








RESEARCH ARTICLE

Cognitive phenotypes in frontal lobe epilepsy

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Abstract

Objective: Neuropsychological profiles are heterogeneous both across and within epilepsy syndromes, but especially in frontal lobe epilepsy (FLE), which has complex semiology and epileptogenicity. This study aimed to characterize the cognitive heterogeneity within FLE by identifying cognitive phenotypes and determining their demographic and clinical characteristics.

Method: One hundred and six patients (age 16–66; 44% female) with FLE completed comprehensive neuropsychological testing, including measures within five cognitive domains: language, attention, executive function, processing speed, and verbal/visual learning. Patients were categorized into one of four phenotypes based on the number of impaired domains. Patterns of domain impairment and clinical and demographic characteristics were examined across phenotypes.

Results: Twenty-five percent of patients met criteria for the *Generalized Phenotype* (impairment in at least four domains), 20% met criteria for the *Tri-Domain Phenotype* (impairment in three domains), 36% met criteria for the *Domain-Specific Phenotype* (impairment in one or two domains), and 19% met criteria for the *Intact Phenotype* (no impairment). Language was the most common domain-specific impairment, followed by attention, executive function, and processing speed. In contrast, learning was the least impacted cognitive domain. The *Generalized Phenotype* had fewer years of education compared to the *Intact Phenotype*, but otherwise, there was no differentiation between phenotypes in demographic and clinical variables. However, qualitative analysis suggested that the *Generalized* and *Tri-Domain Phenotypes* had a more widespread area of epileptogenicity, whereas the *Intact Phenotype* most frequently had seizures limited to the lateral frontal region.

Significance: This study identified four cognitive phenotypes in FLE that were largely indistinguishable in clinical and demographic features, aside from education and extent of epileptogenic zone. These findings enhance our appreciation of the cognitive heterogeneity within FLE and provide additional support for the development and use of cognitive taxonomies in epilepsy.

KEYWORDS

cognition, epilepsy, frontal lobe epilepsy, neuropsychology, phenotypes

1 | INTRODUCTION

Frontal lobe epilepsy (FLE) accounts for ~20%–30% of focal epilepsies¹ and has been associated with a number of neuropsychological impairments. The cognitive domains most commonly impacted in FLE include attention, working memory, processing speed, executive function, and fine motor coordination.^{2,3} Inefficient learning and retrieval deficits have also been observed and hypothesized to result from disruptions in frontally mediated cognitive functions.⁴ Recent research has also found specific deficits in social cognition, such as difficulties with facial affect recognition and humor appreciation.^{5,6}

The extent and severity of neuropsychological deficits have been shown to be related to seizure lateralization/localization and propagation, duration of disease, and age at epilepsy onset.^{3,7–10} However, these associations are inconsistent across studies, and the generalizability of results is limited by small sample sizes. Given that FLE is commonly characterized by complex semiology and epileptogenicity, with significant variability in neuroanatomical abnormalities,^{11,12} the heterogeneity of FLE has presented a unique challenge in characterizing and treating this focal epilepsy, as well as delineating more specific cognitive profiles.¹³

Understanding cognitive phenotypes has gained attention in recent years as a way to offer a more structured framework to understand the variability in cognitive functions within and across epilepsy syndromes.¹⁴ This is particularly important given the role that neuropsychological testing has in lateralizing and localizing brain dysfunction and predicting risk for cognitive decline in surgical patients.¹⁵ In fact, the International League Against Epilepsy (ILAE) and the International Neuropsychological Society (INS) recently adopted a Memorandum of Understanding (MOU) initiative that includes developing a taxonomy of cognitive disorders in epilepsy.¹⁶ Thus far, the majority of this research has been applied to temporal lobe epilepsy (TLE), in which studies have consistently found three to four cognitive phenotypes specific to TLE,^{17–19} with distinct patterns of structural, functional, and network abnormalities.^{20–23} However, work extending this cognitive phenotype framework beyond TLE is lacking.

The purpose of the present study was to determine whether unique cognitive phenotypes exist in FLE, which is examined here for the first time. We also investigated the degree to which identified cognitive phenotypes were

Key Points

- Four unique cognitive phenotypes were found in FLE that ranged from generalized cognitive impairment to cognitively intact profiles.
- Language was the most prominent domain-specific impairment in FLE, followed by attention, executive function, and processing speed.
- More widespread epileptogenicity was associated with phenotypes involving greater cognitive impairment.
- These cognitive phenotypes offer a classification taxonomy for the diverse cognitive deficits that result from FLE.

associated with distinct demographic or clinical characteristics, including the location and extent of the epileptogenic zone and imaging findings, to better understand the underlying mechanisms contributing to the variability in cognitive deficits found in patients with FLE.

