavior problems compared to reference controls (Figure 1B). This pattern remained persistent over all the visits.

3.3 | Longitudinal group comparisons: Latent trajectory modeling

3.3.1 | Phenotyping child's behavior using parent's report

The cross-sectional analysis provides general information of behavioral differences, without any details on similarities or differences in extent or stability of behavioral problems among children with new onset epilepsy. Latent trajectory analysis provides further information and was utilized to evaluate unique longitudinal patterns of behavior among children with new onset seizures over 36 months. This analysis was conducted individually on the T-scores from the internalizing, externalizing, and total behavior summary scales to identify latent phenotype groups for each summary scale. Across each behavioral category, three distinct phenotypes were identified (Figure 2). Cluster 1 within the internalizing, externalizing and total behavior categories consistently exhibited the lowest levels of behavioral problems compared to Clusters 2 and 3 over the five visits and even consistently exhibited lower levels of behavioral problems compared with the sibling control group. There was a significant effect of cluster and time points (internalizing ANOVA: $F = 291.3$, $p < .001$, $\eta = .310$; externalizing ANOVA: $F = 258.4$, $p < .001$, $\eta = .285$; total

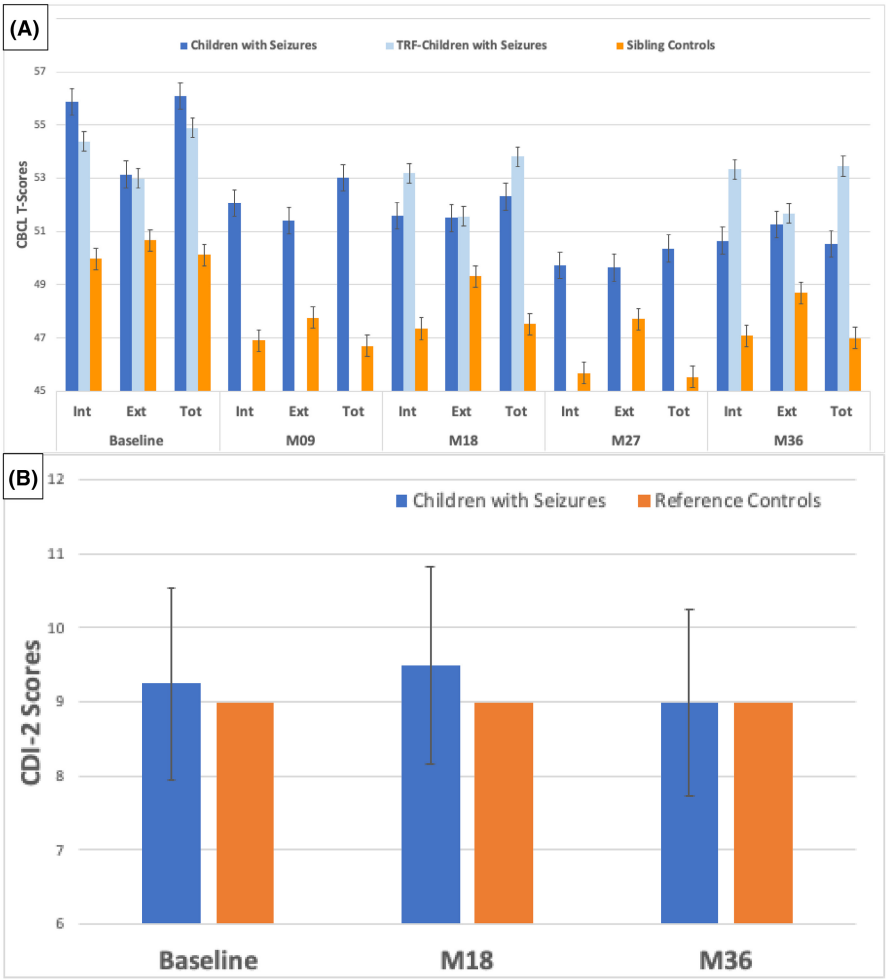

FIGURE 1 (A) Child Behavior Checklist (CBCL) over a 3-year period. Children with new onset seizures (parent report in blue over all five visits and teacher report in gray over three visits only) exhibit significantly higher levels of behavior problems compared to sibling controls. This pattern remains persistent and significant over all visits (all $p < .05$). (B) Children's Depression Inventory (CDI) summary scores over a 3-year period. Children with new onset seizures reported experiencing depression symptoms similarly to reference controls.[46] This pattern remained persistent over all the visits. Ext, externalizing; Int, internalizing; M09, 9 months from baseline; M18, 18 months from baseline; M27, 27 months from baseline; M36, 36 months from baseline; Tot, total behavior; TRF, Teacher Report Form.

