# Establishing the cross-cultural applicability of a harmonized approach to cognitive diagnostics in epilepsy: Initial results of the IC-CoDE in a Spanish-speaking sample

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## Abstract

**Objective:** To evaluate the cross-culture application of the International Classification of Cognitive Disorders in Epilepsy (IC-CoDE) to a cohort of Spanish-speaking patients with temporal lobe epilepsy (TLE) living in the U.S.

**Methods:** Eighty-four Spanish-speaking patients with TLE completed neuropsychological measures of memory, language, executive function, visuospatial functioning, and attention/ processing speed as part of the Neuropsychological Screening Battery for Hispanics (NeSBHIS). The contribution of demographic and clinical variables to cognitive performance was evaluated. A sensitivity analysis was conducted by examining the base rates of impairment across several impairment thresholds. The IC-CoDE taxonomy was then applied and the base rate of cognitive

phenotypes for each cutoff was calculated. The distribution of phenotypes was compared to the published IC-CoDE taxonomy data, which utilized a large, multicenter cohort of English-speaking patients with TLE.

**Results:** Across the different impairment cutoffs, memory was the most impaired cognitive domain, with impairments in list learning ranging from 50–78%. Application of the IC-CoDE taxonomy utilizing a −1.5SD cutoff revealed an Intact cognitive profile in 47.6% of patients, Single Domain impairment in 23.8% of patients, Bi-Domain impairment in 14.3% of patients, and Generalized impairment in 14.3% of the sample. This distribution was comparable to the phenotype distribution observed in the IC-CoDE validation sample.

**Significance:** We demonstrate a similar pattern and distribution of cognitive phenotypes in a Spanish-speaking epilepsy cohort compared to an English-speaking sample. This suggests stability in the underlying phenotypes associated with TLE and applicability of the IC-CoDE for guiding cognitive diagnostics in epilepsy research that can be applied to culturally and linguistically diverse samples.

## Introduction

Epilepsy is the fourth most common neurological disorder, following migraine, dementia, and stroke, affecting approximately 50 million people worldwide and accounting for 0.5% of the global burden of disease[1, 2]. Cognitive dysfunction is a highly prevalent comorbidity in epilepsy, impacting individuals' quality of life[3–5], and leading to poor psychosocial outcomes[6], including lower education[7] and occupational attainment[8]. Given this, understanding the cognitive profiles across and within epilepsy syndromes has been an ongoing research inquiry for over a century. Importantly, a plethora of studies have demonstrated that in the focal epilepsies cognitive dysfunction is less circumscribed than hypothesized by the classical lesion model [e.g., memory impairments in temporal lobe epilepsy (TLE)] and that significant cognitive heterogeneity exists within epilepsy syndromes (for review see Hermann et al.[9]).

In efforts to better understand this heterogeneity, investigations have focused on identifying patterns of cognitive deficits or *cognitive phenotypes*[9]. Across studies in focal epilepsy, three-to-four phenotypes have been identified with stable and reproducible cognitive patterns including a group with generalized impairment, a group with focal deficits, and a third group with intact profiles[9–18]. This phenotype approach has proven useful for establishing links between distinct neural abnormalities and patterns of cognitive impairment[11, 12, 14, 16] and predicting cognitive progression[10] and postoperative outcomes[18]. Despite an extensive literature focused on the neuropsychological syndromes of the epilepsies and the recent advances in cognitive phenotyping, there are no evidence-based criteria for guiding cognitive diagnostics in epilepsy research.

To address this critical gap in epilepsy research, the International Classification of Cognitive Disorders in Epilepsy (IC-CoDE) was developed as a joint initiative between the International League Against Epilepsy (ILAE) Neuropsychology Task Force and the International Neuropsychological Society (for more information see Norman et al.[19]). The IC-CoDE is a consensus-based classification system that incorporates a five-domain

cognitive model (i.e., language, memory, executive function, attention/processing speed, and visuospatial abilities) and provides an operational definition of impairment and an expert consensus-based diagnostic approach[19, 20]. In the first proof-of-principle study, the IC-CoDE taxonomy was found to be stable and reproducible across six independent epilepsy cohorts of adults with TLE (N=1,409) across the United States, and the distribution of phenotypes were similar to previous findings based on data-driven approaches[20], demonstrating its potential utility as a diagnostic tool for research. An important advantage of the IC-CoDE is that it was intentionally developed to be applied to diverse patient cohorts regardless of the tests and normative data used. This approach is critical for the cross-cultural application of such taxonomy to linguistically and culturally diverse samples that have been traditionally underrepresented in epilepsy research.

Spanish-speaking individuals represent the fastest growing linguistically diverse population living in the U.S.[21] Importantly, Hispanic/Latinx individuals are disproportionally impacted by the epilepsies[22], with Hispanic adults having a twofold higher incidence of epilepsy relative to their Non-Hispanic White counterparts[23]. Furthermore, Hispanic/ Latinx individuals are impacted by disparities in access to care, epilepsy treatments, and epilepsy outcomes[7, 24, 25]. Disparities in access to neuropsychological services is further exacerbated by the dearth of neuropsychological resources (e.g., culturally-adapted tests, appropriate norms) available for evaluating Spanish-speaking patients[26, 27] and the lack of validated diagnostic frameworks[28]. In epilepsy specifically, Spanish-speaking populations have been underrepresented in all areas of research with only a few studies examining the clinical utility of neuropsychological tests in this population[29–32]. As the Spanish-speaking population in the U.S. continues to increase, validating neuropsychological frameworks will be critical to address disparities in access to care and advance epilepsy research. To this end, the IC-CoDE initiative aims to apply a consensus-based taxonomy to Spanish-speaking cohorts and examine factors that should be considered when applying the IC-CoDE to non-English speaking patients in order to determine its generalizability and international applicability and to facilitate global research efforts in epilepsy.

In this study, we apply the IC-CoDE to a sample of Spanish-speaking adults with TLE living in the U.S. who completed the Neuropsychological Screening Battery for Hispanics (NeSBHIS) as part of their epilepsy surgery workup. The NeSBHIS was developed to address the dearth of neuropsychological tests available for Spanish-speakers[26, 33], and its clinical utility in epilepsy evaluations has been examined in several epilepsy samples[29–32]. Barr et al., demonstrated that the test battery was sensitive in detecting impairments in cognitive processes commonly observed in patients with epilepsy[29]. In a follow-up study, Bender et al. examined the construct validity of the NeSBHIS, providing evidence for the battery's stable structure and validity as a cognitive assessment tool for epilepsy[30]. Other studies have demonstrated its predictive validity in determining seizure laterality[31, 32]. Here, we also examine the rates of impairment at the individual test level considering several impairment cut-offs and discuss demographic and cultural factors that are important to consider when applying the IC-CoDE.

