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# Neuropsychological Phenotypes in Pediatric Temporal Lobe Epilepsy

William A. Schraegle[1,2,3,*], Nancy L. Nussbaum[1,2,3], Rosario C. DeLeon[1,2,3] and Jeffrey B. Titus[1,2,3]

[1]Division of Neuropsychology, Department of Neurology, Dell Medical School, The University of Texas at Austin, Austin, TX, USA
[2]Comprehensive Pediatric Epilepsy Center, Dell Children's Medical Center, Austin, TX, USA
[3]UT Health Austin Pediatric Neurosciences, Dell Children's Medical Center, Austin, TX, USA

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**Abstract**

**Objective:** Adults with temporal lobe epilepsy (TLE) have been found to have a fairly characteristic pattern of neuropsychological performance, but there is considerably less research and more variability in findings with children. Because the cognitive domains included in most studies with children have been limited, the current study attempted to better characterize the cognitive phenotype of children with TLE using a broader neuropsychological battery. **Methods:** The study included 59 children with TLE (59% male) age 7 to 16 (M = 12.67; SD = 3.12) who underwent comprehensive neuropsychological evaluation. Patient results were grouped into cognitive domains (reasoning, language, visuoperceptual, verbal memory, executive function, and motor function) based upon their test performance. These factor scores were subjected to Ward's hierarchical clustering method with squared Euclidean distance. **Results:** Cluster analysis revealed three distinct cognitive profiles: (1) normal functioning (20% of sample); (2) delayed verbal memory and motor weaknesses (61% of the sample); and (3) global impairment (19% of the sample). Cluster 3 had longer epilepsy duration and a higher incidence of hippocampal sclerosis (HS) compared to Cluster 1 ($p < .05$). There were no significant differences among the three cluster groups on demographic characteristics or remaining clinical characteristics. **Conclusions:** Children with TLE present with distinct cognitive phenotypes ranging from average performance to global impairment. Results partially support previous hypotheses highlighting the cumulative neurobiological burden on the developing brain in the context of chronic epilepsy and provide a preliminary framework for the cognitive domains most vulnerable to the TLE disease process.

**Keywords:** Temporal Lobe Epilepsy, Pediatric, Hippocampal sclerosis Cognitive phenotypes, Taxonomy

## INTRODUCTION

Neurological and psychiatric disorders have generally addressed the overarching pattern of impairment, yet have tended to neglect the heterogeneity inherent in these disorders and the cognitive subtypes that may exist. Therefore, it is helpful to explore the functional phenotypes of patients who have similar syndromic etiologies to establish patterns of cognitive performance that can better characterize the patient group. This approach has been previously utilized in pediatric samples to detect unique cognitive and behavioral phenotypes in idiopathic epilepsy (Hermann et al., 2016), as well as neurodevelopmental disorders, like Autism Spectrum Disorder (ASD) (Frith, Hill, Tager-Flusberg, & Joseph, 2003) and learning disabilities (Nussbaum & Bigler, 1986). Once phenotypes are characterized, comparisons across clinical, neuroanatomical, and psychosocial domains can be carried out to better understand domains associated with diagnostic heterogeneity and domains associated with poor outcome.

Temporal lobe epilepsy (TLE) is the most common focal epilepsy in childhood, occurring in approximately 50–80% of focal cases (Wiebe, 2000). Studies exploring the neuropsychological profiles of children and adolescents with TLE have been varied and frequently demonstrate cognitive deficits implicating network dysfunction beyond the temporal lobes. For instance, deficits in memory, language, psychomotor speed, and executive functioning have been documented. Guimarães and colleagues (2007) compared 25 children with TLE and structural lesions to 25 neurotypical children. The authors found that, despite average intelligence, those with TLE demonstrated deficits in memory, attention, language, visuoconstructional abilities, and executive functioning.

In a review exploring the cognitive sequelae of early onset TLE, Rzezak and colleagues (2014) identified memory and

*Correspondence and reprint requests to: William A. Schraegle, Ph.D., Pediatric Neuroscience, Dell Children's Medical Center, 4900 Mueller Boulevard, Austin, TX 78723, USA. E-mail: William.schraegle@ascension-external.org

executive functioning to be particularly vulnerable to the TLE disease process, and this is concordant with recent work from our group highlighting difficulties with verbal memory and executive functioning. In 2016, Schraegle et al. demonstrated that, in a mixed sample, youth with TLE had significantly greater retroactive interference effects and retrieval deficits on a measure of verbal learning when compared with youth who had Frontal Lobe Epilepsy and Childhood Absence Epilepsy. In a subsequent investigation, pediatric TLE was also associated with generally diminished executive functioning that was worse in the presence of morphological changes to the hippocampus (i.e., hippocampal sclerosis) (Schraegle, Nussbaum, & Titus, 2018). However, when examining the literature as a whole, there is significant variability among studies documenting cognitive outcome in TLE, which is likely emblematic of the cognitive heterogeneity of TLE, a sentiment that has been echoed in the adult literature (Oyegbile et al., 2004).

To date, far less research has been devoted to characterizing cognitive phenotypes that may exist within and across epilepsy syndromes in children. Using cluster analysis, Hermann and colleagues (2007) identified three distinct cognitive profiles in adults with temporal lobe epilepsy. Half of their sample were characterized as having minimal impairment, a quarter as having memory impairments in the context of otherwise intact cognitive function, and the remainder having widespread impairments in memory, executive functioning, and processing speed. The three groups demonstrated different patterns of results on demographic, clinical seizure, cerebral volumes, and cognitive course over a 4-year interval, thus providing evidence for the distinctiveness of the cognitive-based clusters and the predictive utility of this phenotypic approach.

