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Temporal lobe epilepsy is associated with distinct cognitive phenotypes☆

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ABSTRACT

Neuropsychological assessment is critical for understanding the impact of seizures on cognition and informing treatment decisions. While focus is often placed on examining groups based on seizure type/epilepsy syndrome, an alternate approach emphasizes empirically derived groups based solely on cognitive performance. This approach has been used to identify cognitive phenotypes in temporal lobe epilepsy (TLE). The current study sought to replicate prior work by Hermann and colleagues (2007) and identify cognitive phenotypes in a separate, larger cohort of 185 patients with TLE (92 left TLE, 93 right TLE). Cluster analysis revealed 3- and 4-cluster solutions, with clusters differentiated primarily by overall level of performance in the 3-cluster solution (Low, Middle, and High performance) and by more varying cognitive phenotypes in the 4-cluster solution (Globally Low, Low Executive Functioning/Speed, Low Language/Memory, and Globally High). Differences in cognitive performance as well as demographic and clinical seizure variables are presented. A greater proportion of the patients with left TLE were captured by Cluster 3 (Low Language/Memory) than by the other 3 clusters, though this cluster captured only approximately one-third of the overall group with left TLE. Consistent with prior findings, executive functioning and speed emerged as additional domains of interest in this sample of patients with TLE. The current results extend prior work examining cognitive phenotypes in TLE and highlight the importance of identifying the comprehensive range of potential cognitive profiles in TLE.

1. Introduction

Neuropsychological impairment within various neurological and psychiatric disorders is often quite heterogeneous, and exploration of cognitive phenotypes is valuable for identifying subgroups of patients within broader diagnostic populations who have relatively similar profiles of cognitive functioning. Cognitive phenotypes have been explored in many diagnostic groups including Alzheimer's disease [1], bipolar disorder [2], autism [3], and epilepsy [4], to name a few. Once these cognitive phenotypes are characterized, correlation with various clinical, neuroanatomical, and psychosocial factors can be explored to better understand the heterogeneity of these diagnostic groups, with the goal of informing treatment planning and optimizing prognosis.

One of the most common localized epilepsy syndromes is temporal lobe epilepsy (TLE). Historically, TLE has been thought to produce focal deficits. In particular, material-specific episodic memory impairment as a result of a primary seizure focus and pathology within medial temporal structures is commonly highlighted [5,6]. Deficits in language-based cognitive tasks (i.e., verbal memory, confrontation naming, language comprehension, verbal fluency) are typically associated with unilateral left TLE [6,7]. Hermann et al. [7] found that patients with left TLE performed significantly worse than patients with right TLE on five of seven measures from the Multilingual Aphasia Battery, including Visual Naming, Sentence Repetition, Token Test, Aural Comprehension, and Visual Comprehension. Deficits in visuospatial functions have also been demonstrated in TLE, with some evidence of greater impairment in patients with unilateral right TLE [8]; however, others observed visuospatial deficits in both patients with left and patients with right unilateral TLE [6].

More recent work has highlighted deficits in patients with TLE that implicate regions beyond the temporal lobe epileptic zone, suggesting more widespread patterns of cognitive dysfunction. Patients with TLE showed poorer performance not only on measures of memory and language, but also on measures of general intelligence, executive function, and psychomotor functioning compared with healthy controls [9]. Oyegbile and colleagues [9] found that both patients with left and patients with right TLE differed significantly from controls on a wide range of measures, with patients with left TLE performing more poorly

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than controls on 19 of 20 cognitive tests and patients with right TLE performing more poorly than controls on 17 of the 20 tests. Moreover, after controlling for age, gender, and education, only one measure – confrontation naming – approached significance ($p = .10$) in discriminating between patients with left and patients with right TLE, suggesting little specificity to the types of deficits found in these groups with TLE [9]. Duration of seizure disorder and age at onset of seizures also play a role in cognitive functioning, with patients who have earlier onset and longer duration of intractable focal epilepsy exhibiting more generalized cognitive impairment, likely due to pathological mechanisms influencing areas beyond the epileptogenic zone [10,11].