# Methods

## Participants

Data were acquired from a consecutive series of 84 adults (18 years or older) with TLE who had completed a neuropsychological evaluation at the NYU-Langone Comprehensive Epilepsy Center between 2000 and 2012. All participants self-identified as "Hispanic" or "Latino/a/x", emigrated from Spanish-speaking countries, and requested a Spanish-language assessment. A diagnosis of TLE was confirmed in each case through continuous video/EEG (VEEG) monitoring in accordance with the criteria defined by the ILAE[34].

## Procedures and measures

The present study was performed according to the policies of the Institutional Review Board of NYU School of Medicine. Data were collected as part of an IRB-approved data registry. Patients completed an inpatient presurgical evaluation, however, all patients were on antiseizure medication (ASM) at the time of testing per testing protocol. Patients were tested individually in one or two sessions totaling approximately 90 minutes. All tests were administered and scored by bilingual (Spanish-English) examiners. The NeSBHIS was designed to evaluate the domains of language, memory, visuospatial functions, mental control (i.e., attention and concentration), and psychomotor speed[26, 33]. Most measures in the battery were adapted from subtests used internationally by the World Health Organization.

The following measures were selected from the NeSBHIS battery to assess the cognitive domains of language, memory, executive function, visuospatial, and attention and processing speed as outlined by the IC-CoDE taxonomy[20]. Supplementary Table 1 contains a full description of the tests. Language ability included naming measured with the Pontón-Satz Boston Naming Test (P-S BNT)[35] and verbal fluency measured with the Controlled Oral Word Association Test[36] (COWAT; letters F-A-S). Memory was evaluated with the delayed scores of the WHO-UCLA Auditory Verbal Learning Test (AVLT)[37] and the Rey Osterrieth Complex Figure Test (ROCFT)[38]. Only the delayed scores were used in this study to enable a direct comparison with the original IC-CoDE sample. The Taylor scoring system was used to score and evaluate the accuracy of the designs produced for the ROCFT[39]. Attention was measured with the Digit Span subtest from the Escala de Inteligencia Wechsler para Adultos (EIWA)[40]. Processing speed was measured with the Digit Symbol subtest from the EIWA[40] and Color Trails condition 1[41]. Measures of executive function included set-shifting evaluated with Color Trails condition 2[41] and abstract reasoning evaluated with the Raven's Standard Progressive Matrices[42]. Lastly, visuospatial abilities were measured with the Block Design Subtest from the EIWA[40] and the copy condition of the ROCFT. All raw scores were converted to z-scores adjusting for sex, age, and education using the normative data in Pontón et al.[26]

## Test Impairment Analysis

Rates of impairment at the individual test level were calculated to compare the cognitive processes/tests that were most sensitive in this sample. Z-scores were classified as impaired or not impaired using −1.0, −1.5, and −2.0 standard deviation (SD) cutoffs. Although

the IC-CoDE validation study only included −1.0SD and −1.5SD cutoffs, the diagnostic validity study of the NeSBHIS with an epilepsy sample utilized a −2.0SD impairment cutoff[29], so we added this as an additional cutoff for purposes of this study. Base rates were calculated by dividing the number of patients classified as impaired on an individual test to the total number of patients who completed the measure.

### Cognitive Phenotype Analyses

The IC-CoDE taxonomy was applied to patients who had at least two tests per cognitive domain as outlined in McDonald et al.[20] This resulted in a final sample of 63 patients (75% of the initial sample). The cognitive phenotypes were generated using all three impairment cutoffs (i.e., −1.0, −1.5, and −2.0). There were two tests available for language, memory, executive function, and visuospatial abilities and three tests available for attention and processing speed. To be impaired in a domain, at least two tests per domain had to meet the selected cut-off. The total number of impaired domains was used to characterize the cognitive phenotype for each patient. As described in McDonald et al.[20], Single-Domain is defined as impaired in one cognitive domain, Bi-Domain is defined as impaired in two domains, Generalized is defined as impaired in three domains or more domains, and Intact is defined as no impairment in any cognitive domain.

### Statistical analyses

Spearman rho correlations were conducted to examine the association between test scores, education, and age. Chi-square goodness of fit tests were used to compare the proportion of patients in each cognitive phenotype in this sample to the IC-CoDE validation sample at each impairment threshold. Analysis of variance (ANOVA) and Fisher's Exact (FE) tests were conducted to compare clinical, demographic, and cognitive data across the cognitive phenotypes. When results from the ANOVA were significant, group contrasts were assessed using post-hoc pairwise tests with Bonferroni correction. Multiple comparisons were corrected using Benjamini-Hochberg false discovery rate.[43]

### Data Availability Statement

Authors have full access to all study data and take full responsibility for the data, the conduct of the research, the analyses and interpretation of the data, and the right to publish all data.

## Results

### Patient characteristics

Eighty-four patients were included in the study. Demographic and clinical characteristics are presented on Table 1. Patients ranged in age from 18 to 72 years, with the majority being female, right-handed, and 58.3% having an education of a high school degree equivalent or more. A majority of the sample can be categorized as originating from Mexico (7.1%), South America (Ecuador: 10.7% and Colombia: 8.3%), or the Caribbean (Dominican Republic: 13.1% and Puerto Rico: 9.5%). This distribution is consistent with the population trends among Hispanic immigrants residing in Northeastern United States. Regarding clinical characteristics, age of epilepsy onset ranged from before age 1 to 36 years, with

a range of duration of disease from less than one year to 62 years. Approximately 74% of the patients were on ASM polytherapy. The most common pathology was mesial temporal sclerosis (MTS) and on average patients reported approximately 10 seizures per month (range 0.17–30).