behavior ANOVA: $F = 317.1$, $p < .001$, $\eta = .329$), with significant univariate effects using Tukey significant difference across scales and timepoints (all Tukey p's $< .001$). Within all three behavior scales, Cluster 2 remained consistently within the average range but elevated (more problematic) compared to controls and Cluster 1. Finally, Cluster 3 showed the most abnormal behavior (clinically relevant) across all three scales consistently over the 3-year period. The prospective trajectories for the latent cluster groups[1–3] were consistent across all measures at all five time points.

Similar findings were noted in phenotyping the child's behavior using the teacher reports and the youth reports (Figures S1 and S2).

3.4 | Characteristics of internalizing and externalizing behavior phenotypes

3.4.1 | Baseline characteristics

To understand the unique characteristics of each CBCL internalizing and externalizing behavior phenotype cluster, we evaluated baseline clinical and sociodemographic characteristics (Table 2). Notably, baseline characteristics generally show no differences in age, sex, education, age at onset, and ASMs. However, differences in sociodemographic disadvantage were identified. Among both internalizing and externalizing behavior clusters, children with new onset seizures in Cluster 3 averaged a higher level of disadvantage compared with those who fell into Cluster 2 or Cluster 1; with Cluster 1 showing the lowest level of disadvantage. Most importantly, each cluster differed significantly in sociodemographic disadvantage level (all p's $< .05$).

3.4.2 | Predictors of longitudinal phenotype class membership

Using multivariate logistic regression analyses, we determined which risk factors best predicted internalizing behavior phenotype class membership (Table 3) and externalizing behavior phenotype class membership (Table 4). For both the internalizing and externalizing behavior phenotypes, Cluster 1 (least behavioral problems) was used as the reference group.