2 | METHODS

2.1 | Participants

This retrospective study included data from an institutional review board–approved neuropsychology registry that contains clinical data for patients 16 years or older with pharmacoresistant epilepsy who were being considered for epilepsy surgery at the Cleveland Clinic. All patients had a diagnosis of FLE based on the International League Against Epilepsy (ILAE) criteria²⁴ as determined by a board-certified neurologist with expertise in epileptology. To be included in this study, patients were required to have complete neuropsychological data (i.e., three measures within each cognitive domain as described below). The final sample included 106 patients 16–66 years of age (mean = 33.99, SD = 12.79), 44% of whom were female. Approximately 95% of patients self-identified as White, 4% as Black/African American, and 1% as Asian. Only one patient self-identified as Hispanic/Latinx. Mean age at seizure onset was 16.06 years (SD = 12.52), and mean duration of epilepsy was 17.04 years (SD = 12.14).

2.2 | Neuropsychological measures

As part of a pre-surgical workup, all patients completed a comprehensive neuropsychological evaluation. Five cognitive domains were included in this study (language, learning, attention/working memory, processing speed, and executive function), and each domain was comprised of three separate cognitive measures. All cognitive measures included in this study are common, well-researched clinical measures used in the United States, with high reliability and validity. Scores were standardized based on demographically corrected normative data; the individual cognitive measures and normative data used are listed in the Table S1. All norm-referenced standardized scores were converted into T-scores (mean = 50, SD = 10) for interpretability.

Of note, letter fluency is often considered a measure of executive function; however, in our sample, letter fluency had higher correlations with language measures (Boston Naming Test: $r = .514$, $p < .001$; Vocabulary subtest: $r = .403$, $p < .001$) than with executive function measures (Trail Making Test Part B: $r = .430$, $p < .001$; Matrix Reasoning subtest: $r = .441$, $p < .001$; Wisconsin Card Sorting Test–Errors: $r = .223$, $p = .028$). Therefore, letter fluency was included in the language domain.

Because prior literature has not found consistent differences between verbal and visual memory modalities in FLE,²⁵ our learning and delayed recall scores combined visual and verbal memory tests. Furthermore, the learning and recall scores were found to be significantly correlated (Logical Memory 1 & 2: $r = .87$, $p < .001$; Verbal Paired Associates 1 & 2: $r = .82$, $p < .001$; Family Pictures 1 & 2: $r = .933$, $p < .001$) and because inefficient learning is most implicated in FLE⁴ and learning/encoding scores greatly impact recall scores, we determined that using the learning scores had the most empirical support.

2.3 | Cognitive phenotyping

Each cognitive domain was considered impaired if a minimum of two of the three cognitive tests in that domain were more than 1 standard deviation (SD) below the normative mean (i.e., a T-score < 40, 16th percentile). This cut-off criterion is similar to that used in the aging literature,²⁶ and has been applied recently to an epilepsy population.²⁷

The number of impaired cognitive domains and the pattern of impairment were examined to determine phenotypes. The phenotypes were categorized ultimately based on the total number of domains impaired, because no single or specific cognitive domain combination appeared to represent a significant portion of patients.

Thus, based on the data, four phenotypes emerged; the *Generalized Phenotype* was defined as having impairment in at least four of the five cognitive domains, the *Tri-Domain Phenotype* was defined as having impairment in three of the five cognitive domains, the *Domain-Specific Phenotype* was defined as having impairment in one or two of the five cognitive domains (of this group, 60% were impaired in one domain and 40% were impaired in two domains), and the *Intact Phenotype* included patients with no impairment in any of the cognitive domains.

2.4 | Clinical characteristics

Age at seizure onset, duration of epilepsy, location and extent of the epileptogenic zone, and imaging findings were examined. Seizure side and imaging findings were based on the results of preoperative investigations, including video–electroencephalography (EEG) monitoring and clinical magnetic resonance imaging (MRI) results, and expert consensus during a patient management conference. T-1 and T2-weighted MRI images were examined, and the following imaging findings were coded: focal cortical dysplasia (FCD), vascular malformation, tumor, encephalomalacia, multiple lesions, non-lesional, and other. For the purpose of statistical comparison, we combined tumor, encephalomalacia, and multiple lesions into a “lesion” group. Language dominance was determined by results of language lateralization procedures (Wada or functional MRI) for 61 patients, and in cases where language dominance was not evaluated ($n = 45$), patients were considered to have left language dominance. Of the 61 patients with language lateralization data, 49 patients had left-sided language dominance, 5 had right-sided language dominance, and 7 patients had bilateral language representation. Patients with bilateral language representation were excluded from the language dominance analysis.