### Contribution of demographic variables to cognitive performance

Table 2 displays the Spearman rho correlations between age and education and the raw and z-scores across the neuropsychological measures. For the raw scores, older age was associated with poorer performance on processing speed (Digit Symbol) and visuospatial abilities (ROCFT Copy), and fewer years of education was associated with poorer performance across all neuropsychological measures. Although raw scores were corrected for age, education, and sex, given the small sample sizes of the normative data (N=300), we were interested in examining whether residual effects of these demographic variables remained after applying the normative adjustments. Given the small sample size, scores that were greater than three SDs below or above the mean of the patient group were removed for these analyses. This resulted in the removal of five scores across all measures. Fewer years of education was associated with worse performance on naming (P-S BNT), simple attention (Digit Span), and processing speed (Color Trails 1). Figure 1 illustrates scatterplots of the significant correlations. Given the impact of education on the cognitive scores, as a post-hoc analysis we divided patients into low (i.e., <10 years) and high education (i.e.,  10 years). Approximately 73% of the sample were categorized as having high education. For the low education group, education was not associated with performance on the P-S BNT ($\rho$=.250, p=.288), Digit Span ($\rho$ =.390, p=.099), or Color Trails 1 ($\rho$=.435, p=.092). For the high education group, lower scores on the P-S BNT ($\rho$=.432, p<.001) and Color Trails 1 ($\rho$=.406, p=.003) were associated with fewer years of education.

### Impairment across measures

Figure 2 demonstrates the pattern of impairment across measures using the −1.0SD, −1.5SD, and −2SD cutoffs. Across the cutoffs, cognitive impairment was primarily observed in delayed word recall (AVLT-Delayed; 50%−78.3%), visual memory (ROCFT Memory; 31.7%−65.4%), naming (P-S BNT; 55.1% −64.3%), processing speed (Color Trails 1; 48.3% −63.8%) and set-shifting (Color Trails 2; 39%−51.5%).

Given the effects of education on P-S BNT, Digit Span, and Color Trails 1, we also examined differences in the rates of impairment between the high and low education groups for the  −1.5SD cutoff. The rates of impairment for the PS-BNT (FE=5.31, p=.036) were significantly different between the low education (80%) and high education group (50.8%)

As a post-hoc analysis, we also compared the rates of impairment between males and females for the −1.5 cutoff and found differences in AVLT Delayed (FE= 7.127, p= .010; males: 74.1% vs females: 42.9%) and Digit Span (FE= 5.857, p=.022; males: 41.7% vs females: 16.4%) with males demonstrating higher rates of impairment.

### Cognitive phenotypes using the IC-CoDE taxonomy

The distribution of cognitive phenotypes for each cutoff and the distribution of the IC-CoDE validation sample are shown in Figure 3. Using a −1.0 SD cutoff, 34.9% of the sample demonstrated Generalized impairment with three or more domains impaired; 17.5% demonstrated a Bi-Domain phenotype; 22.2% showed a Single-Domain pattern; and 25.4% showed an Intact profile with no impairments across any of the domains. Using a −1.5 SD cutoff, a Generalized phenotype was observed in 14.3% of the sample; 14.3% of the sample demonstrated a Bi-Domain phenotype; 23.8% showed a Single-Domain phenotype; and 47.6% showed an Intact profile. Using a −2 SD cutoff, there were no patients that demonstrated a Generalized phenotype; 6.3% showed a Bi-Domain phenotype; 25.4% demonstrated a Single-Domain phenotype; and 68.3% showed an Intact profile. Post-hoc analyses revealed no differences across phenotype distribution between the low and high education groups for the −1.5 SD cutoff (FE=1.396, p=.652).

### Comparison to the English-speaking validation sample

Supplementary Table 2 includes differences in comparisons between the weighted averages (i.e., across study sites) of demographic characteristics (i.e., age and education) and clinical characteristics (i.e., onset and duration) of the English-speaking validation sample to our Spanish-speaking sample. There were differences in education, age of onset, and duration, with the Spanish-speaking sample having fewer years of education, earlier age of seizure onset, and shorter duration of disease. There were no differences in age. Given that the −1.5SD cutoff was the suggested cutoff proposed by McDonald et al.[20], the phenotype distribution for this cutoff was compared to the English-speaking validation sample. The Spanish-speaking sample demonstrated comparable rates across all the phenotype groups: Generalized phenotype ($\chi^2$= 1.218, p=.269), Bi-Domain ($\chi^2$= .005, p=.946), Single-Domain ($\chi^2$= .125, p=.696), and Intact ($\chi^2$= .139, p=.709). The −1.5SD cutoff was selected for subsequent analyses. Furthermore, the distribution of phenotypes was similar to the distribution reported for data-driven approaches (i.e., 21.1% generalized, 30.6% focal, and 43% intact)[9, 20].

### Demographic, clinical, and cognitive characteristics across phenotypes

Table 3 shows the demographic and clinical characteristics across the cognitive phenotypes. There were differences in the sex distribution across phenotypes, with the Single-Domain group having a lower proportion of females. There were no other differences in clinical and demographic variables.

## Discussion

Here, we provide results on the first cross-cultural application of the IC-CoDE in a Spanish-speaking sample of adults with TLE. We also demonstrate for the first time, the rates and distribution of cognitive phenotypes in this Hispanic cohort, which has been a burgeoning interest in epilepsy and other neurological disorders more broadly. Spanish-speaking individuals represent the fastest growing linguistically diverse population in the U.S., and there is a critical need to increase the representation of this population in epilepsy research. Utilizing the NeSBHIS, a neuropsychological battery that has been

validated across several epilepsy cohorts, we demonstrate that the pattern of test impairment and the distribution of IC-CoDE-derived phenotypes are similar to previous published IC-CoDE findings[20]. We also test different impairment cut-offs and demonstrate the importance of exploring demographic factors that may be critical to consider when applying the IC-CoDE to culturally and linguistically diverse samples. Thus, our findings can serve as a model methodology for similar efforts in other languages. Importantly, the IC-CoDE provides a consensus-based cognitive taxonomic system that facilitates research focused on characterizing the presence and patterns of cognitive impairment within and across epilepsy syndromes and examining the underlying neurobiological, clinical, social, and cultural factors associated with the different phenotypes. Unlike other neurological disorders that share a common language for cognitive disorders thus facilitating harmonized research approaches, a common cognitive classification system in epilepsy had yet to be established. Therefore, the IC-CoDE provides a new approach for global communication and collaboration where researchers can pool large datasets across international samples even when different tests were administered in different languages.