In an effort to replicate these findings with a larger sample, Elverman and colleagues (2019) completed a hierarchical cluster analysis that yielded two clinical cluster solutions, one with three clusters and another with four clusters. The clusters in the three-cluster solution were differentiated primarily by overall level of performance (Low, Middle, and High performance), while the clusters in the four-cluster solution demonstrated more variability in cognitive phenotypes (Globally Low, Low Executive Functioning/Speed, Low Language/Memory, and Globally High). Validating previous findings in adults with TLE, Reyes et al. (2020) identified three cognitive phenotypes in a multisite cohort ($N = 407$) that were characterized by 29% with generalized impairment, 28% with language and memory impairment, and 43% with no impairment. Those in the generalized impairment group showed longer duration of epilepsy, but, interestingly, those in the language and memory impairment phenotype were not found to be associated with cortical pathology (i.e., hippocampal sclerosis) or earlier age of seizure onset. However, recent work has eloquently demonstrated the association between decreased cognitive performance, characterized by phenotype (Intact, Focal Memory, and Generalized Impairment), and increased network disruption (i.e., degree of white matter perturbations and large-scale network architecture) (Rodriguez-Cruces et al., 2018; Rodríguez-Cruces, Bernhardt, & Concha, 2020).

Baxendale and Thompson (2020) examined the utility of cognitive phenotypes in the prediction of postoperative outcomes in a large sample of adult patients who underwent unilateral temporal lobectomy ($N = 445$). Using clinical criteria, the authors identified four cognitive phenotypes that were characterized by 54% intact, 28% with a language and memory impairment, 9% with global impairment, and 9% with a mixed profile. Notably, phenotypes were not associated with postoperative seizure outcome or postoperative declines in verbal memory or language function, but an intact phenotype was associated with a greater risk of decline in visual learning than right-sided surgery.

While no studies to date have examined the cognitive phenotypes exclusively in pediatric TLE, a similar three-cluster solution was identified in childhood idiopathic epilepsies (Hermann et al., 2016). The three-cluster solution was characterized by average performance that was similar to controls (44% of sample), mild impairment across multiple cognitive domains (44% of sample), and impairment across all domains with severe attentional impairment (12% of sample). The phenotypes were associated with differences in brain volumes (i.e., total subcortical gray volume, bilateral cerebellar cortices, bilateral thalamus, and bilateral caudate), parental IQ, and features of early developmental history.

Hermann et al. (2016) found no relationship between cognitive phenotype and epilepsy syndrome in their mixed sample of pediatric idiopathic epilepsies. They concluded that cognitive phenotypes are likely driven by other factors than syndromic taxonomy, such as epilepsy severity or disease progression (Elverman et al., 2019). However, because they used such a heterogeneous sample, it is possible that a syndromic relationship to the clusters was obscured by limitations in statistical power, which is not unsurprising given the broad diagnostic category of idiopathic epilepsy. Moreover, it is important to note that the authors did not include a memory measure in their cluster analysis, as it did not discriminate from controls. Given that memory performance is a common distinguishing feature among epilepsy syndromes, it is likely that this omission affected the relationship of clusters with syndromes and the ultimate generalizability of the findings.

While it appears as though some cognitive phenotypes are "pan-syndromic" (i.e., intact and globally impaired groups), questions remain regarding the existence, and if so make-up, of syndrome-specific cognitive phenotypes in pediatric epilepsy. Therefore, the current study sought to expand the pediatric epilepsy literature by examining potential cognitive phenotypes in a well-defined epilepsy syndrome using a comprehensive neurocognitive battery. The following research questions were explored: (1) Are there specific neuropsychological phenotypes associated with pediatric TLE? (2) If phenotypes are found, are there clinical and demographic characteristics associated with these phenotypes?

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**Table 1.** Overview of neuropsychological measures

| Domain | Ability | Measure/test | |
|---|---|---|---|
| Reasoning | Abstract Verbal Reasoning | Similarities | WISC-IV[2] |
| | Abstract Spatial Reasoning | Matrix Reasoning | WISC-IV[2] |
| Language | Lexical Knowledge | Vocabulary | WISC-IV[2] |
| | Confrontation Naming | Boston Naming Test Total | BNT[1] |
| | Verbal Fluency, Semantic | Category Fluency | DKEFS[3] |
| Visuospatial | Perceptual Organization | Block Design | WISC-IV[2] |
| | Visual Matching | Visual Perception | Beery VMI-6[8] |
| Immediate Memory | Auditory Memory | SDFR | CVLT-C[4] |
| | | MFS | TOMAL-2[5] |
| Delayed Memory | Auditory Memory | LDFR | CVLT-C[4] |
| | | MFSD | TOMAL-2[5] |
| Executive | Cognitive Flexibility | Perseverative Errors | WCST[6] |
| | Verbal Fluency, Phonemic | Letter Fluency | DKEFS[3] |
| | Immediate Attention | Digits Forward | WISC-IV[2] |
| | Working Memory | Digits Backward | WISC-IV[2] |
| Motor | Speeded Fine Motor | Dominant/nondominant | Grooved Pegboard[7] |
| | Graphomotor Precision | Motor Coordination | Beery VMI-6[8] |