The extent of the epileptogenic zone was inferred based on the eventual resection regions, as this reflected the combined consensus of likely epileptogenic zone by the surgical team based on extensive pre-surgical workup. A three-dimensional (3D) tool was employed to visualize postoperative MRI images in two orthogonal planes to determine anatomic localization. Images were coded by neurosurgery residents (E.K., N.S., and S.S.) with peer review when the resection location(s) was less clear. Postoperative MRI results were available for 86 patients included in the final sample and were used to identify whether the following frontal lobe locations were involved in the patient's resection: medial frontal (MF; $n = 45$), lateral frontal (LF; $n = 57$), orbital frontal (OF; $n = 32$), and supplementary motor area (SMA; $n = 25$). The extent of the epileptogenic

zone was coded based on the number of regions that were involved in the resection (i.e., all four regions, three regions, two regions, or one region).

2.5 | Statistical analyses

Analysis of covariance (ANCOVA) was conducted to compare cognitive domains across phenotypes with covariates of age, education, and sex. Analysis of variance (ANOVA) and chi-square tests were used to examine differences in demographic and clinical variables across identified cognitive phenotypes. When results from the ANOVA or ANCOVA were significant, group contrasts were assessed using post hoc pairwise tests with Bonferroni correction (error rate = alpha level of .05).

3 | RESULTS

3.1 | Pattern of performance across phenotypes

Twenty-five percent of the patients met criteria for the *Generalized Phenotype*, 20% met criteria for the *Tri-Domain Phenotype*, 36% met criteria for the *Domain-Specific Phenotype*, and 19% met criteria for the *Intact Phenotype*. [Table 1A](#) outlines the percent of impairment across cognitive domains within each phenotype and [Figure 1](#) visually depicts these domain impairments ([Figure 2](#)).

3.2 | Neuropsychological performance across cognitive phenotypes

For each domain, a composite score was created by averaging the T-scores across tests within each domain to further examine the common patterns of cognitive impairment across phenotypes. [Table 1A](#) includes group comparisons on these composite scores across cognitive phenotypes, and [Table 1B](#) includes group contrasts. There were group differences across all composite scores. Overall, the *Generalized Phenotype* demonstrated worse performance across all cognitive domains compared to the *Intact Phenotype* and the *Domain-Specific Phenotype*. Relative to the *Tri-Domain Phenotype*, the *Generalized Phenotype* showed a lower composite score on learning. The *Tri-Domain Phenotype* group also demonstrated lower composite scores across all domains relative to the *Intact Phenotype*. Relative to the *Domain-Specific Phenotype*, the *Tri-Domain Phenotype* showed lower composite scores in the domains of attention and processing speed. Finally, the *Domain-Specific Phenotype* showed a lower composite

score in the domain of language relative to the *Intact Phenotype*.

3.3 | Demographic and clinical characteristics

[Table 2](#) includes differences in demographic and clinical variables across phenotypes. There were differences in age, education, and age at seizure onset across phenotypes. However, group contrasts revealed only fewer years of education in the *Generalized Phenotype* compared to the *Intact Phenotype* ($p = .023$); the other group contrasts were not significant. There were no group differences in sex, handedness, duration of epilepsy, seizure side (left vs right or dominant vs nondominant), or imaging findings. Analysis evaluating dominance was also repeated using only the 61 patients with confirmed language lateralization to ensure that our aforementioned coding method of this variable did not impact results. The study results did not change when analyses were restricted to this smaller cohort.

Interpretation of epileptogenicity data was limited due to heterogeneity of FLE location, variability across phenotypes, and a limited sample size. When the data were examined by site and extent of epileptogenicity, there were no significant differences across phenotypes. However, qualitative observation of epileptogenic regions involved across phenotypes (see [Table 2](#)) shows a clear pattern that patients with greater cognitive impairment had a higher number of regions involved in epileptogenicity. In fact, follow-up t test comparing mean number of regions of epileptogenicity in the *Generalized Phenotype* ($M = 2.71$) compared to the *Intact Phenotype* ($M = 2.07$) trended toward significance: $t(33) = -1.97, p = .058$. The frequencies included in [Table 3](#) further highlight how the *Generalized* and *Tri-Domain Phenotypes* typically had a more extensive epileptogenic zone. For example, 86% of the *Generalized* and *Tri-Domain Phenotype* patients had two or more regions involved in epileptogenic zone, whereas only 58% of patients within the *Intact Phenotype* showed this pattern. Epileptogenicity in the lateral frontal region only was most common in the *Intact Phenotype* (33%), whereas this was a low occurring frequency in the *Generalized* and *Tri-Domain Phenotypes* (5%–6%).