### Considerations of normative data

The dearth of neuropsychological instruments and normative data for diverse populations has been one of the most significant challenges and limitations to the field of neuropsychology for both clinical practice and research[28]. Several attempts have been made to develop normative data that provide comprehensive demographic adjustments for racial/ethnic and linguistically diverse groups. The NeSBHIS is one of the most frequently used normative datasets available for Spanish-speaking individuals, providing adjustments for age, education, and sex[26]. In our sample, years of education was associated with performance across all 11 cognitive measures, and age was associated with performance on two of the 11 measures (i.e., Digit Symbol and ROCFT Copy). After applying the NeSBHIS norms to the sample, the effects of age were corrected; however, the effects of education were corrected for only 8 of the 11 measures. Despite normative adjustments, fewer years of education continued to be associated with lower scores on naming, simple attention, and processing speed. Post-hoc analyses revealed a differential impact of education on cognitive scores based on high (i.e., 10 years) and low (i.e., <10 years) education, however, no clear pattern emerged. Cross-cultural studies have noted that in culturally and linguistically diverse populations, the relationship between education and neuropsychological performance is curvilinear rather than linear[44]. Thus, exploring different norms, including samples with a wide range of educational levels (e. g., low literacy) and including more than two neuropsychological measures per domain may provide greater insight into the effects of sociodemographic versus clinical factors on performance.

Importantly, when applying normative data to diverse cohorts, it is important to examine the demographic characteristics of the normative sample. The NeSBHIS normative sample was predominantly (i.e., 62%) Mexican-born Hispanics compared to our current sample which is 7.1% Mexican-born. Therefore, the NeSBHIS standardization sample may not accurately represent our sample introducing intracultural variability and potentially explaining the limited adjustments of the normative data for education. Another possibility is variability in quality of education across the cohort given the heterogeneity in country

of origin which could be associated with differences in the education systems across countries. This limitation has been previously reported in other studies with epilepsy cohorts[30, 31]. Despite these limitations, applying other population norms to interpret test performance has been shown to lead to an overestimation of impairment across numerous of neuropsychological tests[45]. This is particularly important for the application of the IC-CoDE given that the diagnostic classification is based on impairment across a range of tests. Therefore, to reduce false-positives, we advocate for the use of population-specific demographically-adjusted norms when applying the IC-CoDE to culturally and linguistically diverse populations. Furthermore, reporting the contribution of demographic characteristics to cognitive performance will provide transparency on the generalizability of the results and highlight potential contributors to differences in cognitive phenotype rates across populations when using the IC-CoDE.

### Patterns of impairment

Similar to previous IC-CoDE results[20] and findings from the cognitive phenotype literature[9], our cohort demonstrated impairments across all cognitive domains examined. Widespread cognitive deficits have been a consistent finding in the TLE literature[19] and have been shown to be associated with widespread brain abnormalities, including cortical thinning, reduction in white matter integrity, and network disruption[19, 46, 47]. However, to the best of our knowledge, the are no neuroimaging studies in Spanish-speaking patients living in the U.S. and, given that these patients present with a host of other health-related risk factors impacting brain health, investigating the brain abnormities associated with the extent of cognitive impairment is warranted.

In this cohort, memory was the most commonly impaired domain, diverging from the results of the IC-CoDE validation sample in which language was the most commonly impaired domain[20]. In our sample, more than half of the sample was impaired in list learning and visual memory demonstrating higher rates of impairment relative to the IC-CoDE sample. Although visual memory tests have been shown to have greater variability in their lateralizing effects and lower sensitivity in detecting medial temporal lobe dysfunction[48–51], Smith et al.[31] demonstrated that the ROCFT Delay scores were significantly different between Spanish-speaking patients with right and left hemisphere seizure onset and it was a significant contributor to their lateralizing predictive model. Thus, it is possible that the sensitivity of visual memory tests is influenced by cultural and linguistic factors that have not been well studied in the neuropsychology of epilepsy. This highlights the potential subtle differences in cognitive profile characterization across linguistically diverse groups that may be due to differences in the underlying etiologies, the tests administered, the impact of culture and language on the cognitive constructs examined, or other non-epilepsy factors.

When examining impairment at the individual test level, P-S BNT had the highest impairment rates ranging from 55.1% to 64.3% depending on the cutoff used. This pattern is similar to the IC-CoDE validation sample, where we report impairment rates ranging from 53% to 67% for the BNT for −1SD and −1.5SD cutoffs, respectively. Furthermore, in the original diagnostic validation study of the NeSBHIS in epilepsy, Barr et al. [29] reported a 41.4% impairment rate for the P-S BNT using a −2SD cutoff in a heterogenous sample

of Hispanic patients with epilepsy. Naming deficits are commonly reported in patients with TLE[52]; however, rates of impairment with the BNT are thought to be inflated due to limitations of the test that have been globally recognized and that we highlight in McDonald et al.[20], including outdated stimuli, skewed distribution, and overestimation of impairment in non-native English speakers. Despite Ponton et al.'s[35] important attempts to ensure cultural relevance and appropriateness of the original BNT in Spanish-speaking populations, in cultures with languages comprised of regional dialects (e.g., Spanish in Hispanics), it is highly unlikely to capture all existing correct synonymous options for a test item in confrontation naming test like the BNT[27]. Thus, it is possible that dialectical differences among our sample are also contributing to the high impairment rates on the P-S BNT. As efforts to apply the IC-CoDE to linguistically diverse samples continue, it is important to take into account the limitation of naming tests and their impact on phenotype classification and to consider other naming tests that have been shown to be more culturally sensitive such as the Multilingual Naming Test (MINT)[53].