There is also growing consensus regarding impaired executive functioning in TLE [12]. Numerous studies have documented executive dysfunction based on the Wisconsin Card Sorting Test (WCST) in patients with TLE [13–16]. One study examining 64 patients with unilateral TLE (38 right, 26 left) found that 44% exhibited clinically significant perseveration on the WCST, with deficits noted in a substantial proportion of both the patient group with left TLE (35%) and the patient group with right TLE (52%) [17]. Similarly, another study investigating executive dysfunction in 85 patients with mesial TLE (43 left, 42 right) found that 56% of patients demonstrated impaired WCST performance prior to anterior temporal lobectomy, with 30% exhibiting severe impairment [18]. Patients with left TLE exhibited significantly more total errors, perseverative errors, and perseverative responses, and completed fewer categories than patients with right TLE in this study. Additional studies documented compromised executive functioning on tasks emphasizing decision-making [19,20], as well as working memory, cognitive flexibility, categorical verbal fluency, set-shifting, categorization, and planning [21]. While executive function impairments in patients with TLE relative to healthy controls have been repeatedly demonstrated, the effect of TLE laterality on executive functioning is less clear.

This pattern of generalized cognitive dysfunction in patients with TLE suggests a neural impact beyond what would be expected with a focal deficit syndrome [4]. However, it has been noted that while this generalized dysfunction may represent the "average" cognitive profile of this patient group, examination of individual profiles reveals substantial variability, with performances ranging from significantly impaired to intact. To more fully explore the heterogeneity of cognitive functioning in patients with TLE, Hermann and colleagues conducted a cluster analysis differentiating three cognitive phenotypes in a sample of 96 patients with TLE [4]. These three cluster groups were characterized as (1) a minimally impaired group, (2) a memory impaired group, and (3) a memory, executive, and speed impaired group.

Across these clusters, no significant differences were found based on gender, age of epilepsy onset, education, or overall seizure frequency [4]. Additionally, within a subset of the sample that underwent ictal monitoring identifying unilateral left ($n = 24$) or right ($n = 21$) temporal lobe onset, there was no significant difference in the distribution of patients with right and patients with left TLE across clusters. Significant cluster differences did emerge for a number of other demographic and clinical seizure variables, such that the memory, executive, and speed impaired group was significantly older, had a longer epilepsy duration, and was taking more antiepileptic medications compared with the minimally impaired group. Additionally, the memory, executive, and speed impaired group exhibited a poorer prospective cognitive course (based on reassessment 4 years postbaseline) compared to the other two clusters, which did not differ from each other. These findings highlight the utility of defining cognitive phenotypes to understand the relationships between these groups and various demographic and clinical seizure variables as well as for better understanding cognitive prognosis.

The current study sought to replicate this prior work and identify cognitive phenotypes in a separate, larger cohort of patients with TLE. We hypothesized that the current cluster analysis would reveal groups with distinct cognitive phenotypes, including deficits in cognitive domains beyond the typically anticipated episodic memory and language deficits. Based on previous research, we anticipated that differences in executive functioning would drive the differentiation of our clusters in addition to memory and language differences.

2. Materials and method

2.1. Participants

This study was reviewed and approved by the Medical College of Wisconsin Human Subjects Committee and followed institutional guidelines for human subject research. All participants provided informed consent for participation. Participants were 185 adult TLE surgery candidates (92 left TLE, 93 right TLE) enrolled prospectively in a research protocol at the Medical College of Wisconsin who met the following selection criteria: 1) localization-related epilepsy of definite or probable temporal lobe origin; 2) Full-scale intelligence quotient (IQ) greater than or equal to 70; and 3) absence of any identifiable structural magnetic resonance imaging (MRI) abnormalities on clinical reading other than medial temporal lobe sclerosis. All participants underwent a standard preoperative workup for epilepsy surgery including continuous video-electroencephalogram (EEG) monitoring, neurological evaluation, neuropsychological testing, language mapping with functional MRI (fMRI) ($n = 22$), Wada ($n = 33$), or both ($n = 114$), and in some cases magnetoencephalography (MEG) ($n = 17$). A subset of patients underwent invasive EEG monitoring of spontaneous seizures with subdural strip or grid electrodes ($n = 48$) for more precise localization of the seizure onset zone. Determination of localization and lateralization of ictal seizure onset was made independently by an electroencephalographer who was blinded to the sociodemographic and neuropsychologic characteristics of the patients.