4 | DISCUSSION

This is the first study to identify specific underlying cognitive phenotypes to characterize the diverse neuropsychological presentations of patients with FLE. Based on patterns of cognitive impairment in our patients with

TABLE 1 (A) Neuropsychological performance across phenotypes; (B) Group contrast across domain composite

| (A) | | | | | | | |
|--------------------|--|---------------------------------------|------------------------------|--------------------------------------|-----------------------------|----------------------------------|------------------------------|
| | Generalized | Tri-domain profile | Domain-specific | Intact | | | |
| n | 26 (25%) | 22 (20%) | 38 (36%) | 20 (19%) | | | |
| | M (% impaired within individual phenotypes) | | | | | | |
| | | | | | ANCOVA | p-Value | η_p^2 |
| Language | 32.21 (92%) | 36.15 (73%) | 40.19 (63%) | 48.82 (0%) | 19.83 | <.001 | .390 |
| Learning | 35.02 (81%) | 42.03 (46%) | 46.89 (16%) | 51.75 (0%) | 29.65 | <.001 | .481 |
| Attention | 35.07 (92%) | 38.29 (68%) | 44.43 (24%) | 51.74 (0%) | 25.57 | <.001 | .444 |
| Processing Speed | 34.85 (85%) | 40.45 (50%) | 43.87 (21%) | 47.89 (0%) | 16.77 | <.001 | .344 |
| Executive Function | 34.54 (89%) | 38.15 (64%) | 47.13 (16%) | 50.58 (0%) | 37.97 | <.001 | .543 |
| (B) | | | | | | | |
| | Generalized vs Tri-domain | Generalized vs Domain-specific | Generalized vs intact | Tri-domain vs Domain-specific | Tri-domain vs Intact | Domain-specific vs Intact | |
| Language | .162 | <.001 | <.001 | .188 | <.001 | .002 | |
| Learning | <.001 | <.001 | <.001 | .073 | <.001 | .041 | |
| Attention | .741 | <.001 | <.001 | <.001 | <.001 | .014 | |
| Processing speed | .034 | <.001 | <.001 | .122 | .003 | .455 | |
| Executive function | .036 | <.001 | <.001 | <.001 | <.001 | .355 | |

Note: Means represent composite *T*-scores. Covariates: age, education, and sex. All *p*-values are adjusted for multiple comparisons with Bonferroni correction. Bold signifies significant difference between groups at *p* < .01.

Abbreviations: ANCOVA, analysis of covariance; η_p^2 , partial eta-squared.

pharmacoresistant FLE, four unique cognitive phenotypes were identified; 25% of patients fell into the *Generalized Phenotype*, 20% in the *Tri-Domain Phenotype*, 36% in the *Domain-Specific Phenotype*, and 19% in the *Intact Phenotype*. Of interest, demographic and clinical factors were mostly indistinguishable between these phenotypes, but the phenotypes may have neurobiological correlates related to epileptogenic foci. Because neurobiological features have consistently differentiated phenotypes in other epilepsy syndromes,^{21,23,28} future efforts identifying patterns of cognitive impairment to specific neurobiological correlates will have important implications for clinical care.

The identification of unique cognitive phenotypes is consistent with prior literature that has found distinct cognitive phenotypes in TLE, with similar “no impairment,” “generalized impairment,” and “domain-specific” groups.^{17–19} These findings suggest that although certain phenotypic characteristics may be more prevalent in FLE than in temporal lobe epilepsy (TLE), there are many

patterns that are shared across syndromes, indicating that certain phenotypes may be driven by a diversity of risk and resilience factors that remain to be determined, and are not necessarily syndrome specific; this is consistent with the conclusions from neuroimaging research that has demonstrated shared neuroanatomic abnormalities across epilepsy syndromes^{29,30} and other research on cognitive phenotypes.²⁰ Twenty percent of patients also fell into a “mixed profile” group in our FLE sample. This finding is likely due to several factors: (1) FLE is generally considered to have more heterogeneity in cognitive sequelae and epileptogenic zones than TLE^{2,3}; (2) because of this increased heterogeneity, this study included five different cognitive domains, whereas previous cognitive phenotype studies have typically included three to four cognitive domains in the analyses; and (3) neuropsychological measures used to assess frontally mediated cognitive abilities are less process-pure, likely resulting in more overlap between cognitive measures. The latter point may also be related to the types of processing (e.g., amodal and