*Note*. [1]Boston Naming Test (Kaplan et al., 1983); [2]Wechsler Intelligence Scale for Children-Fourth Edition (Wechsler, 2003); [3]Delis-Kaplan Executive Function System (Delis et al., 2001); [4]California Verbal Learning Test-Children's Version (Delis & Psychological Corporation, 1994); [5]Test of Memory and Learning - Second Edition (Reynolds & Bigler, 1994); [6]WCST: Wisconsin Card Sorting Test (Heaton et al.,1993); [7]Grooved Pegboard Test (Heaton, 1993); [8]Beery-Buktenica Developmental Test of Visual-Motor Integration- Sixth Edition (Beery et al., 2004)

## METHODS

### Participants

Youth between the ages of 8–16 years with a prior diagnosis of temporal lobe epilepsy who were referred for epilepsy treatment at a tertiary care health system were eligible for inclusion (see Table 2). All children and adolescents were referred to pediatric neuropsychology services based upon the presence of cognitive concerns or as part of a presurgical epilepsy evaluation. Temporal lobe epilepsy (TLE) was confirmed by board-certified epileptologists via clinical evaluation, ictal EEG monitoring, and concordant interictal EEG findings, consistent with ILAE criteria (Engel, 2001). Neuropsychological assessment was only conducted following a 24-hour period of seizure freedom. Hippocampal sclerosis (HS) was identified by magnetic resonance imaging (MRI), namely increased signal intensity on T2-weighted and FLAIR images, and verified by a pediatric neuroradiologist.

Approval was granted by the University of Texas at Austin IRB and Ascension Site Approval Committee to access archival data. Exclusion criteria included the presence of extratemporal epileptiform activity on EEG, previous neurosurgery, and a diagnosis of hearing or visual impairment.

### Sociodemographic and Epilepsy-Specific Variables

Demographic and seizure-related variables were taken directly from a combination of prior medical records, parent interview, and a standardized family information questionnaire completed by a parent the day of evaluation. The following demographic data were collected: participant age, gender, minority status (coded: 0 = No, indicating non-Hispanic White identification; 1 = Yes, indicating either Hispanic, African–American, Asian, Native American, Polynesian, or Other identification), and maternal education level (coded: 0 = < high school; 1 = high school degree/GED; 2 = some college, 3 = college degree; 4 = graduate degree). Moreover, seizure-related variables included the following: age at seizure onset, number of epilepsy-related medications (antiepileptic drugs [AEDs]), number of failed AEDs, seizure frequency (coded: 0 = none; 1, = yearly; 2 = quarterly; 3 = monthly; 4 = weekly; and 5 = daily), duration of epilepsy (i.e., time since the first seizure), and positive identification of hippocampal sclerosis (coded: 0 = negative and 1 = positive identification).

### Neuropsychological Measures

All children and adolescents were administered neuropsychological tests by individuals trained in standardized testing procedures. Table 1 depicts the cognitive domains, cognitive abilities tested, and the tests administered in the present study. Standard and scaled score performances for all psychometric tests were converted to *z*-scores ($M = 0$, $SD = 1$). By placing all test scores on a common metric, relative performance across the various cognitive domains can be compared directly and definitions of abnormality (e.g., *z*-score ≥ –2.0) applied uniformly across tests. Cognitive domain scores were created by computing the average *z*-score of tests falling within the designated cognitive domains (see Table 1).

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### Statistical Analysis

All analyses were conducted using SPSS version 26.0 (SPSS Inc., Chicago IL, USA). Prior to analyses, outliers beyond ± 3.5 *z*-scores for each neuropsychological variable were normalized to values of +3.5 or –3.5 (depending on the direction) so that the cluster solutions were not influenced by skewed distributions. Normalization was performed on five scores across the entire sample (grooved pegboard, nondominant hand, $n = 3$, and Boston Naming Test, $n = 2$).

The present study utilized a similar statistical approach to previously published work examining cognitive phenotypes in adults with TLE (Elverman et al., 2019; Hermann et al., 2007). As a result, Ward's hierarchical agglomerative clustering method was used across reasoning, language, visuospatial, immediate memory, delayed memory, executive, and motor skills domains. Squared Euclidean distance was used as the index of pairwise similarity – dissimilarity between participant profiles. Identification of optimal clustering solutions within the clustering hierarchy was determined through examination of the agglomeration schedule and dendrogram. The desired outcome was to identify a stage within the clustering hierarchy yielding significant increases in the error sum of squares coefficients after having had relatively smaller increases at previous stages (Berven & Hubert, 1977). Further determination of the cluster solution is based on clinically meaningful differences across clusters.

After determining the cluster solutions, a series of one-way multivariate analyses of variance (MANOVAs) with follow-up univariate tests were conducted to compare patterns of cognitive functioning across clusters. Given the large number of pairwise comparisons necessary to fully characterize the clusters, a Bonferroni correction was applied to this set of analyses, resulting in a critical value of $p = .0024$.

Additionally, cluster groups were compared on sociodemographic (i.e., age, race) and clinical seizure characteristics (i.e., age of seizure onset, duration of epilepsy, seizure frequency, number of current antiepileptic medications, number of failed AEDs, and seizure laterality), as well as other relevant clinical variables (i.e., MRI-identified hippocampal sclerosis and surgical candidacy).

