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Epileptic Disorders

REVIEW ARTICLE

A user's guide for the International Classification of Cognitive Disorders in Epilepsy

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Abstract

To present the background, rationale, details pertaining to use and essential computational steps, synopsis of findings to date, and future directions for the International Classification of Cognitive Disorders in Epilepsy (IC-CoDE)—an initiative of the ILAE Neuropsychology Task Force. Examined are: (a) the 6 steps leading to the derivation of a cognitive phenotype from neuropsychological test data with an accompanying case example, (b) concise review of all IC-CoDE research to date, (c) summary of identified correlates of IC-CoDE outcomes, and (d) future research and clinical directions for the initiative. The IC-CoDE is computationally uncomplicated with individual or group data and represents a novel approach leading to new insights in the neuropsychology of epilepsy, with applications to diverse datasets internationally informing the reliability and validity of the approach. The IC-CoDE represents a novel approach to the analysis and interpretation of neuropsychological data in epilepsy that offers to advance a global taxonomy of cognitive disorders in epilepsy facilitating international collaboration and big data science.

KEYWORDS

cognitive phenotypes, IC-CoDE, neuropsychology

2 | INTRODUCTION

The International Classification of Cognitive Disorders in Epilepsy (IC-CoDE) represents a consensus-based, empirically driven approach to diagnosing cognitive disorders in adults with epilepsy. It was developed in 2020 through a Memorandum of Understanding (MOU) between the International League Against Epilepsy (ILAE) and the International Neuropsychological Society (INS) to provide a framework for global collaborations and accelerate research into the neuropsychology of epilepsy worldwide.[1]

The aims of this guide are to (1) provide an updated perspective of the rationale and potential advantages of the IC-CoDE for the neuropsychology of epilepsy, (2) present a concrete teaching example of IC-CoDE methods, which use neuropsychological test data to identify discrete cognitive phenotypes, (3) review the state of the IC-CoDE literature to date, (4) discuss identified correlates of IC-CoDE

phenotypes, and (5) suggest directions for future research including the application of IC-CoDE to linguistically diverse populations.

2.1 | IC-CoDE: Goal, rationale, and advantage

2.1.1 | Goal

The main goal of the IC-CoDE is to accelerate global communication and research in the neuropsychology of epilepsy by providing an internationally applicable framework for cognitive diagnostics in epilepsy with clear operational criteria and established impairment cutoffs. It was developed as a guide for harmonizing multi-site cognitive research in epilepsy but has not yet been validated as a diagnostic tool for individual patients in clinical settings.[2]

2.1.2 | Rationale

Neuropsychology is among the few core disciplines involved in epilepsy care without a systematic classification or taxonomy of its diagnostic outcomes (e.g., see Refs. 3–7 for classifications and taxonomies of seizures, syndromes, neuropathology, and functional seizures). The primary focus of epilepsy neuropsychology has been performance on domain-specific tests—without international consensus as to a uniform test battery, definitions of abnormality, or diagnostic outcomes—which has not served to accelerate international collaboration, big data science, or rapid advances in patient care.

Data-driven research has demonstrated the cognitive heterogeneity that is present in child, adolescent, and adult epilepsies,[8] but direct research and clinical application of these findings in a patient-centered fashion is difficult. Required is a structured approach, key to IC-CoDE, that codifies: (a) target cognitive domains, critical domain-specific cognitive abilities, and the optimal test characteristics to assess them; (b) operational definitions of abnormality; and (c) an algorithm to reach specific cognitive diagnostic classifications. In the context of this overarching structure, researchers have the flexibility to select the most appropriate tests and norms for their nation, culture, and language.

2.1.3 | Potential advantages

A number of potential advantages may be anticipated from the integration of IC-CoDE into the neuropsychology of epilepsy literature that fall into several specific categories including communication, collaboration, clarity, consensus, and potential clinical application (Table 1).

These potential advantages have served to drive interest and collaborative efforts that will be described later in this manuscript.

Key points

- An updated perspective of the rationale and potential advantages of the IC-CoDE for the neuropsychology of epilepsy is presented.
- A concrete teaching example of IC-CoDE methods is given using neuropsychological test data to identify discrete cognitive phenotypes.
- The state of the IC-CoDE literature to date is reviewed.
- Identified correlates of IC-CoDE phenotypes are presented.
- Future directions for IC-CoDE research are offered.

2.2 | How do I use the IC-CoDE?

A frequent question is how one can apply the IC-CoDE process to their site's neuropsychological data to derive cognitive phenotypes. In the material to follow, we demonstrate an application of IC-CoDE to participant data that requires the following key steps, summarized in Figure 1. These steps are overviewed in Figure 1, followed by more detailed instructions in the text below.

2.2.1 | First, create the cognitive domain structure for your administered test battery

The IC-CoDE recommends a 5 cognitive domain model reflecting abilities considered vulnerable across the epilepsies (see Table S1) and generally consistent with contemporary clinical neuropsychology.

2.2.2 | Second, determine test assignment within each domain

Defining an internationally acceptable test battery for the neuropsychology of epilepsy has proven challenging. General indications and guidelines for neuropsychological assessment in routine epilepsy care[9] and epilepsy surgery[10] have been published by the ILAE Neuropsychology Task

TABLE 1 Anticipated advantages of IC-CoDE.