Sample demographics are presented in Table 1. Briefly, participants were between 18 and 68 years of age. A majority of the sample was female (57.3%) and white (87%). Average educational attainment was some college ($m = 13$ years, $SD = 2.5$ years).

Regarding clinical seizure variables, average age at seizure onset was 14.4 years, with average seizure disorder duration of 20.7 years. A sizable minority of the sample experienced secondarily generalized seizures (43.2%) and had a history of status epilepticus (11.1%). Additionally, large subsets of this sample of patients with TLE currently experienced multiple seizure types (68.1%) and had a lifetime history of generalized tonic–clonic seizures (72.9%). Regarding pharmacologic intervention with antiepileptic medication, most patients were treated with polytherapy (40.0% on two medications, 26.5% on three medications, and 4.3% on four medications). For the subsample of patients with TLE who were treated with monotherapy (27.0%), the antiepileptic medications used for treatment included carbamazepine ($n = 14$), phenytoin ($n = 13$), lamotrigine ($n = 7$), gabapentin ($n = 5$), valproate ($n = 3$), and various other medications ($n = 8$). Specific medications were unknown for 4 patients.

2.2. Neuropsychological assessment

All participants were administered a comprehensive neuropsychological test battery as part of their preoperative assessment for surgical consideration. Cognitive testing included standardized clinical measures of intellectual abilities, language, visuoperceptual ability, verbal and visual memory (i.e., immediate, delayed), executive functions, and speeded psychomotor functioning [13,22–31]. Table 2 provides a summary of the cognitive domains, specific cognitive abilities evaluated, and tests administered. Cognitive domain scores were created by computing the average standard scores of the psychometric tests falling within each of the cognitive domains.

2.3. Statistical analyses

The present study was conducted to replicate the prior work on cognitive phenotypes in TLE [4] in a larger, independent cohort of patients

Table 1
Demographic and clinical seizure characteristics.

	Total sample	Cluster 1 (Globally Low)	Cluster 2 (Low EF/S)	Cluster 3 (Low L/M)	Cluster 4 (Globally High)	Cluster differences
	($n = 185$)	($n = 39$)	($n = 47$)	($n = 44$)	($n = 55$)	
Age	37.9 (11.4)	37.1 (10.8)	42.1 (11.0)	35.4 (13.0)	36.7 (10.0)	Low EF/S > Low L/M
Education	13.0 (2.5)	11.7 (2.3)	13.0 (2.2)	13.1 (2.3)	13.9 (2.6)	GL < GH, (*t*) Low L/M GL < All Other Clusters
Full-Scale IQ	92.1 (11.6)	79.9 (5.1)	90.7 (7.3)	90.8 (7.8)	103.0 (10.6)	GH > All Other Clusters GL < Low EF/S, Low L/M < GH
Sex (% Female)	57.3%	64.1%	66.0%	50.0%	50.9%	*ns*
Race (% White)	87.0%	82.1%	87.2%	88.6%	90.9%	*ns*

Note: Mean (Standard Deviation). GL = Globally Low; Low EF/S = Low Executive Functioning/Speed; Low L/M = Low Language/Memory; GH = Globally High; Bonferroni-corrected critical value of $p = .0025$; (t) = Trending difference; *ns* = No significant difference.

with epilepsy. Given this aim, the current study replicated the statistical analytic method described by Hermann and colleagues [4] in which Ward's hierarchical agglomerative cluster analytic method was used to form meaningful clusters based on the seven cognitive domains. Squared Euclidean distance was used as the metric of pairwise dissimilarity between participant profiles. Identification of optimal clustering solutions within the clustering hierarchy was determined through examination of the agglomeration schedule and dendrogram. The desired outcome was to identify a stage within the clustering hierarchy yielding significant increases in the error sum of squares coefficients after having had relatively smaller increases at previous stages [32]. The stage producing four clusters of participants had increases of 6269, 6560, and 9675 in the error sum of squares from one stage to the next at the stages preceding the fourth cluster stage, compared with increases of 16,531, 23,811, and 45,468 at the three subsequent stages in the hierarchy. Further determination of the cluster solution is based on clinically meaningful differences across clusters. In the current data, two clinically meaningful clustering solutions were apparent, one producing three clusters and another producing four clusters.