## RESULTS

### Sample Characteristics

Table 2 provides demographic and clinical seizure characteristics. The study included 59 children and adolescents living with TLE (59% male) aged 8 to 16 years ($M = 12.67$, $SD = 3.12$) with roughly 48% of the sample identifying as non-Hispanic White ethnicity. Most mothers (64%) attended "some college". Most patients experienced seizure onset in childhood ($M = 6.87$, $SD = 3.89$), with roughly 7% of the sample reporting seizure onset in the first year of life. Seizure frequency occurred yearly in around 9%, quarterly in 11%, monthly in 39%, weekly in 19%, and daily in 19%. Medication regimen for children and adolescents averaged one current AED ($M = 1.42$, $SD = .72$) and around one failed AED trial ($M = 1.53$, $SD = 1.57$). In terms of seizure lateralization, roughly 49% of the sample showed a left temporal focus, around 41% showed right temporal focus, and about 10% of patients had bilateral temporal involvement. Approximately, 49% of the sample was referred for presurgical evaluation, and hippocampal sclerosis was identified in roughly 25% of patients.

**Table 2.** Demographic and clinical seizure characteristics

| Characteristics | Total sample Mean (*SD*) or *N* (%) |
|---|---|
| *N*, (males and females) | 59 (35 and 24) |
| Age (years) (SD) | 12.67 (3.12) |
| Racial background *N* (% minority) | 32 (52.5%) |
| Maternal education *N* (%) | – |
| <High school | 8 (13.6%) |
| High school/GED | 13 (22.0%) |
| Some college | 24 (40.7%) |
| College | 11 (18.6%) |
| Graduate degree | 3 (5.1%) |
| Age of seizure onset | 6.87 (3.89) |
| Epilepsy duration (years) | 5.92 (4.95) |
| Seizure frequency *N* (%) | – |
| Yearly | 5 (8.5%) |
| Quarterly | 9 (15.3%) |
| Monthly | 23 (39.0%) |
| Weekly | 11 (18.6%) |
| Daily | 11 (18.6%) |
| Number of failed AEDs | 1.53 (1.57) |
| Number of current AEDs | 1.42 (.72) |
| Seizure laterality *N* (%) | – |
| Left | 29 (49.6%) |
| Right | 24 (40.68) |
| Bilateral | 6 (10.2%) |
| Surgical candidate *N* (%) | 29 (49.2%) |
| Hippocampal sclerosis *N* (% yes) | 15 (25.4%) |

*Note.* AED, antiepileptic drug.

Figure 1 depicts the mean cognitive performance for the entire sample. In summary, the overall performance for the TLE group across cognitive domains demonstrated performance generally in the low average range (Reasoning, $z = -.67$, SD = .90; Language, $z = -1.00$, SD = 1.17; Visuospatial, $z = -.70$, SD = 1.04; Immediate Memory, $z = -.77$, SD = 1.08; Delayed Memory, $z = -.92$, SD = 1.11; and Executive, $z = -.75$, SD = .85) with the exception of below average motor skills ($z = -1.95$, SD = –2.17).

### Cluster Solutions

The mean cognitive performance for the three cluster groups is provided in Table 3. A graphical representation of the cognitive profiles is presented in Figure 2. Despite unequal

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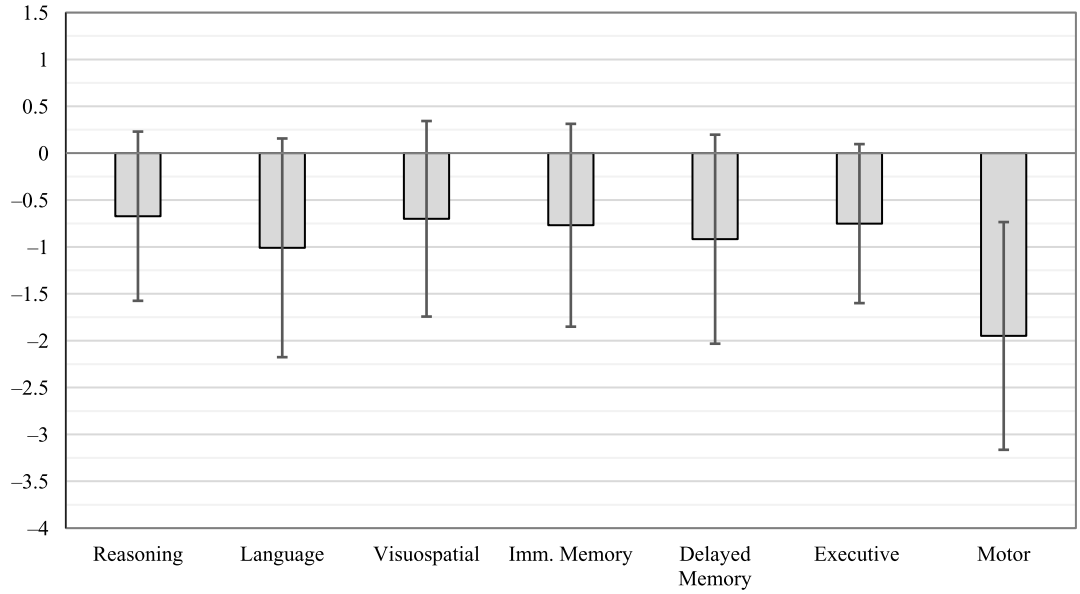