Communication	• Provides a common "language" regarding cognition across centers, nations, languages, and cultures. • Provides unified cognitive structure and diagnostic procedures across centers, nations, languages, and cultures.
Collaboration	• Facilitates cross-center harmonization of data from low prevalence epilepsy syndromes permitting pooling of data that, to date, has been limited to single centers (e.g., parietal lobe epilepsy) • Facilitates investigation of low prevalence diagnostic classifications and clinical outcomes (e.g., single-domain executive). • Facilitates development of large-scale, big-data multi-national datasets and investigations. • Quantitates the impact of global variations of epilepsy etiology on the distribution of cognitive phenotypes.
Clarity	• Provides similar cognitive structure and diagnostic procedures across centers, nations, languages, and cultures. • Requires less dependence on local test-specific practices and outcomes. • Provides common cognitive diagnostic outcomes globally.
Consensus	• Facilitates development of a global consensus of the cognitive phenotypes associated with epilepsy and epilepsy syndromes as well as their comparisons to other neurological and non-neurological disorders. • Develops consensus cognitive outcomes for clinical trials. • Provides common definitions of cognitive abnormality.
Clinical	• Once major validity and reliability issues are determined, clinical application will be warranted. • Allows comparable clinical diagnostic language across centers and specialty areas (e.g., surgery, rehabilitation) • Allows companion disciplines (e.g., psychiatry, epileptology) to garner a better understanding of cognitive outcomes.

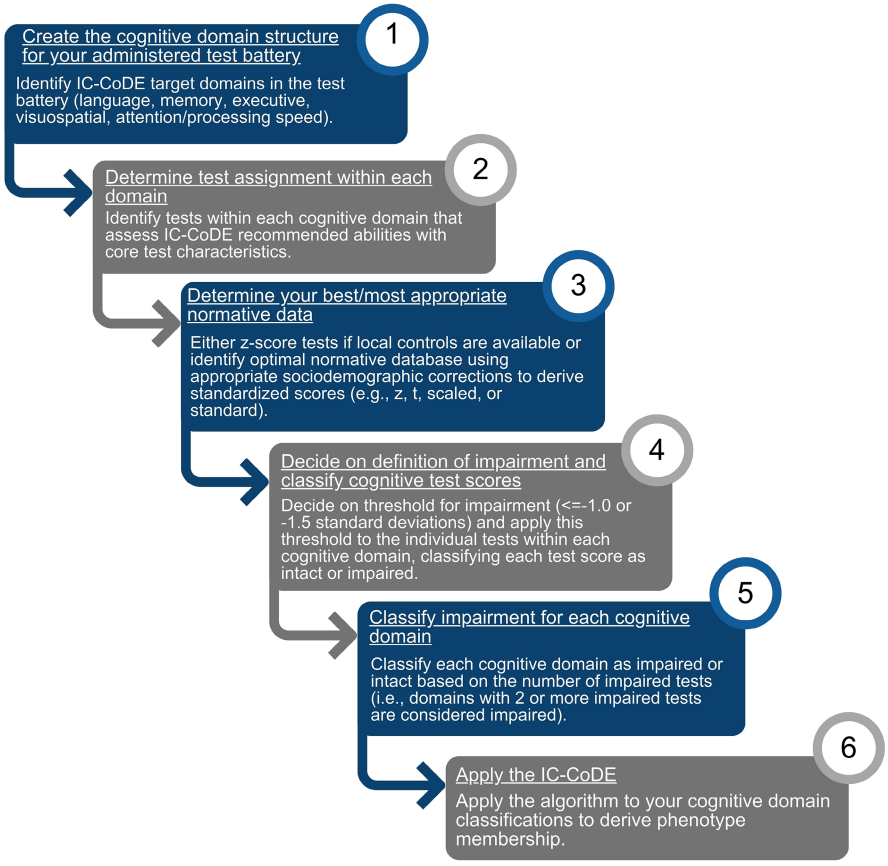

FIGURE 1 Core steps in the IC-CoDE process.

Force, but specific tests that should be administered were not addressed. There have been major efforts to define a consensus battery for epilepsy surgery and other uses,[11–13] but these recommendations have not been adopted internationally. In contrast, the IC-CoDE working group took a different approach and identified a limited number of specific *cognitive abilities* within each cognitive domain that should be assessed given their potential vulnerability across the epilepsies. Table S1 reproduces these target abilities for each cognitive domain, the test characteristics important for assessment of those target abilities, and exemplars of appropriate tests.[2] This approach bypasses prescriptive rules for test utilization and opens the IC-CoDE system to best metric availability across centers, nations, languages, and cultures and also allows flexibility for the clinical researcher to include other clinical or research measures. It is important to have at least 2 cognitive tests within each cognitive domain in order to generate

IC-CoDE phenotypes. To date, using this procedure, outcomes have been stable across centers and studies, which we think is attributable to the robustness of the proposed cognitive model (Table S1).

2.2.3 | Third, determine your best/most appropriate normative data

A participant's raw test data should be compared to either local controls or, more likely, applicable regional or national normative standards containing appropriate sociodemographic adjustments (e.g., see Refs. 14–17). These outcomes may be in *z*-scores, *t*-scores, scaled scores, standard scores, or other standard metrics. Regarding validated translations of tests, this is an issue that is beyond the scope of this instruction guide, but interested readers may consult selected exemplars of efforts where these as well as normative issues have been addressed successfully including in the U.S., India,[18] Spain,[19,20–22] and related extensions to other nations such as Columbia.[23]

2.2.4 | Fourth, decide on the threshold for cognitive impairment (≤−1.0 or −1.5 standard deviations) and classify cognitive tests

After selecting the most appropriate threshold for your population, classify each test identified in Step 2 as "intact" or "impaired" using the selected threshold.