## Application of the IC-CoDE

The application of the IC-CoDE to this sample yielded a similar pattern of phenotypes compared to the IC-CoDE validation sample[20] and other findings using data-driven approaches[10, 13–15]. This suggests that there is stability in the overall pattern of phenotypes identified across cohorts, and now across languages. Importantly, the −1.5SD cutoff suggested by McDonald et al.[20] was defined as an *optimal* cutoff given that it yielded a distribution of phenotypes that was consistent across the different epilepsy centers and approximated the distribution of phenotypes described in the epilepsy literature. This cutoff also appeared to be the optimal cutoff in our Spanish-speaking sample. Notably, the −2SD may have been too stringent given that this cutoff did not capture any generalized impairment. Although the distribution of the phenotypes was similar across both studies, there were within phenotype differences. For example, as noted above memory was the most commonly impaired domain within the Single domain phenotype across all three cutoffs followed by language. The opposite was observed for the original IC-CoDE where language was the most impaired domain followed by memory. For the Bi-Domain phenotype, the distribution of the subgroups for the Spanish sample was restricted to fewer subgroups, whereas the original IC-CoDE sample had six subgroups within the Bi-Domain phenotype for both cutoffs. The differences in the Bi-Domain distribution across studies may be due to a number of factors, including variability in the test batteries, the norms used, and specific patient characteristics. As other sites validate the IC-CoDE, further variability within the Single and Bi-Domain phenotypes groups may emerge which may allow for the examination of factors that are specific to the study versus those are more related to the disorder.

Notably, there were differences in demographic and clinical variables between the Spanish-speaking sample and the IC-CoDE validation sample, specifically the Spanish-speaking sample had fewer years of education and greater disease burden (i.e., earlier age of onset), which have been associated with greater cognitive impairment[9]. Interestingly, in our sample there were no differences in demographic or disease variables among the phenotype groups. The lack of differences in side of seizure onset across the phenotypes has been a consistent finding in the phenotype literature[9], which has been attributed to the network

nature of the focal epilepsies leading to more distributed cognitive and behavioral deficits. Although there has been some variability across the clinical profiles associated with different phenotypes[12–15], a general pattern has emerged with patients with Generalized impairment demonstrating greater disease burden (e.g., longer duration of epilepsy, higher rates of mesial temporal lobe sclerosis, higher seizure frequency, and greater number of ASM), while those with an Intact phenotype have greater years of education and shorter disease duration. It is possible that given our small sample sizes across phenotypes we were not able to capture more subtle differences in clinical and demographic characteristics across the phenotypes. Another possibility is that given the limited research in this population, it is unclear whether classic epilepsy characteristics are associated with the extent of cognitive impairment as research on this topic has been generalized from less ethnically, racially, culturally, and linguistically diverse cohorts. This is particularly important as Hispanic patients are impacted by epilepsy and non-epilepsy related health disparities, and identifying the unique factors associated with cognitive deficits in this population can better inform research and clinical care.

### Limitations and Future Directions

Despite this study being the first attempt at the cross-cultural application of the IC-CoDE, there are several limitations to address in future research. First, our sample was relatively small compared to the IC-CoDE validation sample, which can impact the base rates of cognitive phenotypes and differences in clinical profiles. Given that the NeSBHIS is a widely used tool in epilepsy, the IC-CoDE initiative can provide the infrastructure to develop multi-center collaborations aimed at replicating the current findings and investigating specific cognitive profiles across centers (e.g., single domain memory impairment). Second, there are limitations to the normative data used (e.g., relatively small normative sample), and education continued to be a significant contributor to cognitive performance despite normative adjustment for age, education, and sex. Education being stratified into two educational groups (i.e., < or > 10 years) may be contributing to the limited adjustments for education. Other normative approaches such as regression-based norms or normative data with more refined educational groups can potentially address this issue. Importantly, studies examining the utility of other comprehensive norms available for Spanish-speaking individuals collected in the U.S.[54] including the NP-NUMBRS norms[45] or that have been collected in countries in Latin America including the collection of norms published in the NeuroRehabilitation 2015 Special Issue "Commonly used Neuropsychological Tests for Spanish Speakers: Normative Data from Latin America"[55] are needed. Specifically, it will be important to examine whether U.S. or Latin America collected norms are the most appropriate for Spanish-speaking immigrant populations living in the U.S. Further, studies examining the impact of acculturation and other factors known to impact neuropsychological performance such years living in the U.S. on norms and battery selection and phenotype distribution are warranted. Third, we included two tests per domain given that the NeSBHIS battery has a limited number of tests. Although consensus on the optimal number of tests to include per domain within the IC-CoDE classification system has yet to be stablished, the more tests included the greater probability of finding impairment at the domain level. However, it will be critical to systematically examine the optimal number of tests and which measures are the most sensitive to impairment in this population with a wider range of

neuropsychological tests. Further, we only included delayed scores to probe for memory performance in order to follow the same approach as the original IC-CoDE sample and subsequent application in epilepsy[17] and other disorders[56, 57], however, the learning trials particularly for verbal memory tests can provide additional information that could further identify more defined single-domain phenotypes (e.g., learning impaired versus amnesic phenotype). Lastly, as noted above the NeSBHIS battery provides a limited number of tests per domain (e.g., two measures of language, one measure of verbal memory, two measures of visuospatial abilities). Although the measures included for language, processing speed, and executive function were similar to the original IC-CoDE study, there was less variability in measures of memory and visuospatial abilities. Specifically, the memory domain may have benefited from the inclusion of other measures such as prose recall and associative memory. Given that the NeSBHIS is currently the only battery that has been empirically validated in patients with epilepsy, the clinical utility of other Spanish neuropsychological batteries with a wider range of tests must be first validated in patients with epilepsy in order to deploy their clinical and research use. Despite these limitations, we demonstrate a similar pattern of impairment and phenotypes compared to the IC-CoDE validation sample, suggesting stability of this diagnostic framework that can inform its international applicability.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding:

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**Key points**

- We provide results on the first cross-cultural application of the IC-CoDE in a Spanish-speaking sample of adults with temporal lobe epilepsy.

- Across the different impairment cutoffs, memory was the most impaired cognitive domain.

- The rates and pattern of cognitive phenotypes in this Spanish-speaking sample was similar to previous phenotype findings.