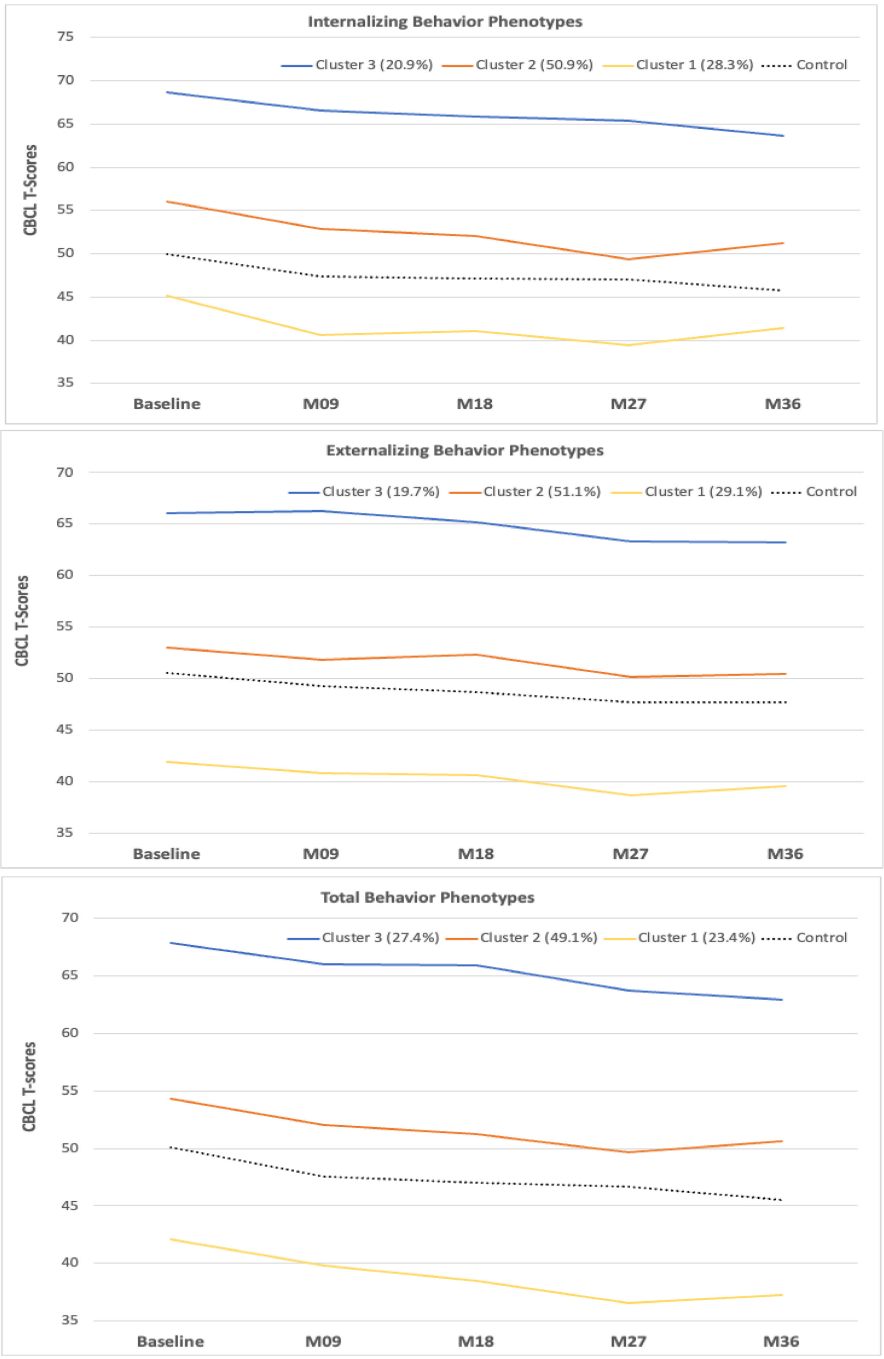

FIGURE 2 Latency trajectory analysis from the five timepoints (baseline, M09 [9 months from baseline], M18 [18 months from baseline], M27 [27 months from baseline], and M36 [36 months from baseline]) resulted in three distinct Clusters. Cluster 1 (~30% in yellow) exhibited behavior within the normal range over the 3-year period, whereas Cluster 3 (~20% in blue) exhibited significantly higher levels of behavior problems compared to Clusters 1 and 2 (~50% in orange) and controls (dotted black line). CBCL, Child Behavior Checklist.

3.4.2.1 | *Predictors of internalizing behavior clusters*

Compared to Cluster 1, seizure type (idiopathic generalized epilepsy [IGE] vs. focal/localization-related epilepsy) and sociodemographic disadvantage played a significant role in predicting class membership in Cluster 3, but not Cluster 2 (Table 3). Specifically, those with IGE or those who come from a more disadvantaged sociodemographic background had increased odds of being in Cluster 3 (highest level of behavioral problems) compared to Cluster 1.

3.4.2.2 | *Predictors of externalizing behavior clusters*

Compared to Cluster 1, seizure type (IGE vs. focal/localization-related epilepsy) and sociodemographic disadvantage played a significant role in predicting class membership in both Clusters 2 and 3 (Table 4). Specifically, those with IGE or those who come from a more disadvantaged sociodemographic background had increased odds of being in Cluster 2 or 3 (higher levels of behavioral problems) compared to Cluster 1.

TABLE 2 Characteristics of internalizing and externalizing phenotype clusters.

	Internalizing phenotypes				
Demographics	**Cluster 1, *n* = 99, 28.3%**	**Cluster 2, *n* = 178, 50.9%**	**Cluster 3, *n* = 73, 20.9%**	***F***	***p***
Age, years (SD)	9.44 (2.6)	9.49 (2.6)	9.32 (2.5)	.103	.902
Sex, % F	50.5%	52.8%	46.6%	.403	.668
Education, years (SD)	3.90 (2.6)	3.78 (2.5)	3.68 (2.3)	.159	.853
Age at onset, years (SD)	9.60 (2.6)	9.62 (2.6)	9.47 (2.5)	.098	.906
% on ASMs at baseline	10.8%	12.9%	14.7%	.352	.704
Disadvantage composite score	3.65 (.11)	3.52 (.09)*	3.32 (.12)**	8.14	<.001
	Externalizing phenotypes				
Demographics	**Cluster 1, *n* = 102, 29.1%**	**Cluster 2, *n* = 179, 51.1%**	**Cluster 3, *n* = 69, 19.7%**	***F***	***p***
Age, years (SD)	9.5 (2.5)	9.4 (2.5)	9.44 (2.8)	.043	.958
Sex, %, F	51%	53.1%	44.9%	.658	.518
Education, years (SD)	3.97 (2.5)	3.73 (2.4)	3.7 (2.6)	.365	.695
Age at onset, years (SD)	9.63 (2.5)	9.6 (2.5)	9.47 (2.7)	.095	.910
% on ASMs at baseline	14.4%	11.1%	15.1%	.657	.519
Disadvantage composite score	3.68 (.11)	3.51 (.08)*	3.29 (.13)**	11.08	<.001