At the current time, IC-CoDE users are given the option of using −1.0 SD and −1.5 SD cutoffs, in part given the variability that exists in the definition of abnormality across clinical and research communities. We wish to avoid being too prescriptive in that reducing flexibility for potential users could be counterproductive. To date, our group[2,18,24] has typically provided results for both the −1.0 SD and −1.5 SD thresholds, as have researchers who have used versions of the IC-CoDE for other disorders.[19,21,22] That said, we should note that for English-speaking and Spanish-speaking populations, the −1.5 SD cutoff has produced the most stable phenotypes and ones that showed the most consistency with phenotypes derived using data-driven approaches.[25] Therefore, −1.5 SD is a preferred/recommended threshold. That said, room is left for flexibility as there may be cohorts for whom this threshold is not appropriate, and researchers may need to examine multiple cutoffs to arrive at the most appropriate one considering their population and tests and norms used. We demonstrated this flexibility in a Spanish-speaking cohort where we examined multiple cutoffs (e.g., −1.0 SD, −1.5 SD, and −2 SD) and determined that −1.5 SD was also the most appropriate for this sample.[26]

2.2.5 | Fifth, classify impairment for each cognitive domain

Examine the number of impaired test scores within each cognitive domain and classify each domain as "intact" or "impaired." Domains with 2 or more impaired test scores are classified as "impaired," while those with 0 or 1 impaired test scores are classified as "intact."

2.2.6 | Finally, apply the algorithm to your cognitive domain classifications

This straightforward process will lead to the determination of cognitive phenotype for each participant in your dataset. Based on the pattern of results derived from the above steps, simply move through the choice points of the algorithm depicted in Figure 2 to arrive at the final cognitive phenotype (i.e., intact, single domain, bi-domain, and generalized).

3 | CASE EXAMPLE

A specific case is now presented to concretely demonstrate the essential IC-CoDE steps reviewed above to arrive at the cognitive phenotype for a specific participant.

A 50-year-old female patient was seen for presurgical evaluation for the treatment of pharmacoresistant mesial left temporal lobe epilepsy (TLE) associated with hippocampal sclerosis. She experienced 2 febrile seizures as a toddler and developed recurrent seizures at age 35. She completed a comprehensive preoperative neuropsychological evaluation, and her scores are summarized in Table 2.

To derive an IC-CoDE phenotype for this participant, a five-domain test structure was first established (Step 1) and then each measure in the battery was assigned to one of the five cognitive domains as shown in Table 2 (Step 2). This participant had also completed measures of motor speed and dexterity, but these were not included as there is no motor domain included in the IC-CoDE taxonomy. Demographically corrected standardized scores from the normative manual for each test were generated as part of the clinical evaluation and summarized in Table 2 (Step 3). Note that the score for each measure based on normative data varied in terms of the scale in which it is reported (e.g., standard or scaled scores for some, t-scores for others). This is not an issue for generating IC-CoDE phenotypes. Once tests are selected for each domain, each score is then classified as "impaired" or "unimpaired" using the desired threshold (Step 4). For purposes of this example, we applied a ≤−1.5 SD threshold. Each score in the final battery of tests is compared to this threshold to categorize impairment

FIGURE 2 IC-CoDE diagnostic algorithm.

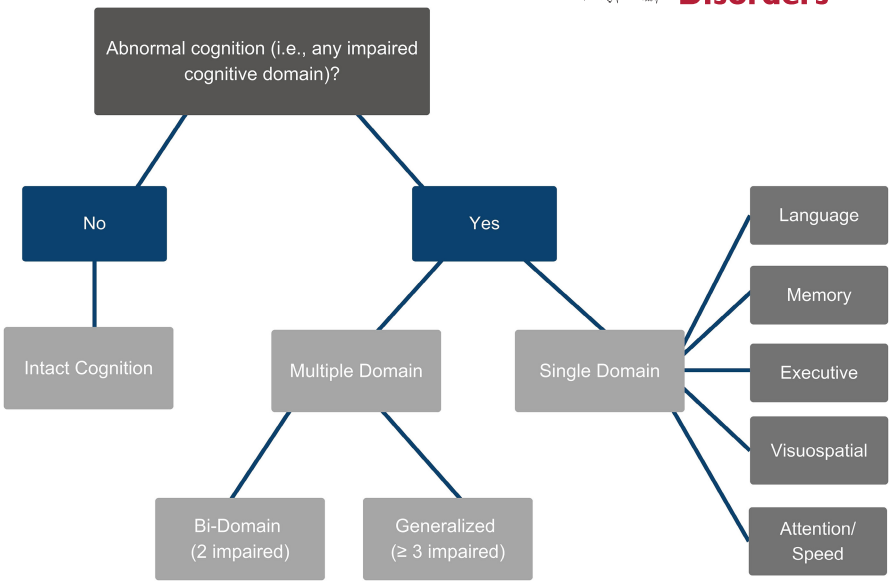

TABLE 2 Case example—neuropsychological battery and scores.

Domain	Test	Scale	Score[a]
Language	Boston Naming Test	Standard score	75
	Phonemic Fluency (F-A-S)	Standard score	97
	Semantic Fluency (Animals)	Standard score	74
Verbal Memory	RAVLT—Delayed Recall	Standard score	72
	WMS-IV Logical Memory II	Scaled score	4
Executive	Trail Making Test—Part B	*t*-Score	35
	Wisconsin Card Sorting Test	Standard score	95
Visuospatial	WMS-IV Visual Reproduction—Copy	Scaled score	12
	WAIS-IV Block Design	Scaled score	11
Attention/Speed	WAIS-IV Digit Span—Forward	Scaled score	13
	WAIS-IV Coding	Scaled score	10
	WAIS-IV Symbol Search	Scaled score	11
	Trail Making Test—Part A	*t*-Score	55

Abbreviations: RAVLT—Rey Auditory Verbal Learning Test; WAIS-IV, Wechsler Adult Intelligence Scale—Fourth Edition; WMS-IV, Wechsler Memory Scale—Fourth Edition.