After determining the cluster solutions, a series of one-way multivariate analyses of variance (MANOVAs) with follow-up univariate tests were conducted to compare patterns of cognitive functioning across clusters. Additionally, cluster groups were compared on sociodemographic (i.e., age, years of education) and clinical seizure characteristics (i.e., age of seizure onset, age of onset of recurrent seizures, duration of epilepsy, number of seizure types, and number of antiepileptic medications), as well as other relevant clinical variables (i.e., Wada language lateralization, MRI-identified hippocampal atrophy, MRI-identified hippocampal sclerosis).

3. Results

3.1. Cluster solutions and cognitive phenotypes

3.1.1. Three-cluster solution

The 3-cluster solution, depicted in Fig. 1A, produced clusters representing a graded level of performance (e.g., Low, Middle, and High performance). This pattern followed across all cognitive domains. A one-way MANOVA was conducted to compare the 3 clusters across the 7 cognitive domains. There was a significant overall effect (Hotelling $T = 3.12$, $df = (14, 350)$, $p < .001$). Given the large number of pairwise comparisons necessary to fully characterize the clusters, a Bonferroni correction was applied to this set of analyses that resulted in a critical value of $p = .0024$ as the threshold for clinical significance. In that context, significant differences emerged in each of the cognitive domains across all three clusters (all p's < .001), with the exception of nonsignificant differences in language between Cluster 2 and Cluster 3 ($p = .023$) and nonsignificant differences in immediate and delayed memory between Cluster 1 and Cluster 2 (both p's = .005). Beyond this graded performance difference, there were minimal differences in the patterns of cognitive performances across clusters. All three clusters showed a relative decrement in language compared to other domains. Results of the 3-cluster solution are presented primarily for the purposes of comparison to the 4-cluster solution, which will be the primary focus of the remaining results and discussion that follows.

3.1.2. Four-cluster solution

The 4-cluster solution, depicted in Fig. 1B, yielded clusters that varied to a greater degree by overall level of performance as well as

Table 2
Neuropsychological assessment.

Domain	Ability	Test
Intellectual abilities	Verbal Nonverbal	WAIS Perceptual Reasoning Index[1, g] WAIS Verbal Comprehension Index[1, g]
Language	Confrontation naming Phonemic fluency	Boston Naming Test[1, e] Controlled Oral Word Association[1, a]
Visuoperception	Facial discrimination Visuoperceptual judgment	Facial Recognition Test[1, b] Judgment of Line Orientation[1, b]
Immediate memory	Unstructured verbal memory Structured verbal memory Visual memory	Selective Reminding Test[1, c] WMS Logical Memory I[1, h] WMS Visual Reproduction I[1, h]
Delayed memory	Auditory memory Visual memory	WMS Logical Memory II[1, h] WMS Visual Reproduction II[1, h]
Executive functions	Speeded set-shifting Working memory Problem solving	Trail Making Test Part B[2, f] WAIS Working Memory Index[1, g] Wisconsin Card Sorting Test[3, d]
Psychomotor functioning	Speeded fine motor dexterity Speeded visuomotor sequencing	Grooved Pegboard[2, f] Trail Making Test Part A[2, f]

Note: Standard scores were based on the following raw scores: [1]Number of correct items; [2]Time to completion; [3]Number of perseverative responses. Citations for the neuropsychological tests are as follows: [a] [22], [b] [23], [c] [24], [d] [13], [e] [26], [f] [25,27], [g] [28,30], [h] [29,31].