**Figure 1.** Mean sample performance across cognitive domains.

**Table 3.** Overview of neuropsychological measures

| Domain | Cluster 1 ($n = 12$) $z$-score (SD) | Cluster 2 ($n = 36$) $z$-score (SD) | Cluster 3 ($n = 11$) $z$-score (SD) |
|---|---|---|---|
| Reasoning | .43 (.58) | –.74 (.61) | –1.65 (.73) |
| Language | .72 (.61) | –1.14 (.59) | –2.46 (.52) |
| Visuospatial | .39 (.65) | –.71 (.75) | –1.87 (.97) |
| Immediate Memory | .39 (.99) | –.80 (.78) | –1.94 (.65) |
| Delayed Memory | .15 (.94) | –1.41 (.80) | –2.11 (.97) |
| Executive | .20 (.61) | –.76 (.56) | –1.95 (.43) |
| Motor | –.69 (.72) | –1.98 (1.09) | –3.15 (.36) |

cluster group size (i.e., Cluster 1, $n = 12$; Cluster 2, $n = 36$; & Cluster 3, $n = 11$), Box's M was nonsignificant ($p = .47$) indicating that the covariance matrices are equal across cluster solutions. Overall, the three-cluster solution produced clusters representing a graded level of performance. This pattern followed across all cognitive domains. A one-way MANOVA was conducted to compare the three clusters across the seven cognitive domains. There was a significant overall effect (Wilks' $\lambda = .11$, $F_{14,100} = 14.44$, $p < .001$, $\eta = .67$). Posthoc analyses revealed significant differences among cluster groups across each cognitive domain ($p < .001$) with the exception of nonsignificant differences in delayed memory between Cluster 2 and Cluster 3 ($p = .02$).

## Cluster 1: Within Normal Limits (WNL) Group

Cluster 1 included 12 patients (20% of the sample) who exhibited a pattern of average functioning across cognitive domains, aside from a low average performance on motor skills. Univariate between-cluster tests revealed that cognitive scores were significantly higher in Cluster 1 than both Clusters 2 and 3 for reasoning, language, visuospatial, immediate memory, delayed memory, executive, and motor skills ($p < .001$). Pairwise comparisons revealed significantly lower scores in motor functioning when compared to all other cognitive domains, aside from delayed memory ($p = .029$, trending with Bonferroni correction).

## Cluster 2: Delayed Verbal Memory and Motor Weakness (Focal) Group

Cluster 2 included 36 patients (61% of the sample) and was characterized by below average performance on delayed verbal memory and motor domains. Results of univariate between-cluster tests revealed significant cognitive differences between Cluster 2 and the other clusters for nearly all cognitive domains ($p < .001$), with the majority of scores lower than Cluster 1 and higher than Cluster 3, with the exception of delayed memory ($p = .02$). Pairwise comparisons for within-cluster performances revealed that motor skills were significantly lower than scores in the domains of reasoning, language, visuospatial, executive, immediate memory, and delayed memory. Delayed memory scores were also significantly lower than scores for reasoning, visuospatial, immediate memory, and executive skills ($p < .001$) with nonsignificant differences for language ($p = .04$).

## Cluster 3: Globally Impaired Group

Finally, the Cluster 3 group included 11 patients (19% of sample) and was characterized by a pattern of below average to exceptionally low scores across all domains. Univariate between-cluster analyses revealed that cognitive scores were significantly lower in Cluster 3 when compared to Cluster 1 and Cluster 2, with the exception of a nonsignificant

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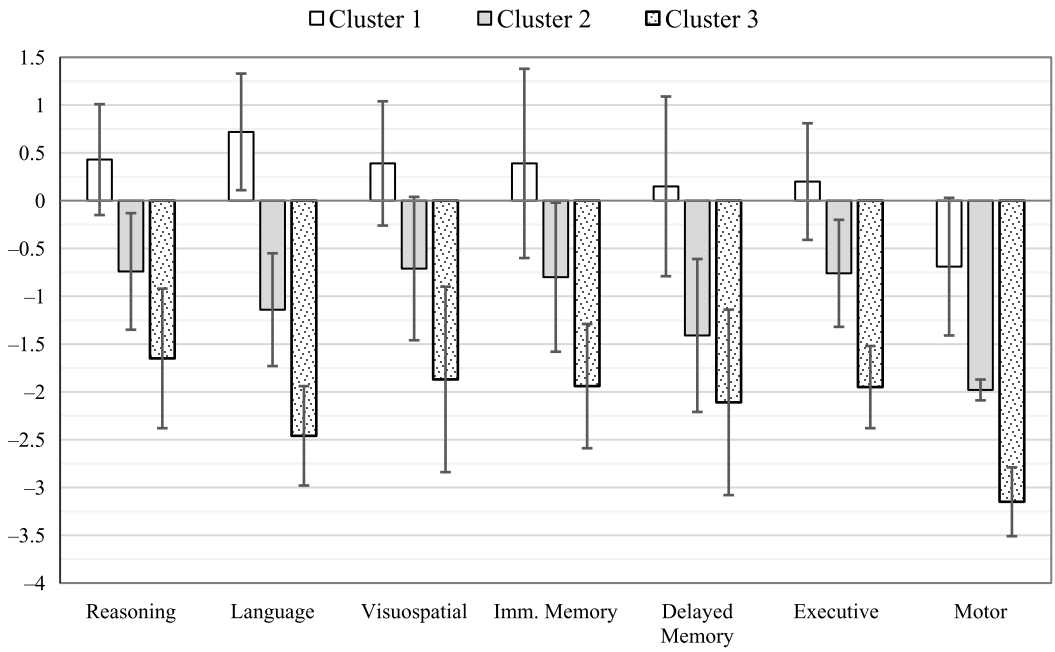


**Figure 2.** Mean cluster performance across cognitive domains.

difference compared to Cluster 2 in delayed memory ($p$ = .02). Within-cluster posthoc analyses revealed significantly lower scores in motor skills when compared to reasoning, language, visuospatial, immediate memory, delayed memory, and executive functioning ($p < .001$). Language performance trended in the direction of poorer performance in Cluster 3, particularly when compared to reasoning ($p$ =.01), immediate memory ($p$ = .05), and executive functioning ($p$ = .02).