Note: In children with new onset across internalizing and externalizing phenotypes, there were no significant differences in age, sex, education, age at onset, or medications. However, there were significant differences in sociodemographic disadvantage such that Cluster 1 in both internalizing and externalizing phenotype groupings showed the least disadvantage, whereas Cluster 3 in both internalizing and externalizing phenotype groupings showed the highest disadvantage. For each characteristic, a score with no asterisk is significantly different from *, which is significantly different from **.

Abbreviations: ASM, antiseizure medication; F, female.

4 | DISCUSSION

The overall goal of this study was to compare the public health picture of behavior in youth with epilepsy provided when it is examined by traditional cross-sectional group comparisons compared to more contemporary latent trajectory modeling, and regarding the latter, determine the existence, consistency, and stability of behavior phenotypes in this large cohort of children with new onset seizures. Three major findings resulted, which are reviewed below.

1. Cross-sectional evaluation

The cross-sectional findings corroborate the existence of pervasive behavioral effects in youth with epilepsy at baseline[1–20] and extend those findings by showing that group differences persist across multiple assessments out to 36 months after baseline, with remarkably consistent reports from parents, teachers, and the children themselves informing the strength of the effect. Notably, the consistency in the data across different reporters must be underscored. We pooled data from parents, teachers, and children over 3 years. Despite different measures and different reporters, the behavioral problems noted in the children with seizures remained consistent over time. The mean profile of the youth with epilepsy, although generally abnormal compared with controls, fell into a range of abnormality that is not expressly "clinically relevant."[36,37] This indicates that youth with epilepsy who exhibit significant clinically relevant behavioral problems would often be overlooked. As a consequence, the longitudinal phenotyping investigation is critical to gain a deeper understanding of epilepsy comorbidities.

2. Longitudinal investigation

The longitudinal findings are also consistent with prior literature,[31–35] indicating the presence of behavioral phenotypic patterns that can be clinically relevant in children with new onset seizures. Here, we extend the findings significantly by reporting the trajectory of these behavioral phenotypes in a large cohort over 3 years. Using latent trajectory analysis, three distinct clusters were identified: an abnormal group (Cluster 3, ~20%), exhibiting the most pronounced behavioral issues; a moderate group (Cluster 2, ~50%), with milder behavioral concerns; and a typical group (Cluster 1, ~30%) that exhibited the least behavioral problems, achieving lower scores than even the control group (likely because controls were treated as a single

TABLE 3 Predictors of internalizing behavior phenotype class membership using baseline clinical epilepsy characteristics and sociodemographic disadvantage.

Internalizing behavior phenotype predictor	Standardized β coefficient	SE	*p*	95% CI lower	95% CI upper
Cluster 2 versus Cluster 1					
Age	−.033	.011	.329	−.220	.125
Child's sex	−.046	.048	.243	−.148	.021
Age at onset of seizures	−.042	.054	.434	.862	1.066
Seizure frequency	−.001	.001	.342	.998	1.001
Idiopathic generalized epilepsy	.440	.315	.164	.347	1.196
Antiseizure medications at baseline (yes)	.045	.137	.285	−.152	.333
Sociodemographic disadvantage score	−.267	.145	.067	.576	1.018
Cluster 3 versus Cluster 1					
Age	−.083	.035	.444	−.120	.121
Child's sex	−.041	.047	.348	−.153	.059
Age at onset of seizures	−.059	.066	.372	.829	1.073
Seizure frequency	−.001	.001	.268	.997	1.001
Idiopathic generalized epilepsy	.714	.367	.048	.239	1.006
Antiseizure medications at baseline (yes)	.089	.117	.354	−.111	.523
Sociodemographic disadvantage score	−.630	.165	<.001	.385	.736

Note: Data are presented as standardized β coefficients, SE, and significance, along with CIs.

