Received: 26 September 2020 | Revised: 9 November 2020 | Accepted: 9 November 2020

DOI: 10.1111/epi.16780

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Diagnosing cognitive disorders in older adults with epilepsy

Anny Reyes[1,2,3] | **Erik Kaestner**[1,3] | **Emily C. Edmonds**[3,4] | **Anna Christina Macari**[1] | **Zhong Irene Wang**[5] | **Daniel L. Drane**[6,7] | **Vineet Punia**[5] | **Robyn M. Busch**[5,8] | **Bruce P. Hermann**[9] | **Carrie R. McDonald**[1,2,3] | **for the Alzheimer's Disease Neuroimaging Initiative***

[1]Center for Multimodal Imaging and Genetics, University of California, San Diego, CA, USA

[2]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

[3]Department of Psychiatry, University of California, San Diego, CA, USA

[4]Veterans Affairs San Diego Healthcare System, San Diego, CA, USA

[5]Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

[6]Departments of Neurology and Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

[7]Department of Neurology, University of Washington, Seattle, WA, USA

[8]Department of Neurology, Cleveland Clinic, Cleveland, OH, USA

[9]Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Correspondence
Carrie R. McDonald, [1]Center for Multimodal Imaging and Genetics, University of California, Altman CTRI building; Floor #: 4W, 9452 Medical Center Drive, La Jolla, CA 92037, USA.
Email: camcdonald@health.ucsd.edu

Funding information
Veterans Affairs San Diego Healthcare

Abstract

Objective: To characterize the nature and prevalence of cognitive disorders in older adults with temporal lobe epilepsy (TLE) and compare their cognitive profiles to patients with amnestic mild cognitive impairment (ie, aMCI).

Methods: Seventy-one older patients with TLE, 77 aMCI, and 69 normal aging controls (NACs), all 55-80 years of age, completed neuropsychological measures of memory, language, executive function, and processing speed. An actuarial neuropsychological method designed to diagnose MCI was applied to individual patients to identify older adults with TLE who met diagnostic criteria for MCI (TLE-MCI). A linear classifier was performed to evaluate how well the diagnostic criteria differentiated patients with TLE-MCI from aMCI. In TLE, the contribution of epilepsy-related and vascular risk factors to cognitive impairment was evaluated using multiple regression.

Results: Forty-three TLE patients (60%) met criteria for TLE-MCI, demonstrating marked deficits in both memory and language. When patients were analyzed according to age at seizure onset, 63% of those with an early onset (<50 years) versus 56% of those with late onset (≥ 50 years) met criteria for TLE-MCI. A classification model between TLE-MCI and aMCI correctly classified 81.1% (90.6% specificity, 61.3% sensitivity) of the cohort based on neuropsychological scores. Whereas TLE-MCI showed greater deficits in language relative to aMCI, patients with aMCI showed greater rapid forgetting on memory measures. Both epilepsy-related risk factors and the presence of leukoaraiosis on MRI contributed to impairment profiles in TLE-MCI.

Significance: Cognitive impairment is a common comorbidity in epilepsy and it presents in a substantial number of older adults with TLE. Although the underlying etiologies are unknown in many patients, the TLE-MCI phenotype may be secondary

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

System, Grant/Award Number: CDA-2 1IK2CX001415; National Institutes of Health, Grant/Award Number: 01NS035140, F31 NS111883-01, K02NS070960, R01 AG027161-11, R01 NS065838, R01 NS088748, R01NS097719, R01NS111022 and T32 MH018399

to an accumulation of epilepsy and vascular risk factors, signal the onset of a neurodegenerative disease, or represent a combination of factors.

KEYWORDS

diagnostic classification, mild cognitive impairment, temporal lobe epilepsy

1 | INTRODUCTION

Older adults represent the fastest growing population of patients with epilepsy.[1] These patients present with a multitude of risk factors for accelerated cognitive and brain aging, including vascular/metabolic risk factors, altered lifestyles, and poor quality of life.[2–4] With a globally aging population, it is critical to fully characterize the cognitive impairment present in older adults with epilepsy and to identify those at increased risk for accelerated aging and progression to dementia.

Temporal lobe epilepsy (TLE) represents the most common form of focal epilepsy in adults.[5] Despite numerous studies demonstrating pervasive cognitive deficits in young to middle-aged patients with TLE,[6,7] the cognitive profiles of older adults has not been comprehensively characterized.[2] Furthermore, the prevalence of cognitive disorders in older patients with TLE is unknown. In a subset of epilepsy patients *at risk* for accelerated aging, cognitive impairments have been described as similar to those in classic amnestic mild cognitive impairment (aMCI),[8,9] often the pre-clinical phase of Alzheimer's disease (AD), including prominent deficits in memory. However, these studies included small samples, a wide range of epilepsy syndromes, or only compared the average cognitive profiles across groups.

We provide the first systematic characterization of the presence and nature of a cognitive disorder in a large group of older patients with refractory TLE and directly compare their cognitive profiles to those with aMCI and normally aging controls. Given the high prevalence of cerebrovascular risk factors (CVRFs) in epilepsy and their impact on the aging brain, we also evaluate the contribution of both epilepsy-related clinical factors and CVRFs to cognitive impairment. We hypothesize that given their multiple risk factors, a majority of patients with TLE will meet criteria for a cognitive disorder and that their performance will be comparable to patients with aMCI. We also predict that both epilepsy-related clinical factors and CVRFs will contribute to the extent of cognitive impairment observed in patients who meet criteria for a cognitive disorder.

Key Points

- We demonstrate that ~60% of older patients with temporal lobe epilepsy (TLE) meet diagnostic criteria for a cognitive disorder when using an actuarial neuropsychological method.
- Patients with TLE who meet criteria for mild cognitive impairment (TLE-MCI) exhibit neuropsychological profiles that are similar, but not identical, to patients with classic MCI.
- Both epilepsy-related factors and vascular risk factors were associated with the extent of cognitive impairment in TLE-MCI.

2 | METHODS

2.1 | Temporal lobe epilepsy patients

This study represents a retrospective investigation of patients obtained from University of California, San Diego (UCSD), Emory University, Cleveland Clinic, and University of Wisconsin-Madison (UWM). Data from UCSD, Emory, and UWM were obtained from separate institutional review board (IRB)–approved studies. At Cleveland Clinic, data were collected as part of an IRB-approved data registry. Seventy-eight older patients with TLE were included in this study from the four data sources. Inclusion criteria included age between 55 and 80 years; treated at a Level 4 epilepsy center; and diagnosed with TLE by a board-certified neurologist with expertise in epileptology, in accordance with International League Against Epilepsy (ILAE) criteria,[10] using video–electroencephalography (EEG) telemetry, seizure semiology, and neuroimaging evaluation. No patients with TLE had a known diagnosis of MCI or dementia at the time of their neuropsychological evaluation and no patients had a history of stroke or other neurological condition. Of the 78 patients with TLE, 5 were excluded due to the presence of tumors on magnetic resonance imaging (MRI).