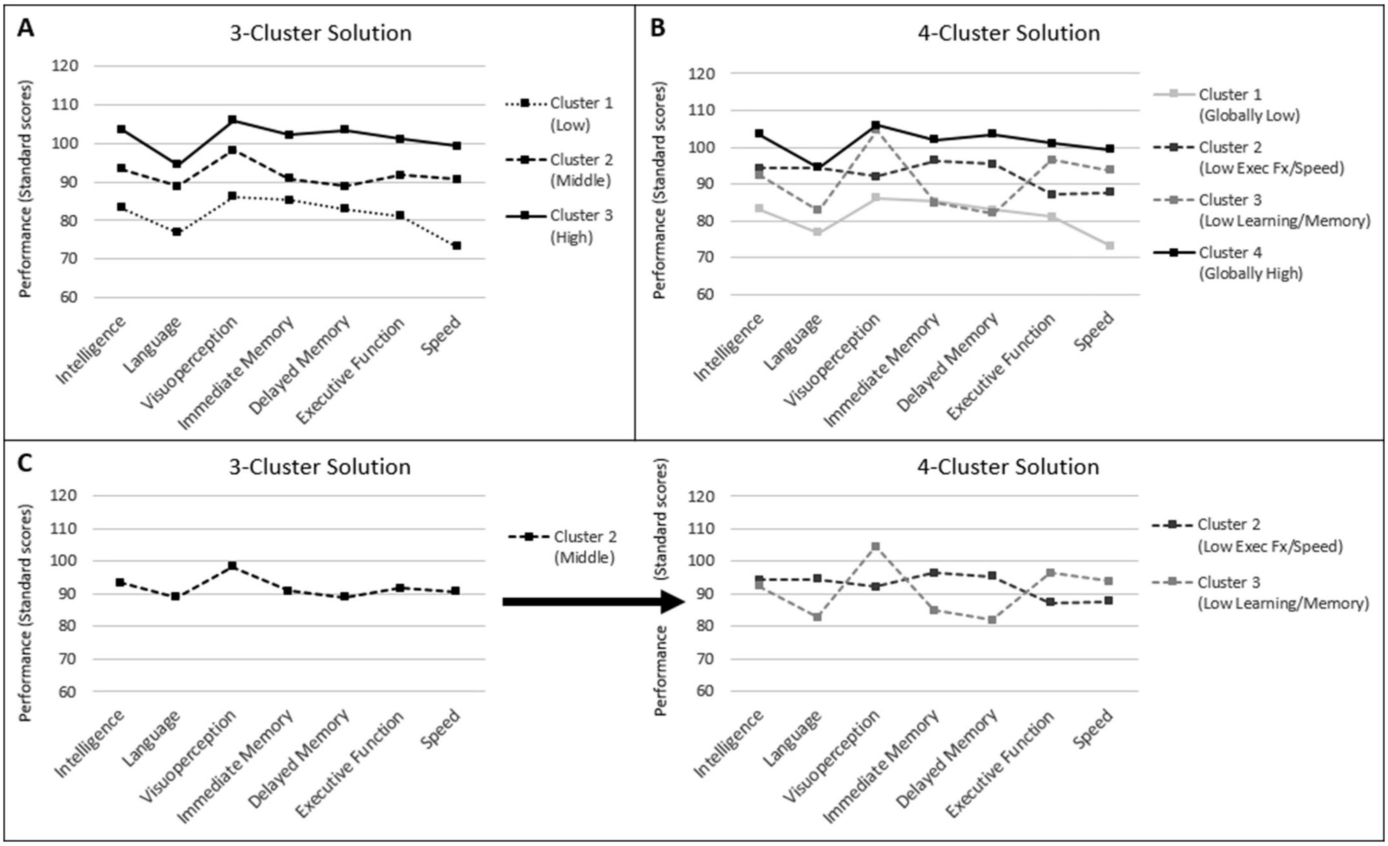

Fig. 1. (A) Mean cognitive performances across clusters for the 3-cluster solution. (B) Mean cognitive performances across clusters for the 4-cluster solution. (C) Mean cognitive performances for the portion of the sample ($n = 91$) comprising Cluster 2 (Middle) in the 3-cluster solution and comprising Cluster 2 (Low Executive Functioning/Speed) and Cluster 3 (Low Learning and Memory) in the 4-cluster solution.