## Cluster Characteristics

The three cluster groups were then compared across demographic (child age at evaluation, gender, racial background, and intellectual functioning) and clinical seizure variables (age of onset, duration of epilepsy, seizure frequency, number of AEDs, number of failed AEDS, seizure laterality, hippocampal sclerosis, and surgical candidacy) (see Table 4). Given the exploratory nature of the following analyses, alpha level was set to .05.

Full scale IQ (FSIQ) significantly differed by cluster solution ($p < .01$). Follow-up analyses revealed FSIQ in Cluster 1 (*WNL;* $M = 108.25$, $SD = 10.75$) was significantly higher than Cluster 2 (*Memory/*Motor; $M = 84.06$, $SD = 9.16$) and Cluster 3 (*Globally* Impaired; $M = 72.36$, $SD = 14.53$) ($p$ <.01). Additionally, patients in Cluster 2 also had significantly higher FSIQ than those patients in Cluster 3 ($p < .01$).

An examination of clinical seizure characteristics revealed significant differences associated with the number of failed AEDs across cluster solutions ($p$ = .03) indicating different levels of seizure control across cognitive phenotypes. Follow-up analyses demonstrated that patients in Cluster 3 (*Globally Impaired*) had significantly more failed AED trials than those in Cluster 2 (*Memory/Motor*) and Cluster 1 (*WNL*) ($p < .05$). Moreover, patients in Cluster 2 had significantly more failed AED trials than those patients in Cluster 1 ($p < .05$).

Results of the $\chi^2$ analysis examining the proportion of patients with left, right, and bilateral TLE across clusters was significant ($p$ = .02), identifying an association between cognitive phenotype and epilepsy lateralization patterns (Figure 3). Specifically, a greater proportion of patients with bilateral TLE were captured by Cluster 3 (*Globally Impaired*) than by the other two clusters ($p < .05$). There were no significant differences in the proportions of patients with left or right TLE across clusters. Finally, $\chi^2$ analysis examining the proportion of patients with and without hippocampal sclerosis by cluster solution was significant ($p$ = .04), indicating an association between cognitive phenotype and hippocampal sclerosis. Follow-up analyses revealed a significantly higher proportion of hippocampal sclerosis between Cluster 3 (*Globally Impaired*) and Cluster 1 (*WNL*) ($p$ = .04); however, statistical differences were not present between Clusters 1 and 2 and Clusters 2 and 3 ($p > .05$).

There were no significant differences across clusters with respect to age ($p$ = .77), gender ($p$ = .17), minority status ($p$ = .10), maternal education level ($p$ = .51), age of seizure onset ($p$ = .85), duration of life lived with epilepsy ($p$ = .44), seizure frequency ($p$ = .28), current number of AEDs ($p$ = .29), and candidacy for epilepsy surgery ($p$ = .20).

## DISCUSSION

The present study sought to add to a growing body of research on cognitive phenotypes in pediatric epilepsy by examining clusters of shared variability in neuropsychological

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**Table 4.** Demographic and clinical sample characteristics by cluster

| Domain | Cluster 1 (WNL) | Cluster 2 (Memory/Motor) | Cluster 3 (Globally Impaired) |
|---|---|---|---|
| Age (years) | 11.27 (3.34) | 12.68 (3.06) | 14.20 (2.49) |
| Gender *N* (% males) | 7 (58.0%) | 19 (53.0%) | 9 (83.0%) |
| Minority status *N* (%) | 3 (25.0%) | 21 (58.3%) | 7 (63.6%) |
| Maternal education | 3.15 (1.14) | 3.06 (.89) | 3.07 (1.19) |
| Full scale IQ** | 108.25 (10.75) | 84.06 (9.16) | 72.36 (14.53) |
| Age of seizure onset (years) | 6.32 (3.19) | 6.27 (4.14) | 6.05 (3.72) |
| Epilepsy duration (years) | 4.52 (4.42) | 5.71 (4.57) | 6.95 (4.20) |
| Seizure frequency | 3.00 (.95) | 3.00 (1.49) | 3.77 (1.10) |
| Current AEDs | 1.17 (.39) | 1.44 (.81) | 1.82 (.60) |
| Failed AEDs* | 1.25 (1.66) | 1.53 (1.59) | 2.82 (1.08) |
| Seizure laterality *N* (%)* | | | |
| Left | 5 (41.7%) | 19 (52.8%) | 5 (45.5%) |
| Right | 6 (50.0%) | 16 (44.4%) | 2 (18.1%) |
| Bilateral | 1 (8.3%) | 1 (2.8%) | 4 (36.4%) |
| Hippocampal sclerosis* | 1 (8.3%) | 9 (25.0%) | 5 (45.5%) |
| Surgical candidates *N* (%) | 3 (25.0%) | 20 (55.6%) | 6 (54.6%) |

*Note.* AED, antiepileptic drug; * $p < .05$, ** $p < .01$.