- These findings demonstrate that the IC-CoDE approach can be applied to culturally and linguistically diverse samples
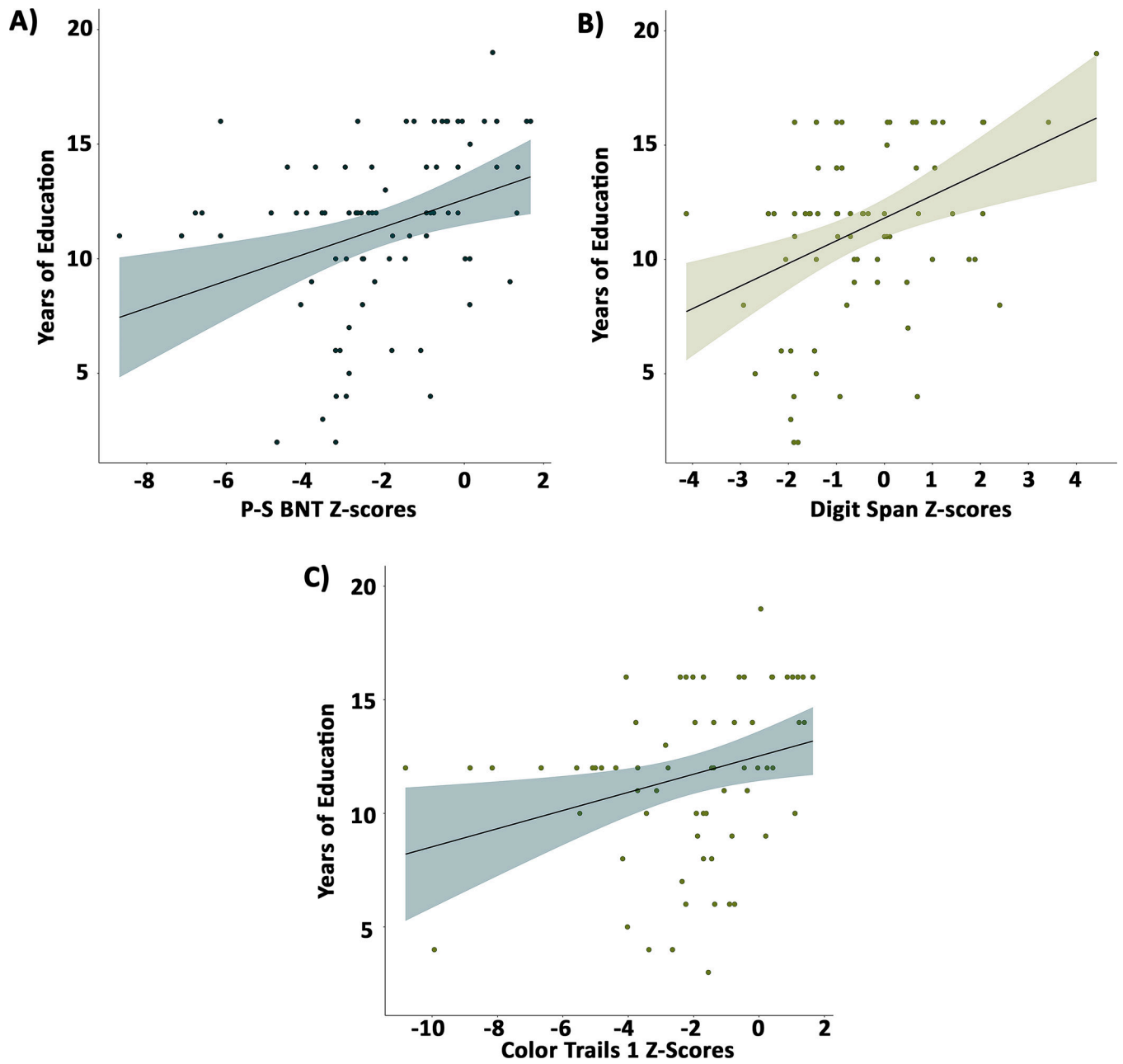
**Figure 1. Association between education and cognitive scores.**

Greater years of education was associated with better performance in (A) naming, (B) simple attention, and (C) processing speed. P-S BNT: Pontón-Satz-Boston Naming Test
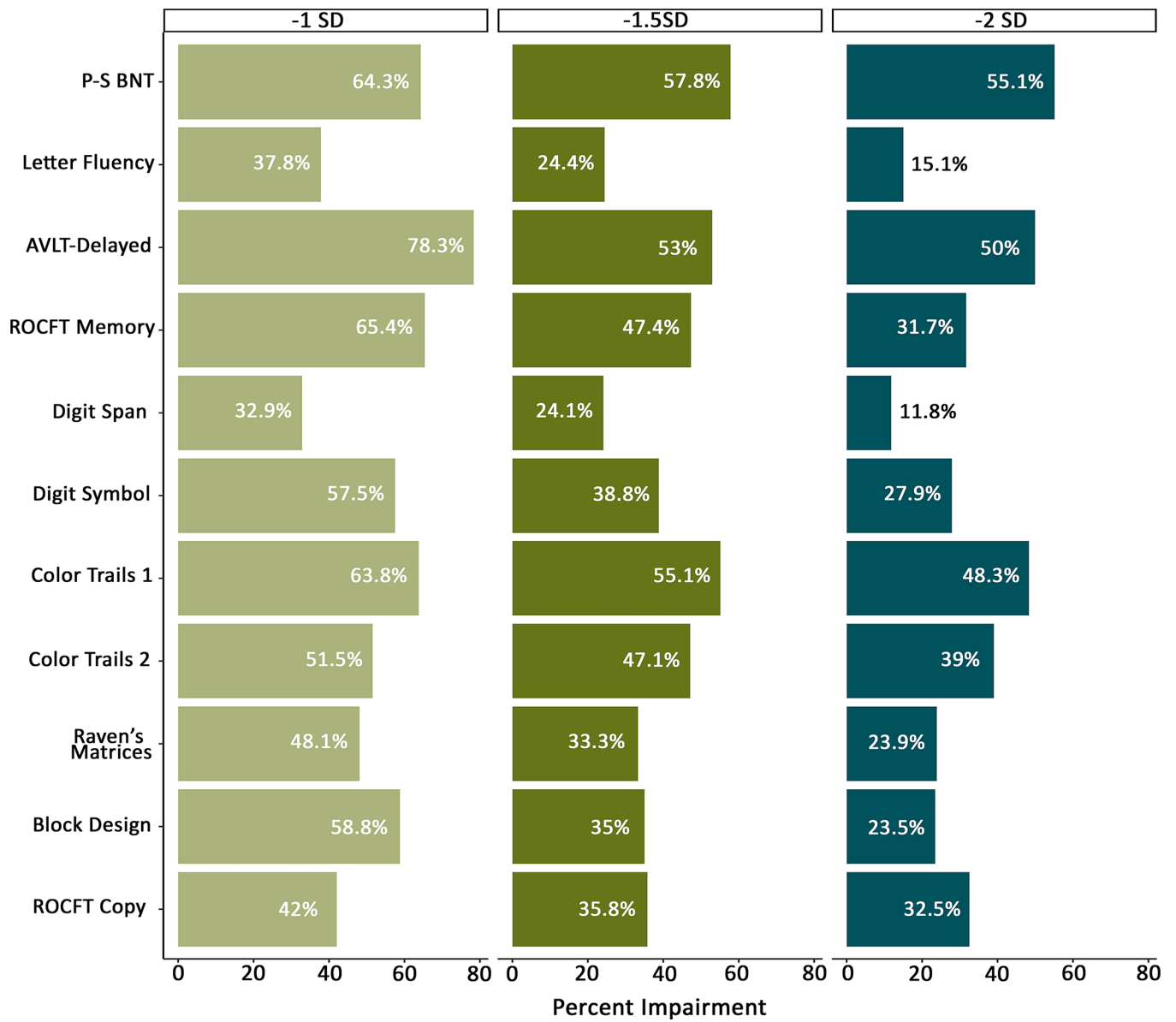
**Figure 2. Impairment rates at the individual test level for −1.0, −1.5, and −2.0 standard deviation cutoffs.**
P-S BNT: Pontón-Satz Boston Naming Test; AVLT: Auditory Verbal Learning Test; ROCFT: Rey–Osterrieth Complex Figure Test