2.2 | Amnestic mild cognitive impairment and NAC groups

Data for the aMCI and normally aging control (NAC) groups used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

Seventy-seven patients with aMCI and 69 NAC between the ages of 55 and 80 were selected from the ADNI database to match the TLE sample as closely as possible in age and sex. Criteria for ADNI eligibility and diagnostic classifications are described at http://www.adniinfo.org/Scientists/ADNIGrant/ProtocolSummary.aspx. All participants were determined to be nondemented by ADNI, and dementia was determined based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable Alzheimer's disease. None of the patients with aMCI had a history of other known neurological disorder, including epilepsy. Following recruitment and ADNI diagnosis, all participants completed a battery of neuropsychological tests.

2.3 | Neuropsychological measures and clinical variables

Measures of episodic memory included the delayed recall and recognition trials from the Rey Auditory Verbal Learning Test (RAVLT-Delayed and RAVLT-Recognition, respectively). Measures of language included visual confrontation naming with the Boston Naming Test (BNT)[11] and semantic fluency with Animal Fluency (AF). Measures of graphomotor speed and executive functioning included Trail-Making Test Parts A (TMT-A) and B (TMT-B), respectively. Language and graphomotor speed/executive function scores were corrected for age, education, sex, and race based on normative data from the expanded Halstead-Reitan Battery.[12] Scores from the RAVLT were age corrected using the Mayo Older Americans Normative Study.[13] Of note, the Mayo older adult norms do not include total AVLT learning, and therefore we only included delayed recall (RAVLT-Delayed) and recognition (RAVLT-Recog) in our analysis. The same norms were used for all three groups (aMCI, TLE, and NAC). For TLE only, Logical Memory -immediate recall (LM1) and Logical Memory -delayed recall (LM2) from the Wechsler Memory Scale-Third Edition (WMS-III)[14] were also included for diagnostic purposes. LM scores were corrected for age using the norms provided by the test manual. All scores were converted to T-scores (mean = 50, standard deviation = 10) for consistency and ease of interpretability.

For all TLE patients, epilepsy-related clinical variables and CVRFs were collected during standard clinical examination. CVRFs included diagnosis of hypertension, hyperlipidemia, diabetes mellitus, and/or obesity defined by a body mass index (BMI; mass [kg]/ height $[m]^2$) ≥ 30. The presence of leukoaraiosis and mesial temporal sclerosis (MTS) was determined by inspection of MRI images by a board-certified neuroradiologist for clinical purposes. Leukoaraiosis was determined based on visual analysis of T2/fluid-attenuated inversion recover (FLAIR) images and was considered present if T2 changes were characterized by numerous or extensive confluent foci in the periventricular/subcortical white matter, greater than expected for age. For the purpose of this study, MTS and leukoaraiosis were included as binary variables (ie, present or not present).

2.4 | Neuropsychological diagnostic classification

There is currently no consensus on a diagnostic definition for cognitive disorders in epilepsy, especially as they intersect with the most common disorders of aging. In an attempt to arrive at diagnostic criteria that can be used in older adults with TLE, we applied a comprehensive neuropsychological method (ie, Jak/Bondi diagnostic classification) that has been used recently to improve diagnosis and classification of MCI cohorts.[15–17] These criteria are based on objective measures of cognition and offer an operational definition of impairment. The following tests were used for TLE patients: BNT, AF, TMT-A, TMT-B, LM1, and LM2. Patients were considered to meet criteria for *TLE-MCI* if any one of the following two criteria were met: (a) they had impaired scores, defined as >1 SD below the demographically corrected normative mean, on two measures within at least one cognitive domain (ie, memory, language, or speed/executive function); or (b) they had one impaired score, defined as >1 SD below the demographically corrected normative mean, in each of the three cognitive domains sampled. Seventy-one patients (91%) had sufficient cognitive data and were therefore included in all subsequent analysis.

To ensure comparability, ADNI aMCI and NAC participants were also classified using the Jak/Bondi criteria[16,17] (described above). In accordance with previous MCI phenotyping studies in ADNI,[18,19] LM was not used in classification because it was used to establish the original diagnosis of MCI for ADNI. Therefore, diagnostic classification was based on the following tests: BNT, AF, TMT-A, TMT-B,

RAVLT-Delayed, and RAVLT-Recog. Sixty-four participants (83.1%) classified as aMCI based on the ADNI criteria met criteria for aMCI based on the Jak/Bondi criteria. The other 16.9% of patients were classified as cognitively normal, likely representing the *false-positive* cases identified in previous ADNI studies,[17,20] Sixty-five NAC participants (94.2%) classified as cognitively normal based on the ADNI criteria were classified as cognitively intact based on the Jak/Bondi actuarial neuropsychological criteria. The remaining participants, as well as the false-positive cases, were excluded from subsequent analyses.

2.5 | Statistical analysis

Analysis of variance (ANOVA), independent *t* tests, and Fisher exact tests were used to test for differences in clinical and demographic variables and neuropsychological performance when appropriate. Analysis of covariance (ANCOVA), controlling for age, sex, and education were conducted to compare neuropsychological performance (*T*-scores) across groups. When results from the ANCOVA were significant, group contrasts were assessed using post hoc pairwise tests with Bonferroni correction. Multiple comparisons were corrected using Benjamini-Hochberg false discovery rate. Stepwise linear regressions were conducted to evaluate the contribution of demographic, epilepsy-related clinical variables, and CVRFs to cognitive performance. Finally, a discriminant function analysis (DFA) was performed to test whether neuropsychological profiles could correctly classify TLE-MCI and aMCI at the individual subject level.

3 | RESULTS

3.1 | Demographic characteristics

There were differences in age across groups $F(1, 197) = 49.01$, $P < .001$; NACs (mean = 67.97; SD = 4.05) were older than patients with TLE (mean = 60.69; SD = 4.85; $P < .001$) and aMCI (mean = 63.57; SD = 3.89; $P < .001$), and patients with aMCI were older than those with TLE ($P < .001$). There were also differences in education across groups F (1, 197) = 25.49, $P < .001$; aMCI (mean = 16.11; SD = 2.93; $P < .001$) and NAC (mean = 16.23; SD = 2.75; $P < .001$) had more years of education relative to TLE (mean = 13.32; SD = 2.41). There were no differences in sex across the groups FE = 0.390, $P = .792$ (TLE = 60% female; aMCI = 58% female; NACs = 63%). Therefore, age and education were included as covariates. Given the expected effects of sex on some neuropsychological tests (eg, verbal memory),[21,22] sex was also included as a covariate.