variation in performance across cognitive domains. Specific cognitive performances in each of the clusters are presented in Table 3. A one-way MANOVA was conducted to compare the 4 clusters across the 7 cognitive domains, yielding a significant overall effect (Hotelling $T = 4.46$, $df = (21, 521)$, $p < .001$). Characterization of these four clusters was based on two sets of comparisons: (1) *between-cluster differences* in cognitive performance, highlighting differences in the overall cognitive profiles of the four different cluster groups and (2) *within-cluster differences* in cognitive performances, representing relative cognitive strengths and weaknesses within each cluster. As was described above, Bonferroni corrections were applied within each of the between-cluster and within-cluster sets of analyses to account for the large number of comparisons necessary to characterize the clusters. This resulted in critical values of $p = .0012$ and $p = .0006$ for the between-cluster and within-cluster analyses, respectively. Four cognitive phenotypes emerged from these analyses, which we label Globally Low, Low Executive Function/Speed (Low EF/S), Low Language/Memory (Low L/M), and Globally High.

Table 3
Cognitive performances across clusters (4-cluster solution).

	Cluster 1 (Globally Low)	Cluster 2 (Low EF/S)	Cluster 3 (Low L/M)	Cluster 4 (Globally High)
	($n = 39$)	($n = 47$)	($n = 44$)	($n = 55$)
Cognitive domain				
Intelligence	83.2 (5.9)	94.2 (8.8)	92.4 (8.4)	103.6 (9.7)
Language	76.8 (8.5)	94.5 (11.2)	82.8 (11.7)	94.4 (13.6)
Visuoperception	86.1 (11.6)	92.1 (13.4)	104.6 (8.0)	106.0 (9.9)
Immediate Memory	85.2 (8.4)	96.3 (8.6)	84.9 (7.3)	102.1 (8.6)
Delayed Memory	82.9 (9.6)	95.3 (9.8)	82.0 (8.6)	103.5 (7.0)
Executive Function	81.2 (7.7)	87.2 (9.4)	96.5 (8.6)	101.0 (10.9)
Speed	73.2 (10.3)	87.7 (10.1)	93.8 (12.7)	99.3 (9.6)

Note: Cognitive domain scores are standard scores presented as Mean (Standard Deviation).

3.1.2.1. Cluster 1: Globally Low. Cluster 1 was characterized by a pattern of low scores across all domains when compared to the other 3 clusters. Results of univariate between-cluster tests revealed that cognitive scores were significantly lower in Cluster 1 (Globally Low) than all other clusters for nearly all domains (p's < .001). Exceptions to this include nonsignificant differences between Cluster 1 (Globally Low) and Cluster 2 (Low EF/S) for visuoperception ($p = .06$) and executive functions ($p = .02$), which trended in the direction of poorer performance in Cluster 1 but did not meet the Bonferroni correction, and nonsignificant difference between Cluster 1 (Globally Low) and Cluster 3 (Low L/M) for the language ($p = .09$), immediate memory ($p = .99$), and delayed memory ($p = .96$). While Clusters 1 and 3 were, thus, fairly comparable with regard to language and memory performance, these clusters were differentiated by the consistently lower scores across other cognitive domains in Cluster 1 (Globally Low) while relative strengths in other domains were apparent in Cluster 3 (Low L/M).

Results of within-cluster pairwise comparisons in the Globally Low group revealed significantly lower scores in speed compared to intelligence, visuoperception, immediate memory, delayed memory, and executive functioning (p's < .0005). Language performance was significantly lower than visuoperception and immediate memory (p's < .0004). Remaining within-subject comparisons were nonsignificant, indicating comparably low scores in all cognitive domains within this cluster. Overall, the pattern of lower domain scores relative to other clusters in the majority of cognitive domains fits with the overall characterization of this cluster as Globally Low.