[a]Demographically corrected standardized score.

using the specific scale in which the score is reported. For example, given the standard deviation for scaled scores is 3, the participant would have to have a score ≤4.5 to be classified as impaired at a ≤1.5 SD cutoff. Similarly, t-scores would have to be ≤35 and standard scores ≤77.5 to be classified as impaired. As can be seen for our example participant, she would be classified as "impaired" on measures of naming, semantic fluency, delayed list and story recall, and sequencing/set-shifting (see Table 3). Once the tests have been classified in this manner, then the number of impaired test scores within each domain is examined and domains are classified as "impaired" or "intact" (Step 5). In order for a domain to be classified as "impaired," at least two cognitive tests within the domain must be impaired. As shown in Table 3, this participant was impaired in the domains of language and memory, but not in executive, visuospatial, or attention/speed.

When applying IC-CoDE to a brief battery or to only a subset of measures in a longer battery, it is important to remember that there must be at least two measures within each cognitive domain in order to generate IC-CoDE phenotypes. We recommend selecting measures that assess different constructs within a specific domain (e.g., naming and fluency measures within the language domain) and selecting different measures (e.g., WCST Perseverative Errors and Trail Making Test—Part B) rather two scores from the same measure (e.g., WCST Perseverative errors and Total Errors) whenever possible. However, when this

TABLE 3 Case example—neuropsychological scores for IC-CoDE phenotyping with impairment classifications.

Domain	Test	Score[a]	Score classification	Domain classification
Language	Boston Naming est	SS = 75	Impaired	Impaired
	Phonemic Fluency (F-A-S)	SS = 97	Intact	
	Semantic Fluency (Animals)	SS = 74	Impaired	
Memory	RAVLT—Delayed Recall	SS = 72	Impaired	Impaired
	WMS-IV Logical Memory II	ScS = 4	Impaired	
Executive	Trail Making Test—Part B	T = 35	Impaired	Intact
	Wisconsin Card Sorting Test	SS = 95	Intact	
Visuospatial	WMS-IV Visual Reproduction—Copy	ScS = 12	Intact	Intact
	WAIS-IV Block Design	ScS = 11	Intact	
Attention/Speed	WAIS-IV Digit Span—Forward	ScS = 13	Intact	Intact
	WAIS-IV Coding	ScS = 10	Intact	
	WAIS-IV Symbol Search	ScS = 11	Intact	
	Trail Making Test—Part A	T = 55	Intact	

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; WAIS-IV, Wechsler Adult Intelligence Scale—Fourth Edition; WMS-IV, Wechsler Memory Scale—Fourth Edition.

[a]Demographically corrected standardized score.

is not possible, any two measures available within the domain can be used (e.g., animal fluency and phonemic fluency). So, in the case example, if the patient had impaired performance on both fluency measures, the language domain would still be considered impaired.

Consistent with prior suggestions,[2] memory can be subdivided into verbal and visual. That said, the status of visual memory in epilepsy, particularly TLE, has been highly inconsistent with tests showing limited ability to distinguish patients based on seizure lateralization or localization or even at times from healthy individuals.[27–29] For this reason, the IC-CoDE group decided to develop an initial model that focused on the most established findings. That said, this model could be expanded as either (1) more sensitive visual memory tests are developed or (2) models of memory with better neuroanatomical specificity are established. It is also important to note that visuospatial and visuoconstruction tests have been found to have varying sensitivity to clinical concerns of interest in epilepsy.[30,31]

3.1 | IC-CoDE research to date

While the IC-CoDE was developed recently, a significant amount of research has accrued to date. Table 4 provides a summary of published papers that have employed the IC-CoDE. In TLE, the IC-CoDE has been validated in a large multicenter US sample,[2] and applicability to Spanish-speaking participants in the U.S. has been demonstrated,[25] as well as utility of this system to other nations, languages, and cultures.[32,33] Neuroimaging procedures have been used to examine neuroanatomical correlates of IC-CoDE cognitive phenotypes,[32] and the applicability of IC-CoDE has been extended to participants with frontal lobe epilepsy (FLE).[24] Other factors that have been associated with IC-CoDE phenotypes include neighborhood deprivation,[34,35] antiseizure and psychotropic medications,[36] psychiatric comorbidities including depression and anxiety,[36] and polygenic risk scores.[37] The IC-CoDE has also been extended to other disorders including multiple sclerosis[19] and post-COVID participants.[21]

Additional details regarding these investigations and their implications follow below.

3.1.1 | IC-CODE validity in temporal lobe epilepsy

Neuropsychological data from a diverse cohort of 1409 participants with TLE across seven epilepsy centers in the U.S. applied the IC-CoDE, examining results as a function of two operational definitions of impairment (≤ −1.0 and ≤−1.5 SD, respectively).[2] Cognitive phenotypes characterized by the following distributions resulted: cognitively intact (30%–50%), single-domain (26%–29%), bi-domain (14%–19%), and generalized (10%–22%) impairment. Importantly, use of the ≤ −1.5 cutoff produced a distribution of phenotypes that was consistent across cohorts and approximated the distribution produced using data-driven approaches in prior studies. This proof-of-principle study offered a promising path for enhancing research

TABLE 4 IC-CoDE research to date.