3.2 | Diagnostic classification in patients with TLE

Forty-three patients (60%) with TLE met criteria for MCI (TLE-MCI), whereas 28 patients did not (40%; TLE-noMCI). Table 1 includes epilepsy-related characteristics/risk factors and CVRFs across TLE-MCI and TLE-noMCI. The only differences between the two patient groups were in age at seizure onset, duration of disease, and history of febrile seizures. Patients in the TLE-MCI group had a younger age at onset and longer duration of disease, and they were more likely to have a history of febrile seizures. When patients were divided into those with an early (<50 years) versus late (≥ 50 years) age at seizure onset, 29 patients with an early onset (63%) and 14 patients with a late onset (56%) met criteria for TLE-MCI.

The TLE-MCI group was further divided into patients with amnestic (single-domain = 12%; multiple-domain = 60%) and non-amnestic (ie, language, executive function/processing speed, single-domain = 14%; multiple-domain = 14%) profiles. Figure 1 displays the distribution of T-scores for each measure across TLE-MCI with amnestic profiles, TLE-MCI with non-amnestic profiles, and TLE-noMCI.

3.3 | Group differences across cognitive measures

Table 2 includes group comparisons on neuropsychological measures across TLE-MCI, TLE-noMCI, aMCI, and NAC. Figure 2 displays the average performance across the four groups. Overall, TLE-MCI and aMCI were significantly worse on every measure compared to NAC. TLE-MCI and aMCI showed similar performance on TMT-A and TMT-B. TLE-MCI demonstrated worse performance on language measures (BNT, Animal Fluency) relative to aMCI, whereas the aMCI showed worse performance on memory measures RAVLT-Delayed and RAVLT-Recognition. The TLE-noMCI showed similar performance to NAC on all measures. Compared to TLE-MCI, TLE-noMCI showed similar performance on RAVLT-Recognition, but demonstrated higher scores on all other measures. Relative to aMCI, TLE-noMCI showed similar performance on BNT and Animal Fluency, but higher scores on all other measures.

3.4 | Contribution of demographic and clinical variables and CVRFs to cognitive impairment in TLE

To reduce the number of variables included in the model, we conducted stepwise regressions to examine the differential contribution of demographics, epilepsy-related clinical variables,

TABLE 1 Clinical and demographic characteristics between TLE-MCI and TLE-noMCI

	TLE-MCI	TLE-noMCI	*t*-value	*P*-value
N	43	28		
Age at Onset	30.02 (20.5)	42.86 (16.12)	**−2.94**[a]	**.005**
Duration (years)	30.58 (20.63)	18.03 (15.65)	**2.91**[a]	**.005**
Current no. of AEDs	2.26 (0.82)	1.93 (0.86)	1.62	.111
No. of failed AEDs	5.67 (2.49)	5.12 (2.61)	0.886	.379
			Fisher's Exact	***P*-value**
Sex: Male/Female				
Handedness: L/R/A	6/35/2	1/24/3	2.65	.300
MTS: Y/N	22/21	13/13	0.009	1.00
Onset Side: L/R/Bilateral	25/12/6	15/7/5	0.357	.888
Late Onset[b]: Y/N	14/29	11/17	0.336	.617
Monotherapy/Polytherapy	7/36	9/19	2.45	.150
Epilepsy Risk Factors				
Febrile Seizures: Y/N	7/36	0/25	**8.82**	**.003**
Family History of Epilepsy: Y/N	5/38	5/22	2.17	.373
Moderate or Severe TBI: Y/N	3/40	3/24	1.94	.391
Vascular Risk Factors				
Leukoaraiosis: Y/N	12/29	10/15	0.805	.426
Diabetes: Y/N	3/40	0/28	2.04	.273
Hypertension: Y/N	14/29	10/18	0.075	.803
Hyperlipidemia: Y/N	9/34	9/19	1.13	.403
BMI > 30: Y/N	11/28	8/18	0.227	1.00
Smoking History: Y/N	14/29	12/16	0.775	.453

Abbreviations: A, ambidextrous; AEDs, antiepileptic drugs; F, female; L, left; M, male; MCI, mild cognitive impairment; MI, minimal impaired; R, right; MTS, mesial temporal sclerosis; TLE, temporal lobe epilepsy; standard deviations are presented inside the parentheses.

Bold represents significance with a Benjamini-Hochberg false discovery rate correction.

[a]Equal variance not assumed.

[b]Late onset: onset of epilepsy 50 or older.

and CVRFs to each neuropsychological test for each TLE group. The contribution of age, sex, and education were first evaluated. For TLE-MCI, age was a significant predictor for TMT-A ($\beta = -0.701$, $P = .040$; $R^2 = 0.115$), with increasing age associated with worse processing speed performance. Sex was a significant predictor for RAVLT-Delayed ($\beta = 8.98$, $P = .001$; $R^2 = 0.280$) and RAVLT-Recognition ($\beta = 5.893$, $P = .032$; $R^2 = 0.140$), with female participants performing better than male participants. Finally, education was a significant predictor for LM1 ($\beta = 1.655$, $P = .007$; $R^2 = 0.167$), with greater years of education associated with better performance. There were no significant predictors for TLE-noMCI.

The following clinical variables were evaluated for each cognitive test: age at seizure onset, side of seizure onset, MTS status, number of antiepileptic drugs (AEDs), and number of failed AEDs. For TLE-MCI, significant clinical predictors included MTS ($\beta = -6.627$, $P = .007$; $R^2 = 0.129$) and side of seizure onset ($\beta = 4.77$, $P = .008$; R^2 change $= 0.165$) for RAVLT-Delayed scores, and age at onset ($\beta = -0.238$, $P = .020$; $R^2 = 0.148$) for TMT-B, with left-sided onset, the presence of MTS, and older age at onset associated with worse performance. For TLE-noMCI, the only significant clinical predictor was age at onset for TMT-B ($\beta = 0.270$, $P = .017$; $R^2 = 0.215$), with an earlier age at onset associated with worse performance. To evaluate the additional contribution of CVRFs, we controlled for side of onset, MTS status, and age at onset given their contribution to neuropsychological performance described earlier. This analysis revealed that the presence of leukoaraiosis on MRI was associated with worse performance on RAVLT-Delayed ($\beta = -5.841$, $P = .034$) in the TLE-MCI group.