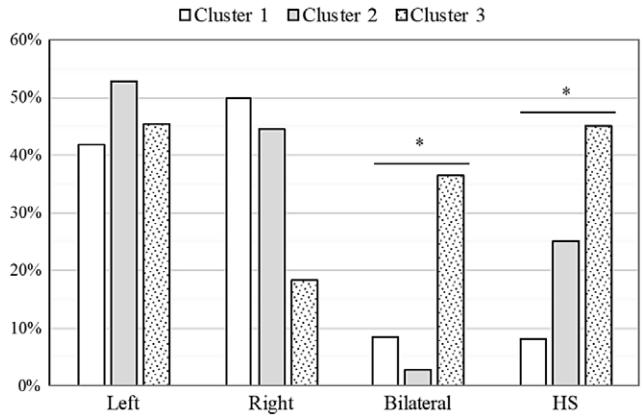


**Figure 3.** Seizure laterality and hippocampal sclerosis by cluster grouping. * $p < .05$.

performance in youth with TLE. Notably, when averaging across all cognitive domains (Figure 1), the overarching cognitive profile of our TLE sample was consistent with previous reports (Guimarães et al., 2007). However, by utilizing a cluster analytic approach, we identified a three-cluster solution that separated primarily by level of functioning and revealed patterns of performance that better elucidate our understanding of TLE in children and adolescents, particularly when considering the association of the clusters to demographic and clinical characteristics.

## Cognitive Phenotypes

Using a cluster analytic approach, three clinically meaningful cognitive phenotypes were identified in a sample of children and adolescents with TLE. Cluster 1 (20% of the sample) demonstrated the most intact profile, aside from a relative weakness on the motor factor. Cluster 1 performed significantly better (higher scores) on all neuropsychological domains compared to Clusters 2 and 3. In the context of broadly average functioning, Cluster 2 (61% of the sample) showed below average performance on the delayed verbal memory and motor domains. Cluster 3 (19% of the sample) was the most cognitively impaired group, and their motor skills were the most impacted. However, it is worth noting that mean domain scores for language, delayed memory, and motor factors fell in the impaired range, potentially indicating areas of greater impact. Compared to the other Clusters, Cluster 3 showed worse sample-wide performance in all cognitive domains, with the exception of similar verbal memory performance as Cluster 2.

In summary, our cluster solutions followed a stepwise pattern of severity ranging from intact (Cluster 1), intact with focal memory and motor weakness (Cluster 2), and global impairment (Cluster 3). Our three-cluster solution is consistent with past research exploring cognitive phenotypes in both pediatric (Hermann et al., 2016) and adult (Baxendale & Thompson, 2020; Elverman et al., 2019; Hermann et al., 2007; Reyes et al., 2020; Rodriguez-Cruces et al., 2018; Rodriguez-Cruces et al., 2020) epilepsy samples. Consistent with the above research, we also identified two similar phenotypes: an intact group and a globally impaired group. An interesting departure highlighted by the present study was that the majority of our sample (61%) demonstrated weaknesses on both motor and delayed verbal memory domains. This finding suggests that challenges with verbal memory and motor functioning may be a core feature of pediatric TLE, which may not be obvious at the group level due to high within-group variability. This may account for

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the inconsistencies reported in the literature on verbal memory outcomes in pediatric TLE. In contrast to adults, children with TLE offer an opportunity to study memory impairment absent of features typically seen in adults with epilepsy, such as decades of exposure to seizures, pharmaceutical agents, and morphological changes (Rzezak et al., 2014). While our findings further confirm that memory difficulty is a characteristic feature of TLE, the presence of additional cognitive impairments across the clusters sheds light on a potential developmental course that reflects network dysfunction beyond primary temporal regions.

## Clinical and Sociodemographic Characteristics Associated with Cognitive Phenotype

In terms of our second study aim, cluster membership was associated with clinical, but not sociodemographic sample characteristics. For instance, patients in Cluster 3 had more failed AED trials, a higher rate of bilateral seizure focus, a greater proportion of hippocampal sclerosis, and a lower FSIQ. Further exploration of clinical characteristics revealed a significant stepwise progression of failed AED trials as well as diminishing FSIQ across cluster membership.

While the proportion of hippocampal sclerosis was the highest in Cluster 3 (~46% of the sample), it did not differ from the proportion of hippocampal sclerosis in Cluster 2 (25%). However, a significant difference in the proportion of hippocampal sclerosis was present between Cluster 1 (8.3%) and Cluster 3. This finding is particularly interesting given that a previous study exploring the relationship between cognitive phenotypes and cortical volumes in pediatric epilepsy showed no volumetric differences across cognitive phenotypes and hippocampi (Hermann et al., 2016). However, it should be reiterated that the Hermann et al. (2016) did not include a memory factor as it did not discriminate controls from epilepsy patients. Also, their sample included a small proportion of TLE patients. These factors likely limit potential associations with memory-specific brain morphology in pediatric TLE.

Surprisingly, the remaining clinical and sociodemographic variables were unrelated to cluster membership. Given the relatively minimal differences in clinical seizure variables across clusters in the current study, it seems unlikely that our cluster solution represents distinct TLE disease entities. Instead, the cluster solutions may represent different aspects of disease progression, such as progression as a function of severity (Elverman et al., 2019), etiological differences (i.e., genetic, cortical malformations, acquired, etc.), or even frequency and/or severity of interictal abnormalities on EEG. In this regard, Cluster 3 (*Globally Impaired*) appears indicative of a more severe disease process given a higher proportion of hippocampal sclerosis, bilateral seizures, failed AED trials, and lower FSIQ. Thus, cognitive phenotypes in pediatric TLE may be driven to a greater extent by structural and/or functional brain changes than by other demographic or clinical variables.