Epilepsy studies	Sample	*N*	Language	Country	Cutoff	Focus of investigation
McDonald et al. (2023)[2]	TLE	1409	English	US	1.0 SD 1.5 SD	Multicenter collaborative validation of IC-CoDE.
Reyes et al. (2023)[25]	TLE	84	Spanish	US	1.0 SD 1.5 SD 2.0 SD	Applicability of IC-CoDE to Spanish-speaking US participants.
Arrotta et al. (2023)[24]	FLE	455	English	US	1.0 SD 1.5 SD	Applicability of IC-CoDE to FLE
Busch et al. (2023)[34]	TLE	800	English	US	1.5 SD	Relationship of IC-CoDE phenotypes to neighborhood deprivation.
Bingaman et al. (2023)[36]	TLE	826	English	US	1.5 SD	Relationship of IC-CoDE phenotypes to depression and anxiety.
Miron et al. (2024)[32]	TLE	124 TLE 117 HC	German	Germany	1.0 SD	Patterns of gray matter thickness across cognitive phenotypes.
Shah et al (2024)[33]	TLE	548	Multiple Indian languages	India	1.5 SD	Cognitive phenotype distribution in diverse language, cultural and ethnic population with comparison to US cohort.
Arrotta et al. (2024)[37]	TLE	202	English	US	1.5	Relation of polygenic risk scores to cognitive phenotypes.
Reyes et al. (2024)[38]	TLE and FLE	51	English	US	1.0	Sensitivity/specificity of MoCA to IC-CODE in older adults (55+)
Other disorders						
Matias-Guiu et al. (2023)[21]	Post-COVID syndrome	404	English and Spanish	Spain	1.0 SD 1.5 SD	Modification of IC-CoDE to participants with "long COVID" (IC-CoDiCOVID).
Hancock et al. (2023)[19]	MS	1281	English and Spanish	US and Spain	1.0 SD 1.5 SD	Modification of IC-CoDE with application to participants with MS (IC-CoDiMS).
Sousa et al. (2024)[39]	MS	300	Portuguese	Portugal	1.0 SD 1.5 SD	Application of IC-CoDiMS to participants with MS.
Delgado-Alonso et al.[22]	Multiple sclerosis and post-COVID	218 MS 218 PCC	Spanish	Spain	1.0 SD	Examination of shared vs. disease-specific cognitive phenotypes.

Abbreviations: HC, healthy controls; MS, multiple sclerosis; PCC, post-COVID condition; SD, standard deviation; TLE, temporal lobe epilepsy.

collaborations in the context of multicenter studies given the stability in underlying phenotypes associated with TLE across U.S.-based cohorts.

3.1.2 | IC-CoDE in linguistically diverse cohorts

Using the Neuropsychological Screening Battery for Hispanics (NeSBHIS), Spanish-speaking participants with TLE completed neuropsychological measures of memory, language, executive function, visuospatial functioning, and attention/processing speed. Application of the IC-CoDE taxonomy utilizing a −1.5 SD cutoff revealed an intact cognitive profile in 47.6% of participants, single-domain impairment in 23.8% of participants with memory the most impaired cognitive domain, bi-domain impairment in 14.3%, and generalized impairment in 14.3%. This distribution was comparable to the phenotype distribution observed in the U.S. IC-CoDE validation sample using a different test battery with Spanish-speaking participants. These findings suggest 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.[25]

3.1.3 | IC-CoDE in India

Assessing the cross-cultural applicability of IC-CoDE to a diverse multilingual and multicultural cohort in India as well as the comparability of the distribution of cognitive phenotypes compared to previous research, Shah et al.[33] investigated 548 TLE patients who underwent neuropsychological assessment as part of their preoperative workup. Compared to the prior U.S. multicenter investigation,[2] the sample from India was younger and had less education, a shorter duration and earlier age of onset of epilepsy, a greater proportion of males, and more patients with mesial

temporal sclerosis (MTS). The results demonstrated comparable rates of intact and bi-domain phenotypes in the India and U.S. samples, with a higher proportion of single domain (specifically memory) in the India cohort and more generalized impairment in the U.S. cohort—these differences hypothesized to be related to the variable distributions of MTS (higher in India) and chronicity of disorder (shorter in India) between the cohorts. More generally, this investigation demonstrated the applicability of IC-CoDE to a diverse, multiethnic, multilingual, international cohort.

3.1.4 | IC-CoDE and frontal lobe epilepsy

Arrotta et al.[24] examined the applicability of IC-CoDE to patients with FLE using a four-center cohort of 445 adults (≥16 years old) with at least two cognitive measures in at least four cognitive domains ($n = 336$). The neuropsychological data underwent analysis through the IC-CoDE using both the −1.0 and −1.5 SD cut points. The results from the FLE cohort were also compared to the distribution of IC-CoDE cognitive phenotypes from the multicenter TLE cohort. The resulting distribution of FLE cognitive phenotypes was found to be comparable across the four centers despite variability in administered test batteries demonstrating the applicability and stability of the resulting phenotypes. This study also highlighted considerable cognitive heterogeneity within patients with FLE, and, in comparison with TLE, more severe cognitive phenotypes were observed in FLE (e.g., 33% of FLE exhibited generalized impairment compared to 22% of TLE using the −1.0 SD threshold).

3.2 | Correlates of IC-CoDE cognitive phenotypes

In the general epilepsy-neuropsychology literature, there has been longstanding interest in the clinical features (e.g., seizure type, syndrome, number and type of antiseizure medications [ASMs]) that may be associated with cognitive performance. The same interests exist with regard to the IC-CoDE cognitive phenotypes, and findings to date are briefly summarized below.