3.5 | Empirical classification of TLE-MCI and aMCI

A discriminant function analysis was performed to test whether neuropsychological profiles could correctly classify

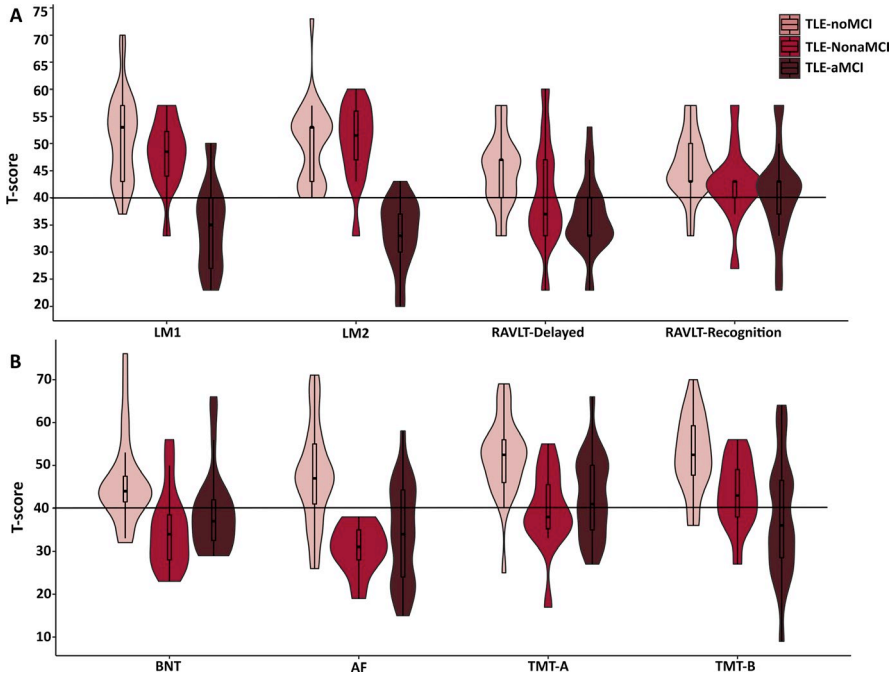

FIGURE 1 *Cognitive scores across TLE subtypes*. The distribution of cognitive scores for each neuropsychological test across TLE-MCI with amnestic profiles (TLE-aMCI), TLE-MCI with non-amnestic profiles (TLE-NonaMCI), and TLE-noMCI. The solid line represents impairment at one standard deviation below the mean of a healthy normative sample. Abbreviations: AF, animal fluency; BNT, boston naming test; LM1, logical memory 1; LM2, logical memory 2; RAVLT-Delayed, rey auditory verbal learning test-delayed; RAVLT-Recognition, rey auditory verbal learning test-recognition; TMT-A, trails making test condition A; TMT-B, trails making test condition B

TLE-MCI and aMCI at the individual subject level. The overall model correctly classified 81.1% of the patients (74.7% with cross-validation) with 90.6% specificity and 61.3% sensitivity (see receiver-operating characteristic [ROC] curve in Figure 3A). Of the 31 TLE-MCI patients with complete data, 12 patients were misclassified as aMCI and 6 aMCI patients were misclassified as TLE-MCI (Figure 3B). The distribution of scores across correctly classified and misclassified patients are presented on Figure 3C. The TLE-MCI misclassified patients were more likely to have left-sided seizure onset (59%), MTS (N = 7), and leukoaraiosis on MRI (N = 7), and a high prevalence of other CVRFs (N = 10) (see Table 3). As expected, the misclassified patients demonstrated greater impairments in LM2 (mean = 33.6), RAVLT-Delayed (mean = 33.2), and RAVLT-Recog (mean = 36.4) with more subtle deficits in BNT (mean = 39.8) and AF (mean = 37.8).

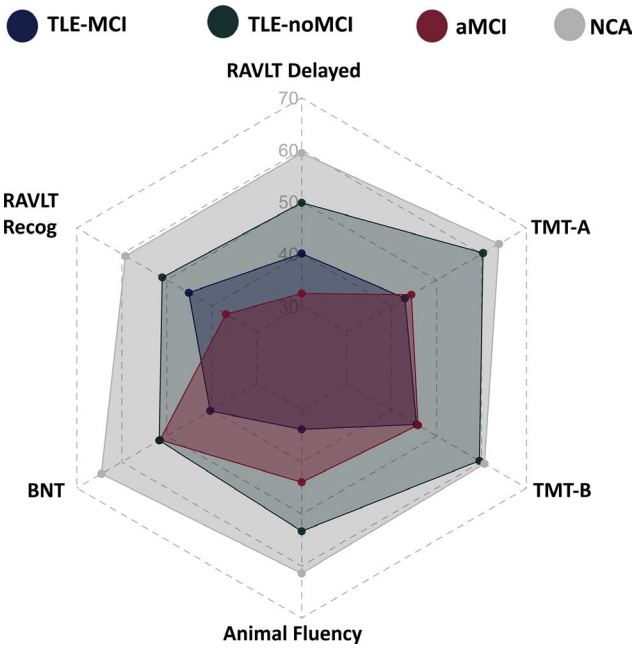

FIGURE 2 *Cognitive profiles across TLE-MCI, TLE-noMCI, aMCI, and NCA*. Radar plot demonstrating the overlap in performance across groups. Each point on the plot represents the average performance for each group

4 | DISCUSSION

Despite older adults with TLE representing a rapidly growing cohort of patients with epilepsy, the neuropsychological profile of these patients has not been comprehensively characterized. Furthermore, there is no consensus on diagnostic

TABLE 2 Neuropsychological differences across TLE-MCI, TLE-noMCI, aMCI, and NAC

	ANCOVA	TLE-MCI vs aMCI	TLE-MCI vs TLE-noMCI	TLE-aMCI vs NAC	TLE-NoMCI vs aMCI	TLE-noMCI vs NAC	aMCI vs NAC
RAVLT-Delayed	$F(3, 170) = 43.52$, $P < .001$	0.006	**0.020**	**<0.001**	**<0.001**	0.358	**<0.001**
RAVLT-Recog	$F(3, 166) = 36.29$, $P < .001$	**0.001**	0.330	**0.002**	**<0.001**	0.636	**<0.001**
BNT	$F(3, 190) = 10.41$, $P < .001$	**0.025**	0.050	**<0.001**	1.00	0.056	**0.001**
Animal Fluency	$F(3, 188) = 23.51$, $P < .001$	**0.022**	**<0.001**	**<0.001**	0.062	0.454	**<0.001**
TMT-A	$F(3, 187) = 17.10$, $P < .001$	1.00	**<0.001**	**<0.001**	**0.005**	1.00	**<0.001**
TMT-B	$F(3, 186) = 24.18$, $P < .001$	1.00	**<0.001**	**<0.001**	**0.001**	0.899	**<0.001**

Abbreviations: aMCI, amnestic mild cognitive impairment; BNT, Boston Naming Test; NAC, normal aging controls; RAVLT-Delayed, Rey Auditory Verbal Learning Test delayed; RAVLT-Recog, Rey Auditory Verbal Learning Test recognition; TLE, temporal lobe epilepsy; TMT-A, Trail Making Test condition A; TMT-B, Trail Making Test condition B.