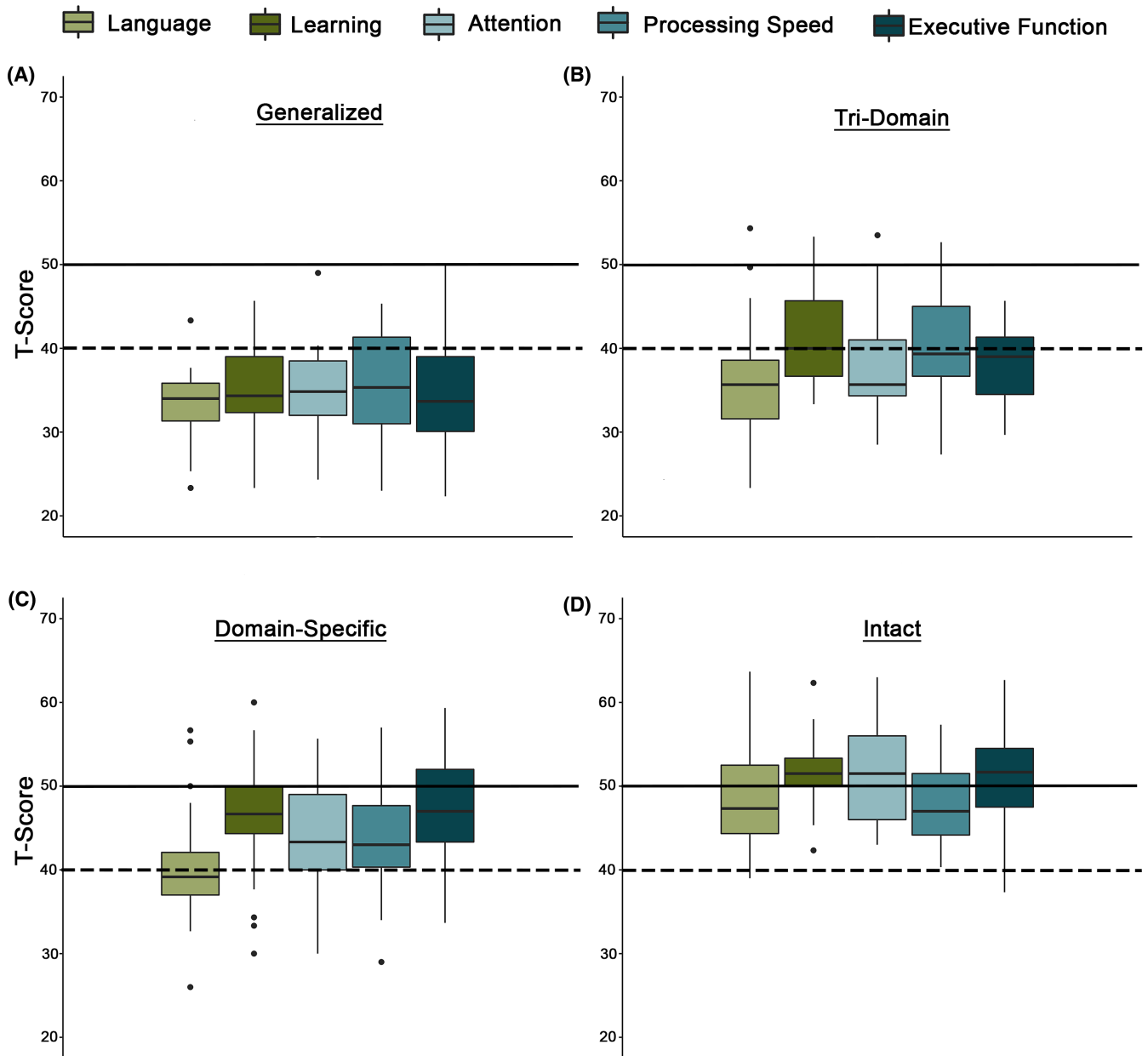


FIGURE 1 Distribution of composite scores across cognitive domains for each cognitive phenotype. Composite scores were calculated as the average T-score across all tests within a domain. The solid line represents the mean T-score and the dashed line represents one standard deviation below the mean of a normative sample

top-down regulation) of the frontal lobe^{31,32} that may result in more diffuse cognitive dysfunction when damaged.

Despite fronto-subcortical deficits being most associated with FLE,^{2,3} we found that language was the most prominent domain-specific impairment in our sample and significantly differentiated the *Domain-Specific Phenotype* from the *Intact Phenotype*. However, from a functional neuroanatomy perspective, this finding is not surprising. Broca's area is represented in the pars opercularis and pars triangularis of the left inferior frontal gyrus, and functional MRI (fMRI) and transcranial magnetic stimulation studies have shown that language sites

often extend beyond Broca's area and the temporal region, covering a wide area of the left lateral frontal cortex.^{33,34}

This extensive network also includes white matter tracts interconnecting the frontal nodes.³⁵ Numerous studies have shown that spontaneous speech and verbal fluency are impacted following resections involving the left dorso-lateral or SMA/premotor areas,^{13,36} further highlighting the important language functions of these areas.