3.2.1 | Neuroimaging

Miron et al.[32] examined 124 patients with pharmacoresistant TLE preoperatively from a German epilepsy center.[32] Application of the IC-CoDE revealed minimal/no impairment in 16.9%, single-domain impairment in 28.9%, and multidomain impairment (bi-domain impairment + generalized abnormality combined) in 53%. These findings, in a German cohort, again inferred applicability of the IC-CoDE to cognitive research across countries and languages as was the case in India. Importantly, through a graph theory-based analysis of MRI, comparing TLE patients to 177 age- and sex-matched controls, different patterns of gray matter thickness were revealed across the different cognitive phenotypes. For example, there was a stepwise increase in the number of abnormal cortical regions with 28 regions adversely affected in the multidomain impaired group, 12 in the focal impaired phenotype, and only 3 in the minimally impaired group.[32]

3.2.2 | Psychiatric comorbidities

Bingaman et al.[36] examined the relationship between psychiatric symptomatology and IC-CoDE cognitive phenotypes in 826 adults with pharmacoresistant TLE. They found that adults with elevated symptoms of depression demonstrated increasingly worse cognitive phenotypes (i.e., more cognitive domains impaired) than those without significant depressive symptoms. In contrast, anxiety symptoms were found to be unrelated to IC-CoDE cognitive phenotype in this cohort. Furthermore, the number of psychotropic medications was associated with more severe cognitive phenotypes (OR = 1.584, $p < .05$).

3.2.3 | Medications—mood altering ASMs

Relatedly, Bingaman et al.[36] also examined each participant's medication regimen at the time of their neuropsychological evaluation to identify participants who were taking psychotropic (e.g., anti-depressants, anxiolytics, anti-psychotics, stimulants) or ASMs at the time of testing. ASMs were separated into those with mood-enhancing (e.g., oxcarbazepine) and mood-worsening (e.g., levetiracetam) effects. Participants taking higher numbers of ASMs had 1.5 times greater odds of having a more severe IC-CoDE cognitive phenotype (OR = 1.507), especially if taking ASMs with mood-worsening effects (OR = 1.748, 95% CI = 1.294–2.372, Holm-corrected $p = .005$).

3.2.4 | Neighborhood disadvantage

There has been a major focus on disease-related factors (e.g., seizure type, frequency, severity, treatments) to advance understanding of the heterogeneity in cognitive presentations among child and adult epilepsy participants. In contrast, considerably less is known about the impact of the social determinants of health (SDOH)[8] on cognition in epilepsy. Epilepsy is more prevalent among

individuals in lower (more disadvantaged) socioeconomic groups and independent of social drift and other known epilepsy risk factors.[40] Furthermore, individuals with epilepsy are more likely to live in households with the lowest annual incomes.[41,42] By contrast, over the past decade, research on the SDOH has grown exponentially and suggests that non-medical factors (e.g., social status outcomes, built environment, community context) are fundamental contributors to health and disease. Metrics of neighborhood disadvantage are now available (e.g., Area Disadvantage Index [ADI])[43] and have been found to be associated with the prevalence, severity, treatments, and outcomes of diverse diseases.[44] Busch et al.[34] examined the relationship of the ADI with cognition in a large cohort of participants with epilepsy and observed significant declines across nearly all measured cognitive domains (e.g., attention, memory, and language) and significant increases in symptoms of depression and anxiety as a function of increasing ADI (i.e., greater disadvantage). Furthermore, participants in higher ADI quintiles had increased odds of having a more severe IC-CoDE defined cognitive phenotype. In a group of older adults with focal epilepsy, Reyes et al.[35] demonstrated that patients with a cognitively impaired profile based on the IC-CoDE had higher ADI values, suggesting greater neighborhood disadvantage.

3.2.5 | Polygenic risk burden and cognitive phenotypes

Only a modest amount of human research has addressed the contribution of genetic variations to cognitive status in patients with epilepsy. Arrotta et al.[37] examined the relation of polygenic scores for neurological (Alzheimer's disease [AD]) and neuropsychiatric (depression, IQ) disorders in 202 adults with pharmacoresistant epilepsy. Proportional logistic regression models were fit to IC-CoDE phenotypes and possible relationships were detected between cognitive phenotypes and polygenic scores, specifically higher AD and lower IQ polygenic scores. Statistical significance was not reached after correction for multiple corrections suggesting that larger multicenter investigations may help to detect promising but modest genetic effects.

3.3 | Application to other disorders

3.3.1 | Multiple sclerosis

The IC-CoDE was modified by Hancock et al.[19] (i.e., IC-CoDiMS) and applied to a large cohort of participants with diverse subtypes of multiple sclerosis (MS) who underwent neuropsychological evaluation across three MS centers including two in the U.S. and one in Spain. Results were tabulated for each participant to determine the type of impairments across the samples and centers. Using a −1.5 SD threshold for abnormality, 72.9% of participants were intact, 14.0% were single-domain impaired, 8.2% bi-domain impaired, and 5.0% multidomain impaired. Processing speed was the most frequent single-domain impairment, followed by executive function and memory, with little difference across centers and languages. These findings have several implications as they advance the taxonomy of cognitive phenotypes in MS, offer to accelerate cognitive research across neurological diseases, and demonstrate the cross-national applicability of this phenotypic approach. Arguably these efforts may help to pave the way for further investigation of associated biomarkers and accelerate individualized treatment and rehabilitation.