Bold represents significance with a Benjamini-Hochberg false discovery rate correction.

criteria for cognitive disorders associated with aging in TLE, or epilepsy in general. This is concerning given the large number of patients meeting criteria for TLE-MCI in our study. Furthermore, a number of these patients may be at increased risk for dementia.[3] A uniform definition will help researchers and clinicians, (a) stratify the risk for dementia, (b) study the effects of cognitive impairments on quality of life and functional independence, (c) improve long-term health outcomes associated with aging, and (d) converse in a standard language regarding cognitive diagnoses using clear operational criteria.

We provide the first characterization of the presence and nature of a cognitive disorder in a large and well-characterized group of older adults with TLE. We demonstrate that approximately 60% of older TLE patients in our sample meet diagnostic criteria for a cognitive disorder. Second, we demonstrate that these patients exhibit neuropsychological profiles that are similar, but not identical, to patients with aMCI. In fact, 61% of patients with TLE-MCI could be distinguished from those with aMCI based on their language and memory profiles. Finally, we demonstrate that both epilepsy-related factors and CVRFs may play an important role in their impairment profiles. These data suggest that over half of older adults with TLE may meet clinical criteria for MCI, but that the nature of this impairment in a majority of patients is phenotypically different from prodromal AD and may reflect underlying epileptogenic and vascular pathology, along with changes secondary to years of ongoing seizures.

4.1 | THE TLE-MCI PHENOTYPE

Decades of research in epilepsy have demonstrated that cognitive dysfunction is a highly prevalent and debilitating comorbidity in TLE.[23,24] However, the TLE literature has focused mainly on characterizing the cognitive trajectories of children and young to middle-aged adults, and very little is known about cognitive impairment in older adults.[2] Critically, the prevalence of clinical diagnoses associated with abnormal cognitive aging (eg, MCI, dementia) remains unknown. A small number of empirical studies have compared the average cognitive profiles of older patients with epilepsy to healthy controls and have reported worse cognitive performance in epilepsy patients.[8,9,25–27] However, these studies have included heterogeneous groups of patients with a wide range of epilepsy syndromes and have not applied uniform diagnostic criteria. Here, we demonstrate that older adults with TLE who meet diagnostic criteria for MCI (TLE-MCI) harbor significant cognitive impairment characterized by an amnestic, multi-domain profile with deficits most commonly in memory and language. By applying widely used empirically derived diagnostic criteria for MCI, we were able to identify the presence of a cognitive disorder in 63%

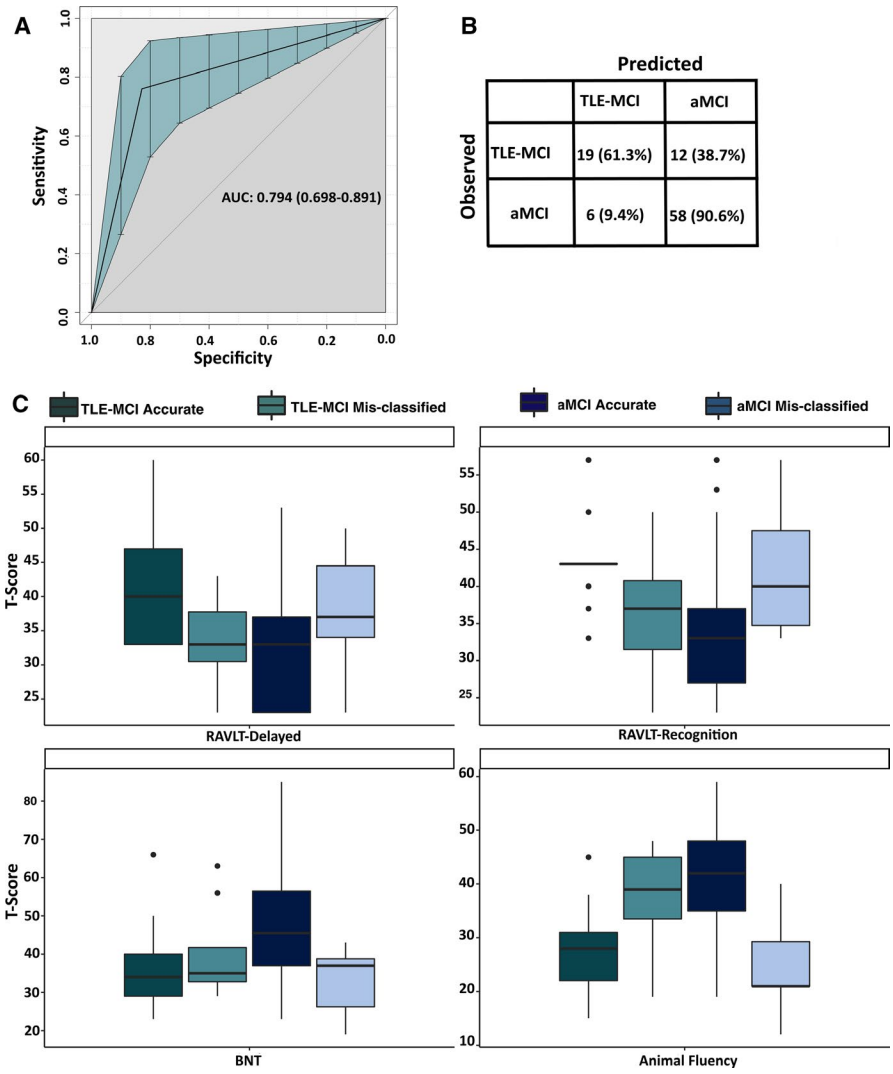

FIGURE 3 *Empirical Classification of TLE-MCI and aMCI.* A, Receiver-operating characteristic (ROC) curve. B, Number of predicted and observed cases for TLE-MCI and aMCI. C, Distribution of scores for patients that were correctly classified and patients that were incorrectly classified

TABLE 3 Clinical and cognitive characteristics of misclassified TLE-MCI patients

Patient	Onset	Side	MRI	Leukoaraiosis	CVRFs	LM2	RAVLT-Delayed	RAVLT-Recog	BNT	AF
1	0	Left	Other	No	HTN	53	43	27	56	38
2	44	Right	MTS	Yes	HTN, HLD		23	43	35	32
3	52	Left	MTS	No	HLD	20	23	27	37	19
4	5	Left	MTS	No	HTN, HLD	33	37	37	32	34
5	53	Right	Nonlesional	No	DM, Obesity	37	33	23	63	45
6	10	Left	Other	No	-	20	33	33	35	41
7	56	Left	Encephalomalacia	Yes	DM	40	33	50	29	45
8	11	Bilateral	MTS	Yes	-	30	40	37	33	40
9	28	Right	MTS	Yes	HTN, Obesity	37	37	40	56	47
10	44	Left	MTS	Yes	HLD	27	23	40	30	34
11	26	Bilateral	MTS	Yes	HTN, Obesity	33	40	43	34	48
12	55	Left	Other	Yes	HTN, HLD, Obesity	40	33	37	37	31

Abbreviations: AF, Animal fluency BNT, Boston Naming Test; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; LM2, Logical Memory 2; MTS, mesial temporal sclerosis; RAVLT, Rey Auditory Verbal Learning Test; Recog: recognition.