Alterations in executive function and attention/working memory were the second most impacted cognitive domains in our study, followed by processing speed. This finding is consistent with prior literature on FLE

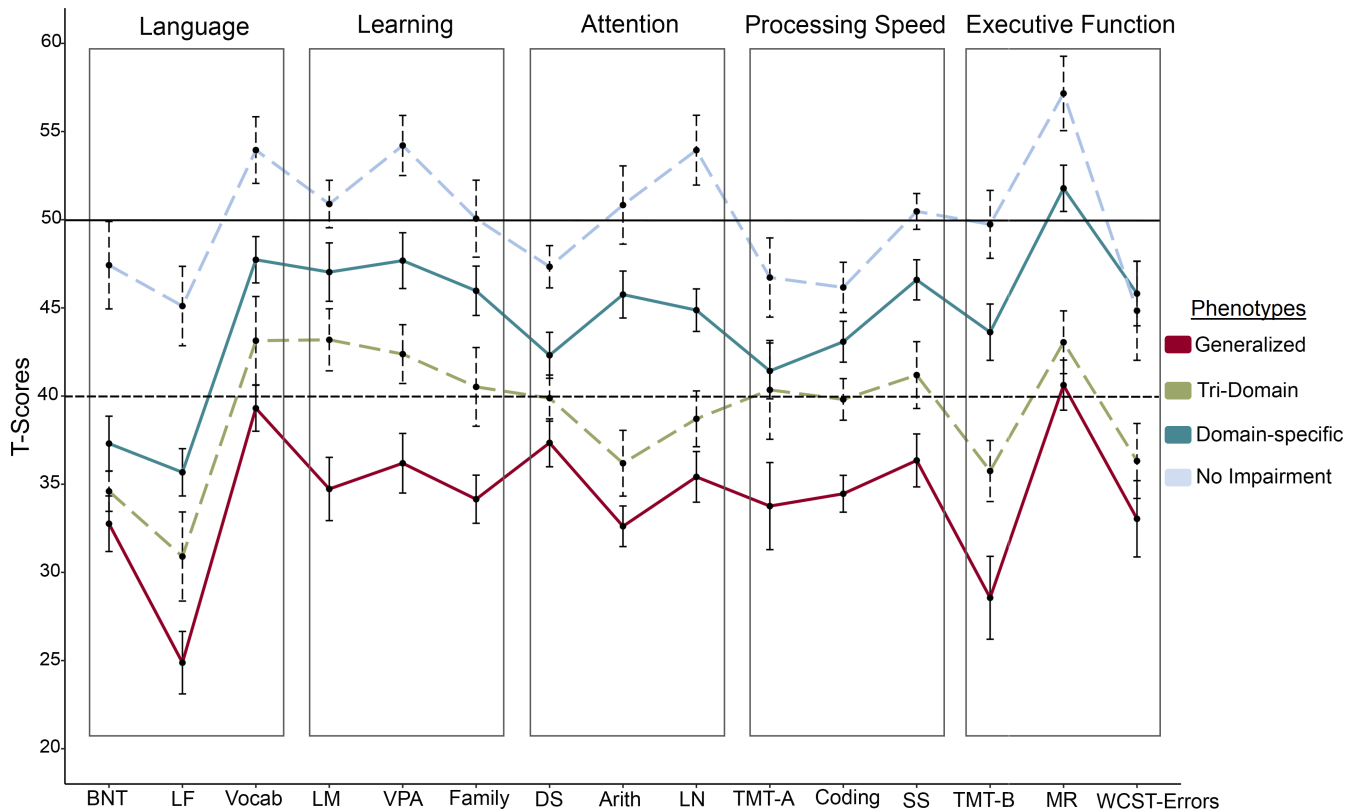


FIGURE 2 Distribution of impairment within and across cognitive domains for each cognitive phenotype. The solid line represents the mean and the dashed line represents impairment at one standard deviation below the mean of a healthy normative sample. Arith, arithmetic; BNT, Boston Naming Test; DS, digit span; LF, letter fluency; LM, logical memory; LN, letter-number; MR, matrix reasoning; SS, symbol search; TMT-A: Trail Making Test Part A; TMT-B, Trail Making Test Part B; Vocab, vocabulary; VPA, verbal paired associates; WCST-Errors, Wisconsin Card Sorting Test total errors

patients³ and our understanding of frontal lobe functions.³⁷ Moreover, reductions in attention and processing speed appeared to be the main cognitive domains that differentiated the *Tri-Domain Phenotype* from the *Domain-Specific Phenotype*. Both attention and processing speed are uniquely associated with fronto-subcortical networks^{32,38,39} that are commonly impacted in FLE, and future research would benefit from examining whether these cognitive phenotypes are associated with specific patterns of white matter integrity in FLE.