Sousa et al.[39] examined 300 patients with relapsing–remitting MS (RRMS) who underwent cognitive assessment with two disease-specific cognitive batteries (Brief Repeatable Battery of Neuropsychological Tests [BRBN-T] and Brief International Cognitive Multiple Sclerosis [BICAMS]). At the −1.0 SD threshold, 49% were cognitively intact, 25% exhibited single-domain impairment, 17% bi-domain impairment, and 9% generalized. Processing speed was the most frequent single-domain impairment, followed by memory and verbal fluency. At the −1.5 SD threshold, 74.7% were cognitively intact, 17% had single-domain impairment, 6% bi-domain impairment, and 3% generalized impairment. Memory was the most frequent single-domain impairment, followed by processing speed and verbal fluency. It was concluded that IC-CoDiMS advanced the classification of cognitive phenotypes in patients with RRMS. Again, this taxonomic approach generalized to another nation and language.

3.3.2 | COVID-19

Two centers in Spain examined participants with post-COVID condition (PCC) and controls who were evaluated neuropsychologically.[21] The IC-CoDE framework was adapted and implemented using the −1.5 threshold of abnormality. 17.3% of the sample was classified as having at least one cognitive domain impaired with attention/processing speed the most frequently impaired domain. There were no differences in the rates of cognitive impairment between the two centers. Cognitive impairment was associated with younger age and lower education levels, but not hospitalization. Overall, with this harmonization of criteria to define and classify cognitive impairment in

the PCC, these criteria can be extrapolated to other neuropsychological batteries and settings, contributing to the diagnosis of cognitive deficits after COVID-19 and facilitating multicenter studies to guide biomarker investigation and therapies.

Delgado-Alonso et al.[22] examined the degree of shared versus disease-specific cognitive phenotypes in MS compared to PCC. Cognitive profiles of patients with PCC and MS largely overlapped with a more substantial abnormality in episodic memory in MS. Attention and processing speed were the most abnormal domains for both PCC and MS groups. Comparative studies of this type will yield important information regarding the presence and type of unique disease-specific cognitive effects compared to abnormalities that are widely shared across diseases.

3.4 | Future directions

Considerable work on IC-CoDE is ongoing and the following are directions for future research.

3.4.1 | IC-CODE web-based user platform

Deriving IC-CoDE phenotypes can be labor-intensive, particularly in large datasets with variable test batteries. To address this issue, a web-based platform for IC-CoDE is under development. This new platform will allow users to enter information regarding their cognitive battery along with the specific tests they would like to use within each cognitive domain to generate IC-CoDE phenotypes. Once this information is provided, the user will have the option of entering test scores for a single participant directly into the portal or to download a spreadsheet, customized to their test battery, which will allow generation of cognitive phenotypes in multiple participants simultaneously. Test scores for each measure can be entered in whatever standard score format the user desires (i.e., z-score, scaled scored, t-score, standard score). Once the test scores are entered or uploaded to the portal, the IC-CoDE calculator automatically generates IC-CoDE phenotypes for each participant in whom sufficient cognitive data are provided (i.e., at least 2 test scores within at least 4 cognitive domains). Users also have the option of entering scores on common depression or anxiety screening measures to flag potential modifiers for mood. Once complete, it is hoped that the IC-CoDE portal will enable additional research in this area and facilitate large-scale, multicenter studies to address important questions in epilepsy neuropsychology.

3.4.2 | Application of IC-CoDE to pediatric epilepsy and common epilepsy syndromes

Efforts are underway to examine the distribution of IC-CoDE classifications among children with new and recent onset idiopathic focal and generalized epilepsies (ages 8–18) (Almane et al., in preparation) as well as youth with chronic temporal lobe epilepsies (ages 5–18) (Ferguson et al., in preparation). Comparison of the relative prevalence of neuropsychological abnormalities across common childhood epilepsy syndromes (e.g., Juvenile Myoclonic Epilepsy [JME], Self Limited Epilepsy with Centrotemporal Spikes [SeLECTS], Childhood and Juvenile Absence, TLE and FLE) is uncommon and complicated by divergent assessment measures across investigations, but will be interrogated through the IC-CoDE.

3.4.3 | Application to other countries/languages/cultures through the ILAE NP taskforce

As noted (Table 4), the IC-CoDE has been successfully applied to patients with TLE in Germany[32] and India,[33] and steps are underway among the international members of the ILAE Neuropsychology Task Force to apply the IC-CoDE to other patient cohorts from South Africa and Japan. As the IC-CoDE expands to other regions, cultures, and languages, it will be important to identify or develop validated norms and test translations. Ongoing research in these areas will be important for the IC-CoDE but also for clinical neuropsychology globally.

3.4.4 | Integration of an expanded list of social determinants of brain health

To date, the relationship between IC-CoDE phenotypes and neighborhood deprivation has been reported by Busch et al.[34] and Reyes et al.[35] but associations of many other metrics of disadvantage (e.g., personal disadvantage) and broad metrics of SDOH remain to be explored that include but are not limited to socioeconomic status, health insurance coverage and access to epilepsy care, disease self-management, and perceived stigma and discrimination, all of which have been associated with health disparities and outcomes in diverse chronic conditions, including epilepsy.[45–48] Research focused on investigating the relationship between the well-documented disparities among ethnoracial minorities and those from socioeconomically disadvantaged backgrounds and IC-CoDE phenotypes is warranted. Importantly, factors such as socioeconomic status, racial/ethnic composition, systemic and structural

racism (e.g., housing discrimination, educational segregation, unfair lending practices, and environmental injustice), and systematic inequalities often force minoritized racial and ethnic groups to reside in regions with greater deprivation (i.e., social selection).[49] The IC-CoDE provides an opportunity to investigate the mediating pathways through which SDOH influence cognitive outcomes in epilepsy.