Scores for LM2, RVLT-Recog, BNT and AF represents T-scores with impairment defined as 1 SD (>40) below normative data.

of patients with longstanding TLE and 56% of those with a more recent epilepsy diagnosis. There is an increasing number of studies demonstrating progressive cognitive decline and brain atrophy in patients with longstanding TLE.[3,4,23] Whether progressive changes represent an accelerated aging process or an exacerbation of preexisting cognitive impairment as they interact with the normal aging process remains unknown.[3,28,29] An alternative view is that cognitive decline observed in older adults with epilepsy may result from a "second hit" (ie, an early developmental injury followed by seizures as a second "hit"). Of interest, in our cohort, a great proportion of patients with late-onset TLE met criteria for MCI. Recent studies have documented the presence of cognitive deficits around the time of diagnosis in patients with late-onset epilepsy that eventually follows a progressive course.[8,30] Thus the "second hit" hypothesis may also explain why patients with a new epilepsy diagnosis late in life may experience cognitive decline. Longitudinal studies are needed to determine the mechanism(s) involved in the cognitive impairment observed in older adults with epilepsy. Nonetheless, diagnostic approaches such as the one employed in our study are the first step toward identifying patients that may be at risk for further cognitive decline and/or dementia and may benefit from early intervention (eg, control of CVRFs) and close monitoring of their cognitive functioning.

Although a large proportion of the TLE patient cohort met criteria for MCI, 39% of the TLE patients did not meet criteria despite having similar clinical profiles. Previous work on cognitive phenotypes has demonstrated that approximately 31% to 47% of young to middle-age adults do not demonstrate cognitive impairments despite having clinical features known to impact cognition.[7,31–33] Furthermore, neuroimaging findings have shown that these patient demonstrate no or minimal brain abnormalities relative to healthy controls. This group of patients may represent a group with high cognitive or brain reserve or may have protective factors (eg, complex occupational histories, bilingualism, or genetics) that could protect against epilepsy-related pathology. Future studies examining the health and psychosocial factors associated with unimpaired profiles in older adults with epilepsy may help to shed light on this resilient group.

Notably, when comparing the cognitive profiles of TLE-MCI to aMCI, an interesting pattern emerged. The TLE-MCI patients were highly similar to those with aMCI on measures of verbal learning, processing speed and executive functioning. Unique to TLE-MCI were impairments in language, whereas aMCI demonstrated evidence of more rapid forgetting. It is notable that we were able to correctly classify 81% of the patients based on cognitive scores alone. Therefore, a majority of TLE-MCI patients appear phenotypically different from aMCI, which could have diagnostic value and implications for differentiating their cognitive trajectories and risk for progression to AD.

4.2 | Similarities in the TLE-MCI phenotype and aMCI

In addition to the shared cognitive dysfunction observed in aMCI and older adults with TLE,[9] there is evidence suggesting a bi-directional relationship between TLE and AD. For instance, patients with epilepsy are at increased risk for developing AD,[34] and patients with AD have a 6- to 10-fold higher risk of developing seizures.[35] This bi-directional relationship has been linked to the presence of tau pathology,[36] amyloid beta precursor protein,[37] and senile plaques,[38,39] in TLE, all of which are pathologic hallmarks of AD. Nardi Cesarini et al[8] reported that patients with late-onset epilepsy of unknown origin who met criteria for MCI had AD-like cerebrospinal fluid profiles that were similar to those of patients with MCI without seizures. However, AD-related biomarkers have also been identified in the resected tissue of young to middle-age TLE patients with *chronic* epilepsy. Therefore, it is unclear whether deposition of AD-related pathology contributes to the development of seizures, is the consequence of many years of seizures,[3] or is unrelated to epilepsy. Although we were able to correctly classify 81% of the patients based on cognitive scores alone, ~39% of TLE-MCI patients were misclassified as aMCI. This is of interest given that a subset of older adults with TLE have AD-related pathology and progress to AD. Of interest, these misclassified patients include those with early and late seizure onsets as well as patients with elevated CVRFs. Thus it is possible that this subset of patients with a more classically MCI-like cognitive profile may represent a subgroup that is on a progressive course to AD. There are no established recommendations for biomarkers or neuropsychological tests specific for older adults who present first with epilepsy but may harbor a progressive neurodegenerative disorder. Therefore, AD-related MCI may be missed in these patients as cognitive impairments are attributed to their known seizure disorder and comorbid disorders are often overlooked.

4.3 | Contribution of epilepsy and CVRFs to cognitive impairment

We found that the presence of MTS and left-sided seizure onset was associated with worse cognitive performance in delayed memory and executive function. These clinical variables have been shown to impact cognition and predict long-term cognitive and postoperative outcomes.[6] In addition, we found that female sex, greater years of education, and younger age were associated with better performance across different cognitive measures. Of note, compared to other surgical studies of older adults with TLE, our patient sample had similar characteristics in terms of duration of epilepsy (range of published samples 30.39 to 38 years[40–44]), age at onset

(range = 18.48 to 24[40,43]), and proportion of patients with MTS (range = 43.8%-76%[40,42,44]). Unique to our study is the large proportion of patients with late-onset (onset <50 years) TLE who often have unknown etiologies, are less likely to have MTS, and have a much shorter duration of epilepsy. Taken together, we demonstrate that in patients with TLE-MCI there are important clinical and demographic features that contribute to their cognitive profiles. It is possible that with advancing age these clinical features further exacerbate an already diminished cognitive capacity and could be used to identify the patients at increased risk for further cognitive decline.

In our cohort, approximately 60% of TLE patients had at least one CVRF and 31% of patients had evidence of leukoaraiosis on MRI. After controlling for important epilepsy-related clinical variables, leukoaraiosis was associated with poorer delayed memory performance. This pattern emerged in patients with both early and late-onset seizures, suggesting that vascular pathology may lead to a worsening of pre-existing memory impairments in older adults with epilepsy. A 50-year follow-up population-based study, revealed increased MRI markers of cerebrovascular disease in adults with childhood-onset epilepsy.[45] Thus patients with early onset epilepsy may start with a greater cerebrovascular risk when they reach middle-age and those with a late onset may already have a diminished brain and cognitive reserve that have resulted in the clinical manifestation of seizures. However, the cumulative effect of CVRFs and epilepsy-related factors is not well understood. Prospective longitudinal studies are needed to identify modifiable risk factors that could mitigate cognitive and functional decline, and potentially halt progression to dementia in high risk patients.