The learning domain was the least implicated across phenotypes, suggesting that the role of encoding is often preserved in FLE, relative to the other cognitive domains assessed. This finding is in contrast to TLE phenotypes in which memory impairment is usually a unique feature.¹⁹ Although research has also found inefficient encoding and retrieval deficits in FLE,⁴ these deficits are typically mild. Patients with FLE tend to recruit more widely distributed brain regions to support memory functions, particularly within the frontal lobe contralateral to the seizure onset; thereby creating an effective compensatory mechanism for memory.²⁵ However, learning impairment was a unique characteristic of the *Generalized Phenotype*

and significantly differentiated the *Generalized Phenotype* from the *Tri-Domain Phenotype*.

Lower education was associated with greater cognitive impairment, with education significantly differentiating between the *Intact Phenotype* and *Generalized Phenotype*. Other clinical and demographic variables did not differentiate significantly between cognitive phenotypes; however, this might be due to limited sample sizes across phenotypes. It is possible that current age and age at seizure onset might uniquely contribute to cognitive phenotypes based on positive ANOVA findings, although follow-up group contrasts were nonsignificant.

Interpretation of epileptogenicity data was also limited by variability and small sample sizes across phenotypes. However, there was a clear trend showing that the phenotypes associated with greater cognitive impairment had more widespread seizure involvement, whereas those with seizures restricted to the lateral frontal region appeared to have a lower risk of cognitive impairment as this was most commonly found in the *Intact Phenotype*. These findings are similar to research on TLE phenotypes that have found unique neuroanatomic correlates and patterns of white matter integrity underlying various cognitive phenotypes,

TABLE 2 Demographics and clinical variables across groups

| | Generalized | Tri-domain profile | Domain-specific | Intact | ANOVA | p-Value |
|---|--------------|--------------------|-----------------|--------------|----------|-------------|
| n | 26 | 22 | 38 | 20 | | |
| Age (years) | 31.63 (10.9) | 36.51 (11.9) | 30.95 (12.9) | 40.09 (13.7) | 2.97 | .035 |
| Education (years) | 11.96 (1.58) | 12.95 (2.42) | 13.16 (1.83) | 13.70 (2.20) | 3.26 | .025 |
| Age at seizure onset (years) | 14.21 (12.6) | 18.95 (13.6) | 12.65 (11.2) | 21.78 (11.7) | 2.77 | .046 |
| Duration (years) | 17.62 (11.9) | 16.19 (11.3) | 17.09 (11.9) | 17.09 (14.5) | .049 | .985 |
| | | | | | χ^2 | p-Value |
| Sex | M: 16 (62%) | M: 9 (28%) | M: 19 (50%) | M: 16 (80%) | 7.59 | .055 |
| Handedness: L/R/A | 5/21/0 | 2/19/1 | 1/35/2 | 2/17/1 | 6.08 | .415 |
| Seizure side | L: 10 (45%) | L: 11 (55%) | L: 19 (51%) | L: 8 (42%) | .842 | .939 |
| Seizure Dominance: | D: 10 (40%) | D: 10 (53%) | D: 15 (43%) | D: 7 (35%) | 1.33 | .723 |
| Seizure site ^a | | | | | | |
| All regions | 6 | 3 | 4 | 0 | | |
| Involving LF | 12 | 11 | 22 | 12 | .906 | .824 |
| Involving MF | 9 | 11 | 18 | 7 | 2.55 | .446 |
| Involving OF | 7 | 4 | 16 | 5 | 1.83 | .608 |
| Involving SMA | 5 | 6 | 8 | 6 | 1.21 | .751 |
| Extent of epileptogenicity ^a | | | | | | |
| All regions | 6 | 3 | 4 | 0 | 5.77 | .124 |
| Involving three regions | 5 | 7 | 12 | 6 | 1.42 | .701 |
| Involving two regions | 8 | 4 | 10 | 3 | 2.08 | .557 |
| Involving one region | 2 | 3 | 8 | 5 | 3.13 | .373 |
| Mean regions involved | 2.71 | 2.59 | 2.35 | 2.07 | | |
| Imaging findings | | | | | | |
| FCD | 12 | 9 | 20 | 10 | .837 | .841 |
| Vascular malformation | 4 | 2 | 8 | 3 | 1.52 | .677 |
| Lesion ^b | 2 | 1 | 1 | 4 | 6.05 | .109 |
| Nonlesional | 2 | 1 | 0 | 0 | 4.16 | .245 |
| Other | 2 | 1 | 3 | 0 | 1.81 | .613 |

Note: Bold signifies significant differences between group at $p > .05$.