3.1.2.2. Cluster 2: Low Executive Function/Speed (Low EF/S). Cluster 2 (Low EF/S) was characterized by a pattern of low executive functioning and speed. Results of univariate between-cluster tests revealed significant cognitive differences between Cluster 2 (Low EF/S) and all other clusters for nearly all cognitive domains (p's < .001), with most scores falling above those of Cluster 1 (Globally Low), below those of Cluster 4 (Globally High), and varying between above and below those of Cluster 3 (Low L/M). Exceptions to this were nonsignificant differences between Cluster 2 (Low EF/S) and Cluster 3 (Low L/M) for intelligence ($p = .72$) and speed ($p = .04$), between Cluster 2 (Low EF/S) and Cluster 4 (Globally High) for language ($p = .99$) and immediate memory ($p = .003$), and between Cluster 2 (Low EF/S) and Cluster 1 (Globally Low) for visuoperception ($p = .06$) and executive functions ($p = .02$). Again, a selection of these nonsignificant findings trend in the correct direction based on the relative characterizations of the clusters, but did not meet the more stringent Bonferroni correction.

Results of within-cluster pairwise comparisons revealed that executive functioning scores were significantly lower than scores in the domains of intelligence, language, immediate memory, and delayed memory (p's < .0005), with a trending difference compared to visuoperception ($p = .03$). Speed scores were also significantly lower than scores for immediate memory and delayed memory (p's < .0005), with trending differences for intelligence ($p = .001$) and language ($p = .002$). Scores for the executive functioning and speed domains were not significantly different from each other within this cluster. Taken together, these findings support Low Executive Functioning and Speed (Low EF/S) as the phenotypic profile of this cluster.

3.1.2.3. Cluster 3: Low Language/Memory (Low L/M). Cluster 3 (Low L/M) was characterized by a pattern of low language and memory (immediate and delayed). Univariate between-cluster tests revealed poorer language and memory for Cluster 3 (Low L/M) relative to Cluster 2 (Low EF/S) and Cluster 4 (Globally High) (p's < .001). Nonsignificant differences in language and memory relative to Cluster 1 were previously described above. With the exceptions of the nonsignificant between-cluster differences mentioned previously and nonsignificant differences in visuoperception, executive functions, and speed between Cluster 3 (Low L/M) and Cluster 4 (Globally High), all other univariate between-cluster tests were significant with regard to cognitive differences between Cluster 3 (Low L/M) and the other clusters, with most scores falling above those of Cluster 1 (Globally Low), below those of Cluster 4 (Globally High), and varying between above and below those of Cluster 2 (Low EF/S) (p's < .001).

Results of within-cluster pairwise comparisons indicated that language, immediate memory, and delayed memory performances were all significantly lower than intelligence, visuoperception, executive functioning, and speed (p's < .0005). Visuoperception was also significantly higher than intelligence and speed (p's < .0005), with a trending difference compared to executive function ($p = .0008$) that did not meet the Bonferroni correction.

Overall, these findings support Low Language and Memory (Low L/M) as the phenotypic profile of this cluster, with a relative strength in visuoperception being another notable characteristic.

3.1.2.4. Cluster 4: Globally High. Cluster 4 (Globally High) was characterized by a pattern of high scores across all domains when compared to the other three clusters. Results of univariate between-cluster tests revealed that cognitive scores were significantly higher in Cluster 4 (Globally High) than all other clusters for intelligence, language, visuoperception, immediate memory, delayed memory, executive function, and speed (p's < .001), with the exception of nonsignificant differences compared to Cluster 2 for language ($p = .99$) and immediate memory ($p = .003$; trending but did not meet Bonferroni correction) and nonsignificant differences compared to Cluster 3 (Low L/M) for visuoperception ($p = .93$), executive functions ($p = .09$), and speed ($p = .05$).

Results of within-cluster pairwise comparisons revealed that intelligence, visuoperception, immediate memory, delayed memory, and executive functioning performances were all significantly higher than language (p's < .0005), with a trending difference in the same direction for speed ($p = .02$). Trending differences between other cognitive domains (e.g., higher visuoperception relative to executive function, $p = .02$, and speed, $p = .002$; higher intelligence relative to speed, $p = .02$) did not meet significance with the Bonferroni correction.

Overall, cognitive domains scores within this cluster were consistently higher than those of other clusters, fitting with the overall characterization of this cluster as Globally High.