4.4 | Limitations

There are several limitations to our study. Although the tests included in our study are among the most commonly used measures in epilepsy clinics, we did not include measures designed to assess for cognitive decline in older adults that are commonly used in memory-disorder clinics. However, our test selection is representative of common clinical practice and can be used to identify patients who may benefit from referral to a memory disorders/dementia clinic. As the number of older adults with epilepsy continues to increase, neurologists and neuropsychologists who see patients with epilepsy will need updated guidelines on the diagnosis and treatment of older adults with epilepsy who may also be presenting with cognitive deficits suggestive of a progressive disorder of aging. Second, our study is cross-sectional, and we did not have longitudinal data or information on progression to dementia. Thus it was not possible to determine if the cognitive impairments observed in our cohort were longstanding and static over time or represent a significant decline as these patients reached older age. Although there are some similarities in cognitive impairment between older adults and young to middle-age patients, given the differences in the cognitive domains assessed, etiologic differences between early and late-onset TLE, and the use of surgical vs nonsurgical samples, it is difficult to compare the cognitive profiles of young to middle-age TLE to those of older adults. Furthermore, given the age of our cohort, we did not have a detailed history of developmental or psychiatric conditions, and thus we were not able to determine the contribution of these comorbidities to their cognitive profiles. Longitudinal studies of older patients with early and late-onset epilepsy are greatly needed to risk-stratify patients for progression to dementia and implement early interventions aimed at delaying the negative impact of cognitive decline on quality of life and functional independence. Third, we did not have biomarker or genetic data on our epilepsy cohort given that they are not routinely collected as part of standard medical care. Collecting biomarkers and genetic data could help to further identify patients in the prodromal state of AD. Finally, our sample consisted of patients with drug-resistant TLE who were being treated at an epilepsy surgical center, and therefore our results may not be applicable to older adults being treated at community neurology clinics or patients with more benign forms of TLE who may have a lower risk profile. Furthermore, population-based studies are needed to determine whether the rate of impairment observed in our TLE sample reflects the true prevalence of cognitive disorder associated with aging in the broader TLE population.

5 | CONCLUSION

We demonstrate that 60% of patients with TLE who are over the age of 55 meet diagnostic criteria for a cognitive disorder when comprehensive neuropsychological criteria are applied. As the field of epilepsy moves toward *precision neuropsychology*—an emerging approach for neuropsychological assessment and intervention that takes into account individual variability in genes, environment, and lifestyle for each person—it is critical to develop a diagnostic framework that can be applied to older adults with epilepsy across clinics and geographic locations. The diagnostic method applied in our study is the first step in this direction, providing an operational definition to impairment that can be used with different neuropsychological batteries.

ACKNOWLEDGMENTS

Supported by National Institute of Health/National Intitute of Neurological Disorders and Stroke (NIH/NINDS) R01 NS065838 (CRM); T32 MH018399 (EK); F31 NS111883-01 (AR); R01 NS088748 and K02NS070960 (DLD);

R01NS111022 and R01 AG027161-11 (BPH); NIH/NINDS R01NS097719 and R01NS035140 (RMB); and the US Department of Veterans Affairs CSR&D Service (CDA-2 1IK2CX001415; ECE). Dr Herman receives support by grants from Citizens United for Research in Epilepsy. Thanks to participants as well as the many collaborators (faculty, staff, students) who were instrumental in the success of the original investigation from which these older participants were derived.

CONFLICTS OF INTEREST

Dr Drane receives grant/contract funding from Medtronic, Inc. All other authors have no disclosures to report. ADNI: Data collection and sharing for this project was funded by the Alzheimer's Disease; Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904), and DOD ADNI (Department of Defense award number W81XWH-12-2–0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc; Cogstate; Eisai Inc; Elan Pharmaceuticals, Inc; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen. Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for NeuroImaging at the University of Southern California. 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.

ORCID

Anny Reyes https://orcid.org/0000-0003-0625-6990
Erik Kaestner https://orcid.org/0000-0003-3252-5365
Daniel L. Drane https://orcid.org/0000-0001-8747-672X
Vineet Punia https://orcid.org/0000-0002-0552-6736
Robyn M. Busch https://orcid.org/0000-0002-5442-4912
Bruce P. Hermann https://orcid.org/0000-0003-0133-4427

REFERENCES

1. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol. 2003;16:165–70.
2. Hermann B, Seidenberg M, Sager M, Carlsson C, Gidal B, Sheth R, et al. Growing old with epilepsy: the neglected issue of cognitive and brain health in aging and elder persons with chronic epilepsy. Epilepsia. 2008;49:731–40.
3. Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. Brain. 2018;141:1592–608.
4. Galovic M, van Dooren VQH, Postma TS, Vos SB, Caciagli L, Borzì G, et al. Progressive cortical thinning in patients with focal epilepsy. JAMA Neurol. 2019;76:1230.
5. Tellez-Zenteno JF, Hernandez-Ronquillo L. A Review of the Epidemiology of Temporal Lobe Epilepsy. Epilepsy Res Treat. 2012;2012:630853.
6. Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy.Nat Rev Neurol. 2011;7:154–64.
7. Reyes A, Kaestner E, Ferguson L, Jones JE, Seidenberg M, Barr WB, et al. Cognitive phenotypes in temporal lobe epilepsy utilizing data- and clinically driven approaches: Moving toward a new taxonomy. Epilepsia. 2020;61(6):1211–20.
8. Nardi Cesarini E, Babiloni C, Salvadori N, Farotti L, Del Percio C, Pascarelli MT, et al. Late-onset epilepsy with unknown etiology: a pilot study on neuropsychological profile. Cerebrospinal Fluid Biomarkers, and Quantitative EEG Characteristics. Front Neurol. 2020;11:199.
9. Griffith HR, Martin RC, Bambara JK, Marson DC, Faught E. Older adults with epilepsy demonstrate cognitive impairments compared with patients with amnestic mild cognitive impairment. Epilepsy Behav. 2006;8:161–8.
10. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
11. Kaplan E, Goodglass H, Weintraub S. Boston naming test. Austin, TX: Pro-ed; 2001.
12. Heaton R, Miller SW, Taylor MJ, Grant-Isibor I. Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. 2004.
13. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC, Kokmen E, et al. Mayo's older Americans normative studies: updated AVLT norms for ages 56 to 97. Clin Neuropsychol. 1992;6:83–104.
14. Wechsler D. WMS-III. Wechsler memory scale administration and scoring manual. San Antonio, TX: Psychological Corporation; 1997.
15. Bondi MW, Jak AJ, Delano-Wood L, Jacobson MW, Delis DC, Salmon DP. Neuropsychological Contributions to the Early Identification of Alzheimer's Disease. Neuropsychol Rev. 2008;18:73–90.
16. Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, Corey-Bloom J, Salmon DP, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. Am J Geriatr Psychiatry. 2009;17:368–75.
17. Bondi MW, Edmonds EC, Jak AJ, Clark LR, Delano-Wood L, McDonald CR, et al. Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. J Alzheimers Dis. 2014;42:275–89.