## Implications for Network Dysfunction and Cognitive Phenotypes

The present study supports the notion that pediatric TLE is a network disorder impacting proximal and distal brain regions beyond the temporal lobe in the context of neurodevelopment (Paldino et al., 2017). For instance, imaging studies of children and adolescents with TLE have demonstrated regional cortical thinning of hippocampal and extra-hippocampal volumes (i.e., posterior cingulate, cerebellum, and inferior frontal gyrus) (Guimarães et al., 2007), reduced gray matter density in subcortical structures and cerebellum (Cormack et al., 2005), alterations to white matter tracts (Hildebrandt et al., 2008; Meng et al., 2010), functional alteration between fronto-temporal networks (Guimarães et al., 2007; Oyegbile et al., 2018), and large-scale network disruption (Widjaja et al., 2015). Notably, compared to adult onset TLE, childhood onset (<14 years) TLE is associated with a significant reduction in both regional (i.e., hippocampal volume) and generalized volumetric abnormalities, which has been found to accompany worse intellectual and memory outcomes (Hermann et al., 2002).

While the current study did not have access to neuroimaging data for quantitative analysis, studies examining neuroimaging correlates (structural and functional) with adult TLE phenotypes have shown that patients with generalized impairment have cortical abnormalities that are diffuse in nature, those with material-specific memory, language, and executive function deficits have focal alterations within the temporal lobes, and patients with intact cognition have brains comparable to healthy controls (Hermann et al., 2020; Reyes et al., 2019). Future studies will need to apply similar imaging methods to explore the neural correlates of cognitive phenotypes in pediatric TLE.

## Limitations and Future Directions

The results of the current study must be interpreted in the context of several limitations. First, all children and adolescents were referred for epilepsy treatment at a Level 4 Epilepsy Center, which may reflect a greater severity of epilepsy. As such, these findings may be especially useful for those in similar settings, but may not generalize to those children and adolescents with less severe forms of TLE. Second, due to missing data we were unable to include tests that captured visual memory and attention domains in the analysis. We acknowledge that omitting nonverbal memory and attention domains ultimately limits the generalizability of our findings. Including nonverbal memory as well as attention measures in investigating cognitive phenotypes in pediatric epilepsy should be a point of emphasis.

Third, measure selection and grouping into domains was based on clinical judgment. At times this posed challenges, as neuropsychological measures are not unitary measures of one specific construct of interest thereby complicating their placement in certain cognitive domains. For instance, we placed phonemic fluency in the Executive Function domain, due in part because it correlated strongly with the other measures

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within that domain; however, it also loads onto the Language domain. Given that these neuropsychological tests are potentially capturing constructs beyond the cognitive domain in which they were placed, it is possible that certain domain-specific effects were less apparent.

Fourth, while the current findings are reproducible, they rely heavily upon the statistical approach. As such, the present study requires replication from independent datasets utilizing similar neuropsychological measures. While the present study utilized a normative control group, future studies may also benefit from incorporating a typically developing control group to assist with more precise characterization of cognitive phenotypes in pediatric TLE. Fifth, given the high rates of psychiatric comorbidity (i.e., depression) in pediatric TLE, the current study cannot rule out the impact of mood. As recent work has demonstrated the importance of both cognitive and psychological factors in health-related quality of life in pediatric TLE (Schraegle & Titus, 2021), future research examining both factors in pediatric TLE should also be of interest. Sixth, while the number of failed AED trials is typically an appropriate proxy for seizure control, we are unable to account for additional reasons for AED discontinuation (i.e., behavioral, cognitive, and/or physical side effects), which may limit the precise interpretation of this variable. Finally, we did not have neuroimaging data on our patients and therefore could not explore brain-behavior relationships associated with each phenotype above and beyond the presence or absence of hippocampal sclerosis.

### Concluding Remarks

The present findings enhance our understanding of how cognitive function is differentially impacted in pediatric TLE and provides additional support for the use of cognitive taxonomies in pediatric epilepsy. We hypothesize that these cognitive phenotypes are emblematic of disease progression associated with epilepsy severity. Problems with delayed verbal memory and motor functioning may be intrinsic markers of temporo-frontal network dysfunction that then generalizes to large-scale network disruption as seen in the Globally Impaired Cluster. However, these hypotheses will need to be tested via prospective neuropsychological studies incorporating structural and resting-state MRI. Graph theory has also been shown to be a powerful tool to explore global and intrinsic network properties of cognitive phenotypes in adult TLE (Hermann et al., 2020) and may be applicable in pediatrics. Recently, in the adult TLE literature, alternative approaches to phenotype derivation (e.g., actuarial vs. empirical) have been explored with identified phenotypes appearing robust across methods (Reyes et al., 2020). An actuarial or clinically driven approach to phenotype construction, given its accessibility, may be a useful direction for future pediatric research.

The present study provides preliminary insights into cognitive domains particularly vulnerable to the disease process in pediatric TLE as well as clinical and demographic markers associated with these phenotypes. Given the high prevalence of pediatric TLE and the high probability for neurosurgical intervention, it is hoped that this work will provide helpful clues to assist with early detection and, ultimately, more precise management. More specifically, a better understanding of distinct neuropsychological phenotypes may facilitate research into other aspects of these more homogeneous phenotypic groups, such as identifying developmental trajectory and associated clinical, neuroanatomical, psychosocial characteristics. This, in turn, has the hope of improving treatment and quality of life outcomes.

## ETHICAL 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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## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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