Abbreviation: CI, confidence interval.

TABLE 4 Predictors of externalizing behavior phenotype class membership using baseline clinical epilepsy characteristics and sociodemographic disadvantage.

Externalizing behavior phenotype predictors	Standardized β coefficient	SE	*p*	95% CI lower	95% CI upper
Cluster 2 versus Cluster 1					
Age	−.036	.022	.411	−.045	.024
Sex	−.065	.014	.323	−.27	.081
Age at onset of seizures	−.047	.054	.387	.859	1.061
Seizure frequency	.001	.001	.101	.997	1.000
Idiopathic generalized epilepsy	1.013	.327	.002	.191	.689
Antiseizure medications at baseline (yes)	.012	.037	.345	−.215	.263
Sociodemographic disadvantage score	−.310	.145	.033	.552	.975
Cluster 3 versus Cluster 1					
Age	−.029	.051	.481	−.025	.027
Sex	−.055	.044	.377	−.176	.042
Age at onset of seizures	−.064	.068	.344	.821	1.071
Seizure frequency	−.002	.001	.104	.996	1.000
Idiopathic generalized epilepsy	.795	.397	.045	.207	.983
Antiseizure medications at baseline (yes)	.086	.022	.399	.029	.120
Sociodemographic disadvantage score	−.664	.170	<.001	.369	.718

Note: Data are presented as standardized β coefficients, SE, and significance, along with CIs.

Abbreviation: CI, confidence interval.

group, probably with significant variability). This similar cluster pattern emerged in internalizing, externalizing, and total behavior phenotypes in both parent and teacher reports.

Second, we observed a consistent trend among all evaluators (parents, teachers, and children) over time. The abnormal group (Cluster 3), with the most pronounced behavioral issues as assessed by parents, also exhibited the highest levels of behavioral issues as assessed by teachers and children consistently over 36 months; the moderate group (Cluster 2), with better behavior scores than Cluster 3 as assessed by parents, also exhibited moderate levels of behavioral issues as assessed by teachers and children consistently over 36 months. Lastly, the typical group (Cluster 1) scored the lowest in behavior scores, reflecting the best behavioral outcomes as assessed by parents, and also exhibited the lowest levels of behavioral issues as assessed by teachers and children consistently over 36 months.

3. Baseline and longitudinal predictors of cluster membership

Finally, we investigated both baseline and longitudinal predictors of class membership and noted that social determinants of health (sociodemographic disadvantage) were a powerful predictor of cluster membership, such that those with a more disadvantaged background had increased odds of having more behavioral problems (being in Cluster 3). In addition, the longitudinal analysis indicated that seizure syndrome also played a role in cluster membership, as those with IGE had increased odds of having clinically relevant behavioral problems.

4.1 | Contrasting perspectives of behavioral risk

A major finding is the perception of the behavioral risk associated with epilepsy provided based on the methods of behavioral analysis. In the traditional cross-sectional analysis of epilepsy versus control participants, significantly worse behavior was reported in the epilepsy group by parents, teachers, and the children themselves. This pattern was not only consistent as a function of behavioral rater, but also as a function of time, as identical findings were reported through the cross-sectional assessments at baseline, 9 months, 18 months, 27 months, and 36 months after seizure onset. The message provided by this analytic approach was clear and consistent, that is, children with epilepsy are at increased behavioral risk, with consensus among parents, teachers, and the children themselves. This has been a very conventional and commonly used analytic approach[8,19,39,47] that has informed the literature on behavioral issues in youth with epilepsy and, essentially, colored the view of the disorder.