3.4.5 | Predictive significance (for epilepsy surgery, epilepsy course)

Important validity-based questions for IC-CoDE include the prognostic significance of clinical outcomes for interventions of multiple types (e.g., surgery, medication, diet, neurostimulation) as well as characterization of cognitive outcomes of those interventions or lack thereof.

3.4.6 | Determining the biological distinctness of IC-CoDE phenotypes (e.g., neuroimaging correlates)

A major task going forward is to understand the neurobiological correlates of distinct IC-CoDE cognitive phenotypes. Miron et al.,[32] reviewed above, provided initial evidence of cortical thickness correlates of the broad IC-CoDE phenotype classifications (unimpaired, single-, and multidomain impairment). In addition, at a deeper level of phenotypic analysis, Reyes et al.[50] demonstrated that cognitive phenotypes in patients with TLE demonstrate distinct patterns of microstructural abnormalities within the superficial white matter compared to controls. Interestingly, the language and memory impaired group showed widespread alterations in white matter tracts and altered global superficial white matter network topology, whereas patients with isolated memory impairment demonstrated more circumscribed microstructural changes.

3.4.7 | IC-CoDE-Lite for resource/ neuropsychology limited regions

Knowledge regarding the neuropsychology of the child and adult epilepsies has come predominantly from high resource countries. But epilepsy, as a global disease, is over-represented in middle- and especially lower-income countries where a significant treatment gap exists, not only with regard to the treatment of epilepsy but also with regard to the recognition, diagnosis, and treatment of cognitive and behavioral/psychiatric conditions.[51] Neuropsychology, as an ongoing developing clinical science, is underrepresented in middle- and especially low-income countries.[52,53] The question that arises under these circumstances is how best to identify, characterize, and address cognitive anomalies in people with epilepsy in these regions. Efforts to merge IC-CoDE with internationally available extended mental status screening measures, such as the MoCA, may advance efforts to identify, categorize, and better communicate findings regarding cognitive abnormality in those regions of the world where formal neuropsychological assessment and practitioners are less available. Recently, we provided validation of the MoCA as a cognitive screener for older adults with epilepsy using the IC-CoDE as the gold standard for classifying cognitive impairment.[38] Thus, the IC-CoDE provides a system to validate the sensitivity of cognitive screeners that are widely accessible to regions of the world where neuropsychology remains underdeveloped.

3.4.8 | Other IC-CoDE correlates and potential modifiable risk factors

While some IC-CoDE correlates have been identified as reviewed previously, more work is needed regarding the potential impact of other potentially important clinical epilepsy factors (e.g., seizure frequency and severity, etiology), diverse sociodemographic features, and presence of subjective cognitive complaints to name only a few. Especially important is determining whether some factors represent modifiable risk factors (ASMs, psychiatric comorbidities) whose treatment may improve IC-CoDE membership.

3.4.9 | Examine an ipsative approach to IC-CoDE

The core IC-CoDE approach to determining impairment, and subsequently assigning phenotype membership, has been based on a normative model whereby "intact" scores for all individuals are expected to lie within 1 to 1.5 standard deviations of the normative mean (i.e., an inter-individual approach). Although this is the most common model applied in research and in group-level analyses, this approach does not consider how inter-individual differences in premorbid IQ or global abilities impact other neuropsychological performances. An alternative model is to consider an intra-individual, or ipsative approach, whereby impairment for each individual is determined relative to an estimate of his/her own global ability (e.g., an IQ score) rather than a normative mean. This type of approach emulates how neuropsychological profiles are generally interpreted in the clinical setting and may

increase sensitivity by setting a more liberal impairment threshold for someone with a high IQ (e.g., .5 standard deviations below the normative mean) and a more conservative threshold in someone with low IQ (e.g., 2 standard deviations below the normative mean). Although the ipsative approach offers some advantages in terms of tailoring the approach to an individual, it also makes the assumption that all skills should be uniformly anchored to a person's IQ—an assumption which is oversimplified in most individuals who show natural patterns of strengths and weaknesses. This approach to the IC-CoDE is of interest, but is inherently more complex. As a result, this approach has yet to be applied and empirically tested.

3.4.10 | Digital assessment approaches and IC-CoDE

The IC-CoDE was developed with traditional assessments in mind. With the increased use of digital assessments, an important future direction will be to test and/or develop a comparable IC-CoDE process following the steps overviewed.[2]

3.4.11 | Expansion to other populations of persons with epilepsy

Finally, it is critical to inquire into the utility of a cognitive phenotyping system for individuals with intellectual and developmental disorders (IDD) and other important subpopulations of adults and youth with epilepsy.

4 | CONCLUSIONS

The IC-CoDE offers an approach to the neuropsychology of epilepsy that appears to have promise in characterizing the underlying cognitive phenotypes of epilepsy—an approach that at this early stage appears to have applicability across centers, nations, cultures, and languages—circumventing longstanding problems in the field that have slowed global communication, collaboration, and understanding of the factors that drive cognitive heterogeneity in epilepsy.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. IC-CoDE results in the identification of:
   A. Cognitive phenotypes
   B. Cognitive test scores
   C. Cognitive abnormalities
2. IC-CoDE data have been examined using findings from:
   A. Multiple epilepsy centers within a nation
   B. Epilepsy centers across nations
   C. Both
3. IC-CoDE recommends how many cognitive domains in its algorithm:
   A. 3
   B. 5
   C. 6

Answers may be found in the Supporting information