18. Edmonds EC, McDonald CR, Marshall A, Thomas KR, Eppig J, Weigand AJ, et al. Early versus late MCI: Improved MCI staging using a neuropsychological approach. Alzheimers Dement. 2019;15:699–708.
19. Edmonds EC, Eppig J, Bondi MW, Leyden KM, Goodwin B, Delano-Wood L, et al. Heterogeneous cortical atrophy patterns in MCI not captured by conventional diagnostic criteria. Neurology. 2016;87:2108–16.
20. Edmonds EC, Delano-Wood L, Clark LR, Jak AJ, Nation DA, McDonald CR, et al. Susceptibility of the conventional criteria for mild cognitive impairment to false-positive diagnostic errors. Alzheimers Dement. 2015;11:415–24.
21. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. Psychol Aging. 2016;31:166–75.
22. Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. J Int Neuropsychol Soc. 2005;11:290–302.
23. Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy. J Int Neuropsychol Soc. 2007;13:12–20.
24. Allone C, Lo Buono V, Corallo F, Pisani LR, Pollicino P, Bramanti P, et al. Neuroimaging and cognitive functions in temporal lobe epilepsy: a review of the literature. J Neurol Sci. 2017;381:7–15.
25. Martin RC, Griffith HR, Faught E, Gilliam F, Mackey M, Vogtle L. Cognitive functioning in community dwelling older adults with chronic partial epilepsy. Epilepsia. 2005;46:298–303.
26. Miller LA, Galioto R, Tremont G, Davis J, Bryant K, Roth J, et al. Cognitive impairment in older adults with epilepsy: characterization and risk factor analysis. Epilepsy Behav. 2016;56:113–7.
27. Piazzini A, Canevini MP, Turner K, Chifari R, Canger R. Elderly people and epilepsy: cognitive function. Epilepsia. 2006;47(Suppl 5):82–4.
28. Breuer LEM, Grevers E, Boon P, Bernas A, Bergmans JWM, Besseling RMH, et al. Cognitive deterioration in adult epilepsy: clinical characteristics of "Accelerated Cognitive Ageing". Acta Neurol Scand. 2017;136:47–53.
29. Breuer L, Boon P, Bergmans J, Mess WH, Besseling R, de Louw A, et al. Cognitive deterioration in adult epilepsy: Does accelerated cognitive ageing exist? Neurosci Biobehav Rev. 2016;64:1–11.
30. Liguori C, Costa C, Franchini F, Izzi F, Spanetta M, Cesarini EN, et al. Cognitive performances in patients affected by late-onset epilepsy with unknown etiology: A 12-month follow-up study. Epilepsy Behav. 2019;101:106592.
31. Hermann B, Conant LL, Cook CJ, Hwang G, Garcia-Ramos C, Dabbs K, et al. Network, clinical and sociodemographic features of cognitive phenotypes in temporal lobe epilepsy. Neuroimage Clin. 2020;27:102341.
32. Elverman KH, Resch ZJ, Quasney EE, Sabsevitz DS, Binder JR, Swanson SJ. Temporal lobe epilepsy is associated with distinct cognitive phenotypes. Epilepsy Behav. 2019;96:61–8.
33. Reyes A, Kaestner E, Bahrami N, Balachandra A, Hegde M, Paul BM, et al. Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities. Neurology. 2019;92:e1957–e1968.
34. Breteler MM, de Groot RR, van Romunde LK, Hofman A. Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study. Am J Epidemiol. 1995;142:1300–5.
35. Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: A population-based nested case-control analysis. Epilepsia. 2013;54:700–7.
36. Smith KM, Blessing MM, Parisi JE, Britton JW, Mandrekar J, Cascino GD. Tau deposition in young adults with drug-resistant focal epilepsy. Epilepsia. 2019;60:2398–403.
37. Sheng JG, Boop FA, Mrak RE, Griffin WS. Increased neuronal beta-amyloid precursor protein expression in human temporal lobe epilepsy: association with interleukin-1 alpha immunoreactivity. J Neurochem. 1994;63:1872–9.
38. Gouras GK, Relkin NR, Sweeney D, Munoz DG, Mackenzie IR, Gandy S. Increased apolipoprotein E epsilon 4 in epilepsy with senile plaques. Ann Neurol. 1997;41:402–4.
39. Mackenzie IR, Miller LA. Senile plaques in temporal lobe epilepsy. Acta Neuropathol. 1994;87:504–10.
40. Chapin JS, Busch RM, Silveira DC, Wehner T, Naugle RI, Ferguson L, et al. Memory performance in older adults before and after temporal lobectomy for pharmacoresistant epilepsy. Clin Neuropsychol. 2013;27:1316–27.
41. Murphy M, Smith PD, Wood M, Bowden S, O'Brien TJ, Bulluss KJ, et al. Surgery for temporal lobe epilepsy associated with mesial temporal sclerosis in the older patient: a long-term follow-up. Epilepsia. 2010;51:1024–9.
42. Thompson PJ, Baxendale SA, McEvoy AW, Duncan JS. Cognitive outcomes of temporal lobe epilepsy surgery in older patients. Seizure. 2015;29:41–5.
43. Moura LMVR, Eskandar EN, Hassan M, Salinas J, Cole AJ, Hoch DB, et al. Anterior temporal lobectomy for older adults with mesial temporal sclerosis. Epilepsy Res. 2016;127:358–65.
44. Boling W, Andermann F, Reutens D, Dubeau F, Caporicci L, Olivier A. Surgery for temporal lobe epilepsy in older patients. J Neurosurg. 2001;95:242–8.
45. Sillanpaa M, Anttinen A, Rinne JO, Joutsa J, Sonninen P, Erkinjuntti M, et al. Childhood-onset epilepsy five decades later. A prospective population-based cohort study. Epilepsia. 2015;56:1774–83.

How to cite this article: Reyes A, Kaestner E, Edmonds EC, et al; for the Alzheimer's Disease Neuroimaging Initiative. Diagnosing cognitive disorders in older adults with epilepsy. *Epilepsia*. 2021;62:460–471. https://doi.org/10.1111/epi.16780