In contrast, when the analytic approach involves a search for underlying latent behavioral groups, an entirely different perspective of the behavioral risk associated with epilepsy emerges. In this manner, three groups of children with epilepsy emerge, one group comparable to controls (~30%), one group with very elevated and clearly abnormal behavior (~20%) representing an arguably distinct minority of children, and a third group with scores that are elevated compared to controls but not in the impaired range (~50%). Again, the consistency of findings is impressive. This latent group approach sends a distinctly different message about the relationship between epilepsy and behavior. Across raters, time, and behavioral measures, the youth with epilepsy fall into very distinct groups, and only one phenotype differs markedly from controls in a pathological way; the other two epilepsy clusters are comparable to controls or better. This sends a very different message about behavioral risk compared to the usual modal profile approaches.

4.2 | Implications for timing and targeting of intervention

An additional advantage of latent trajectory modeling involves its implications for the identification of high-risk groups, their trajectory, and the timing of intervention imperative. Regardless of whether the raters were parents, school personnel (teachers), or the children themselves, the cross-sectional behavioral trajectories were stable, neither worsening nor improving to a significant degree. The longitudinal trajectories are further informative as "progression" (worsening) of behavior over time was not observed, nor was behavioral normalization evident among those with problems. Given that these were youth with new onset seizures, the obvious opportunity for early intervention is clear. The important question then becomes what sociodemographic, clinical epilepsy, or treatment factors are associated with these divergent latent groups. Predictors of phenotype class membership analysis notably showed two consistent characteristics of the externalizing and internalizing phenotype clusters: IGE and a higher sociodemographic disadvantage score associated with clusters involving higher levels of behavioral problems. Currently, the literature suggests differing conclusions regarding the relationship between seizure type and behavioral problems. Some evidence suggests IGE syndromes are more closely linked with behavioral problems[48,49]; other evidence suggests focal epilepsy syndromes are more associated with behavioral problems[50] or there are no differences at all.[21] Focused

studies addressing these associations would further clarify these predictive risk categories.

There is growing evidence of the role of social determinants of health in long-term medical outcomes, including epilepsy-related outcomes.[42,43,51–58] This disadvantage is multifaceted, including both individual (lower income levels, lower levels of education, reduced household stability, etc.) and structural (e.g., limited neighborhood resources due to historically inequitable zoning laws, resulting in continued poor transportation access, limited health care facilities and providers nearby, more food deserts) factors that play a determinant role in access to health care in this country and ultimately affect long-term health outcomes (social determinants of health). Our investigation indicates that children with epilepsy from more disadvantaged backgrounds had increased odds of exhibiting behavioral problems. Mental health distress is associated with socially deprived neighborhoods as well as less favorable health care outcomes in the long term.[59] With further research, high-risk groups can be delineated clearly, and interventions can be characterized and can be incorporated into the standard of care to improve overall quality of life for patients with epilepsy.

4.3 | Limitations and future directions

This investigation has limitations:

1. We relied on a behavioral measure rather than on psychiatric diagnoses, which many might argue would be more clinically relevant. Research of this type, particularly longitudinal research, is needed. However, the consistency in findings across raters and over time lends credence to the findings.
2. We did not have detailed syndrome subtyping, and future work examining discrete syndromes of focal/localization-related epilepsy and IGE are needed to fine-tune the relationships reported here.
3. The results and inferences from this study may be limited because the control group were siblings. Sibling controls are believed to be a biased group in childhood epilepsies research because childhood epilepsies have significant genetic associations and siblings could be too similar genetically, making them similar in neurocognitive, behavioral, and neuroimaging measures.
4. Our approach was to anchor the identification of the phenotypes to their initial (baseline) presentation and follow their course longitudinally. The rationale was that if the phenotypes can be identified early in the course of the epilepsy, and if they have a stable course over time under "usual care" conditions, then it becomes imperative to intervene earlier rather than later—a key clinical implication. The phenotypes over 36 months did appear surprisingly stable, but the degree of movement of individuals across clusters over time and the responsible factors deserves to be investigated in the future.

4.4 | Conclusions

The analytic approach used for behavioral analysis of children with epilepsy has major implications for understanding the risk, course, and predictors of behavioral problems in youth with epilepsy. Initiation of investigation of children with epilepsy as soon as feasible after seizure onset provides numerous opportunities for optimal timing of intervention—a critical need going forward.

Further research is needed to specifically identify what characteristics represent significant underlying causes leading to the variable behavior patterns observed in different groups. Identifying such characteristics could help clinicians better provide early targeted interventions to improve behavioral outcomes and cognitive ability in patients with epilepsy.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

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