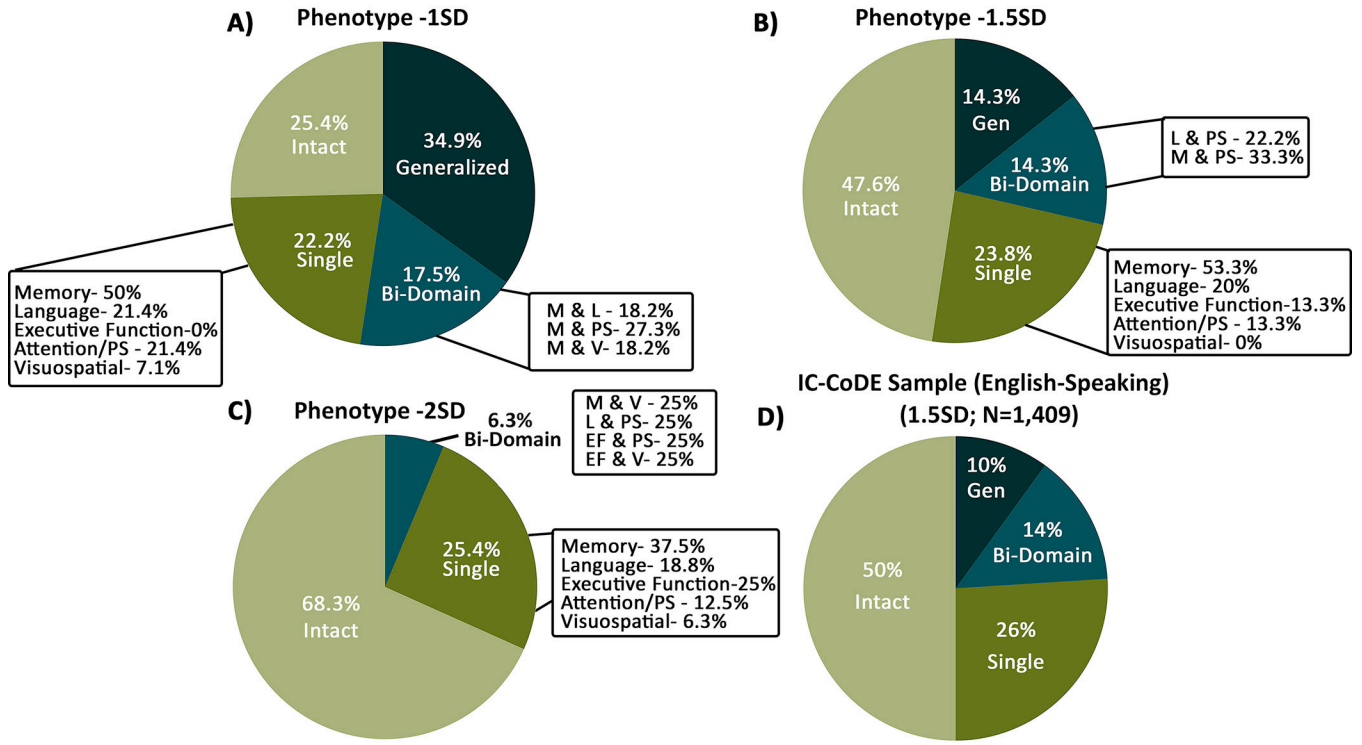## Phenotype Distribution at Different Impairment Thresholds



**A) Phenotype -1SD**

- 34.9% Generalized
- 17.5% Bi-Domain
  - M & L - 18.2%
  - M & PS- 27.3%
  - M & V- 18.2%
- 22.2% Single
  - Memory- 50%
  - Language- 21.4%
  - Executive Function-0%
  - Attention/PS - 21.4%
  - Visuospatial- 7.1%
- 25.4% Intact

**B) Phenotype -1.5SD**

- 14.3% Gen
- 14.3% Bi-Domain
  - L & PS - 22.2%
  - M & PS- 33.3%
- 23.8% Single
  - Memory- 53.3%
  - Language- 20%
  - Executive Function-13.3%
  - Attention/PS - 13.3%
  - Visuospatial- 0%
- 47.6% Intact

**C) Phenotype -2SD**

- 6.3% Bi-Domain
  - M & V - 25%
  - L & PS- 25%
  - EF & PS- 25%
  - EF & V- 25%
- 25.4% Single
  - Memory- 37.5%
  - Language- 18.8%
  - Executive Function-25%
  - Attention/PS - 12.5%
  - Visuospatial- 6.3%
- 68.3% Intact

**D) IC-CoDE Sample (English-Speaking) (1.5SD; N=1,409)**

- 10% Gen
- 14% Bi-Domain
- 26% Single
- 50% Intact

**Figure 3. Cognitive phenotype distribution across impairment thresholds.**

Distribution of phenotypes across (A) −1.0 SD cutoff, (B) −1.5 SD cutoff, and (C) −2.0 SD cutoff in the Spanish-speaking sample. Panel D shows the phenotype distribution of the IC-CoDE validation English-speaking sample utilizing the 1.5SD cutoff (McDonald et al., 2022). For the Bi-Domain distribution, subgroups (i.e., combinations of domains) with less than two patients are not illustrated. For the −2SD cutoff, all subgroups within the Bi-Domain phenotype had less than two patients and are not illustrated. PS: processing speed; M: memory; L: language; V: visuospatial