Standard deviations are presented inside the parentheses.

Abbreviations: A, ambidextrous; D, dominant; FCD, focal cortical dysplasia; L, left; LF, lateral frontal; M, male; MF, medial frontal; OF, orbitofrontal; R, right; SMA, supplementary motor area.

^an = 86 patients with data regarding epileptogenic zone.

^bIncludes tumors, encephalomalacia, multiple lesions.

with greater pathology being associated with greater cognitive impairment.^{20,21,28}

There are several limitations to this study. Test selection and cognitive domain inclusion were determined based on the clinical neuropsychological battery administered. A subset of patients were excluded because they were not administered every test included in this study; this was primarily due to the long period of data collection and changing clinical practices of the neuropsychology team over time. A visuospatial domain was not included as three neuropsychological measures were not administered in this domain. A single cutoff of 1 SD below the

mean was used across multiple tests with varying degrees of reliability, and other clinical centers may use different cognitive tests. However, by including average T-scores for each cognitive test and domain composite, we hope to increase the generalization of our results to similar test measures not included in the present analyses. Although the tests used to represent each cognitive domain were thoughtfully selected, we recognize that many tests assess multiple cognitive domains and our findings relate to how we categorized specific cognitive tests. Furthermore, our sample included patients with pharmacoresistant epilepsy who were being considered for surgical intervention

TABLE 3 Site(s) of epileptogenicity across phenotypes^a

| | Generalized | Tri-domain profile | Domain-specific | Intact |
|-------------|-------------|--------------------|-----------------|---------|
| All regions | 6 (30%) | 3 (18%) | 4 (13%) | 0 (0%) |
| LF/MF/OF | 5 (25%) | 4 (24%) | 9 (29%) | 3 (25%) |
| LF/MF/SMA | 0 (0%) | 3 (18%) | 3 (10%) | 2 (17%) |
| LF/MF | 2 (10%) | 3 (18%) | 2 (6%) | 0 (0%) |
| LF/OF | 1 (5%) | 0 (0%) | 4 (13%) | 0 (0%) |
| LF/SMA | 3 (15%) | 0 (0%) | 0 (0%) | 2 (17%) |
| MF/SMA | 1 (5%) | 1 (6%) | 2 (6%) | 1 (8%) |
| LF only | 1 (5%) | 1 (6%) | 4 (13%) | 4 (33%) |
| SMA only | 1 (5%) | 2 (12%) | 3 (10%) | 0 (0%) |
| Total | 20 | 17 | 31 | 12 |

Abbreviations: LF, lateral frontal; MF, medial frontal; OF, orbitofrontal; SMA, supplementary motor area.

^aCombinations with fewer than five patients were removed from this table.

within the context of a specialized epilepsy center. This allowed for a highly selective patient sample that had extensive seizure workup; however, it does limit the generalizability of the sample. Data regarding epileptogenic zone were determined by subsequent surgical resection, although these resections were based on extensive pre-surgical workup, typically including scalp and stereotactic EEG, MRI, positron emission tomography (PET), single proton emission computed tomography (SPECT), and/or magnetoencephalography (MEG), it is possible that the resection included areas beyond the epileptogenic zone or that regions of epileptogenicity were missed in patients who did not achieve seizure freedom. Due to variability in sites of epileptogenicity across phenotypes, formal analyses were limited. Future research examining structural, diffusion, and functional imaging data will be useful in increasing our understanding of the underlying neuro-anatomic mechanisms associated with each FLE cognitive phenotype. Although the primary purpose of this study was to characterize the cognitive profiles most commonly seen in FLE, we recognize that a number of etiological factors need to be considered in future research to further understand these phenotypes. For example, frequency of seizures, history of generalized tonic-clonic seizures, and antiseizure medications were not included in this study due to incomplete data, but these factors are associated with frontally mediated cognitive processes and could be contributing to the phenotypes.

In conclusion, this study demonstrated a clinical approach to identifying four distinct cognitive phenotypes in FLE. These phenotypes improve our understanding of the type and extent of cognitive deficits seen across FLE syndromes. In addition, this study provides a more comprehensive classification framework from which to make clinical impressions, decisions, and prediction models

and supports the ILAE and INS initiative of creating a consensus-based cognitive taxonomy for epilepsy.¹⁶

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CONFLICT OF INTEREST

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. None of the authors have any conflicts of interest to disclose.

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