**Table 1:**

Demographics and clinical variables across entire sample

|  | **All TLE** |
| --- | --- |
| N | 84 |
| Mean age | 37.81 (12.12) |
| Education | 11.33 (4.05) |
| Age of onset[*] | 13.96 (9.87) |
| Duration of epilepsy[*] | 25.37 (14.35) |
| Number of ASM | 1.83 (.787) |
| Seizure frequency per month (n=32) | 9.812 (8.35) |
| Side of seizure onset: L/ R/ B | 33 (39.8%) / 38 (45.8%) / 12 (14.5%) |
| MRI Etiology (n=51) | |
| Mesial temporal sclerosis (MTS) | 18 (35.3%) |
| Temporal lesions (non-MTS) | 8 (15.7%) |
| Mutilobar (including temporal) | 4 (7.8%) |
| Evidence of atrophy | 3 (5.9%) |
| Multifocal | 1 (2%) |
| MRI within normal limits | 17 (33.3%) |
| Sex: Female | 57 (67.9%) |
| Handedness: Right | 73 (88%) |
| Region of origin | |
| North America | 6 (7.1%) |
| Central America | 7 (8.3%) |
| South America | 26 (31%) |
| Caribbean | 20 (23.8%) |
| Unknown | 25 (29.8%) |

[*] 83% of patients had data available

ASM: antiseizure medications; TLE: temporal lobe epilepsy; L: left; R: right; B: bilateral

**Table 2:**

Pearson correlations between neuropsychological score and demographic characteristics

| | Raw Scores | | Corrected Z-scores | |
|---|---|---|---|---|
| | **Age** | **Education** | **Age** | **Education** |
| Language | rho (p-value) | rho (p-value) | rho (p-value) | rho (p-value) |
| P-S BNT | .137 (.215) | **.589 (<.001)** | −.137 (.220) | **.411 (<.001)** |
| Letter Fluency | .144 (.198) | **.415 (<.001)** | .048 (.670) | .165 (.142) |
| Memory | | | | |
| AVLT-Delayed | −.143 (.194) | **.273 (.012)** | −.142 (.201) | .072 (.521) |
| ROCFT Memory | −.176 (.123) | **.461 (<.001)** | −.003 (.978) | .207 (.069) |
| Attention/Processing Speed | | | | |
| Digit Span Total | .111 (.332) | **.471 (<.001)** | .135 (.235) | **.339 (.002)** |
| Digit Symbol | **−.341 (.002)** | **.546 (<.001)** | −.112 (.325) | .154 (.176) |
| Color Trails 1 | .122 (.318) | **−.506 (<.001)** | −.042 (.731) | **.329 (.006)** |
| Executive Function | | | | |
| Color Trails 2 | .156 (.205) | **−.486 (<.001)** | −.116 (.353) | .240 (.052) |
| Raven's Matrices | *−.225 (.043)* | **.544 (<.001)** | −.165 (.142) | *.248 (.027)* |
| Visuospatial | | | | |
| Block Design | −.142 (.210) | .613 (<.001) | .042 (.710) | *.234 (.036)* |
| ROCFT Copy | **−.271 (.014)** | **.339 (.002)** | −.110 (.330) | .069 (.542) |

P-S BNT: Pontón-Satz Boston Naming Test; AVLT: Auditory Verbal Learning Test; ROCFT: Rey–Osterrieth Complex Figure Test

Bold: Significant with a false-discovery rate correction q* = .018

Italics: Significant at a p-value of .05

**Table 3:**

Clinical and demographic characteristics across cognitive phenotypes

| | Generalized | Bi-Domain | Single-Domain | Intact | F | p-value |
|---|---|---|---|---|---|---|
| N (%) | 9 (14.3%) | 9 (14.3%) | 15 (23.8%) | 30 (47.6%) | | |
| Age | 31.9 (8.24) | 37.3 (13.2) | 33.8 (13.1) | 39.5 (11.2) | 1.436 | .241 |
| Education | 10.1 (4.59) | 12.1 (3.65) | 12.8 (3.06) | 12.03 (3.46) | 1.005 | .397 |
| Onset | 14.8 (6.42) | 10.4 (11.9) | 12.5 (9.91) | 17.00 (9.71) | 1.192 | .323 |
| Duration | 16.4 (6.19) | 25.1 (13.9) | 23.5 (15.5) | 23.6 (13.9) | .460 | .712 |
| # ASMs | 1.77 (.667) | 2.00 (.534) | 1.86 (.833) | 1.96 (.865) | .176 | .912 |
| Seizure frequency (n=25) | 15 (6.00) | 5.67 (5.68) | 13.63 (11.46) | 4.12 (2.19) | 3.615 | .030 |
| | | | | | **Fisher's Exact** | **p-value** |
| Sex: Female | 6 (66.7%) | 7 (77.8%) | 6 (40.0%) | 26 (86.7%) | **10.37** | **.012** |
| Handedness: R | 8 (100%) | 8 (88.9%) | 13 (86.7%) | 26 (86.7%) | 1.018 | .877 |
| Side of seizure onset | | | | | 5.324 | .497 |
| Left | 2 (22.2%) | 3 (33.3%) | 8 (53.3%) | 11 (37.9%) | | |
| Right | 5 (55.6%) | 6 (66.7%) | 6 (40%) | 12 (41.4%) | | |
| Bilateral | 2 (22.2%) | 0 (0%) | 1 (6.7%) | 6 (10.7%) | | |
| MRI Pathology (n=34) | | | | | 4.19 | .716 |
| MTS | 2 (40%) | 1 (20%) | 3 (42.9%) | 5 (29.4%) | | |
| Non-MTS | 3 (60%) | 2 (40%) | 2 (28.6%) | 5 (29.4%) | | |
| WNL | 0 (0%) | 2 (40%) | 2 (28.6%) | 7 (41.2%) | | |

ASM: anti-seizure medications; R: right; mesial temporal sclerosis: MTS; WNL: within normal limits

Bold signifies significant with a false discovery rate correction