3.2. Cluster differences

3.2.1. Demographic differences

Demographic differences across the 4 clusters are displayed in Table 1. Cluster 2 (Low EF/S) was significantly older than Cluster 3 (Low L/M) ($p = .027$). Cluster 1 (Globally Low) had significantly fewer years of education than Cluster 4 (Globally High) ($p < .001$), and there was a trending difference in the same direction between Cluster 1 (Globally Low) and Cluster 2 (Low EF/S) ($p = .066$). Overall intellectual functioning based on the Wechsler Adult Intelligence Scale (WAIS) FSIQ was significantly lower in Cluster 1 (Globally Low) than all other clusters and significantly higher in Cluster 4 (Globally High) than all other clusters (p's < .001). Cluster 2 (Low EF/S) versus Cluster 3 (Low L/M) was the only comparison for which there was no significant difference in WAIS FSIQ. There were no significant differences across clusters with regard to sex and race.

3.2.2. Differences in clinical seizure variables

Differences in Clinical Seizure Variables across the four clusters are displayed in Tables 4 and 5. As data were not available for all clinical seizure variables for each participant, separate univariate analysis of variance (ANOVA) were run for all continuous variables to maximize the sample size for each analysis (rather than conducting a larger MANOVA). Sample sizes for each analysis are presented in the tables.

Results of a chi-square analysis examining the proportion of patients with left TLE and patients with right TLE across clusters was significant ($p = .028$), indicating an association between cognitive phenotype and epilepsy lateralization. Specifically, a greater proportion of the patients with left TLE were captured by Cluster 3 (Low L/M) than by the other 3 clusters. There were no significant differences in the proportions of patients with right TLE across the clusters. The proportions of subjects with left and right TLE across clusters are presented in Table 4.

Differences across clusters in other clinical seizure variables are presented in Table 5. Cluster 2 (Low EF/S) had a significantly later age of recurrent seizures than Cluster 1 (Globally Low) ($p = .003$) with a trending difference in the same direction relative to Cluster 3 (Low L/M) ($p = .066$). Also, Cluster 1 (Globally Low) was significantly less left-lateralized for language (based on the Wada) than Cluster 2 (Low EF/S) ($p = .001$) and Cluster 4 (Globally High) ($p = .002$). There was a trending difference toward greater seizure frequency in Cluster 2 (Low EF/S) relative to Cluster 3 (Low L/M; $p = .051$).

Table 4
Proportions of subjects with left and right TLE across clusters.

	Left TLE ($n = 92$)	Right TLE ($n = 93$)	Total sample
Cluster 1: Globally Low	20_a	19_a	39
Cluster 2: Low Executive Function/Speed (EF/S)	20_a	27_a	47
Cluster 3: Low Language/Memory (L/M)	30_b	14_a	44
Cluster 4: Globally High	22_a	33_a	55
Total Sample	93	92	185

Note: Each subscript denotes a subset of patients with left and right TLE whose column proportions do not differ significantly.

Table 5
Clinical seizure variables.

	n	Total sample	Cluster 1 (Globally Low)	Cluster 2 (Low EF/S)	Cluster 3 (Low L/M)	Cluster 4 (Globally High)	Cluster differences
Age of Onset (Yrs)	184	14.4 (12.2)	12.(12.7)	17.8 (13.2)	14.2 (11.0)	13.3 (11.6)	*ns*
Age of Recurrent Seizures (Yrs)	181	17.4 (12.1)	13.(11.7)	22.1 (13.0)	15.9 (10.6)	17.7 (11.8)	Low EF/S > GL, Low L/M
Number of Seizure Types	180	1.9 (0.72)	1.8 (0.86)	2.0 (0.69)	1.9 (0.67)	1.8 (0.67)	*ns*
Seizure Frequency	172	17.1 (32.4)	15.9 (29.3)	28.5 (53.3)	11.1 (14.0)	12.7 (13.1)	(*t*) Low EF/S > Low L/M
Number of Seizure Medications	183	2.1 (0.88)	2.3 (0.87)	2.1 (0.97)	1.9 (0.86)	1.9 (0.81)	*ns*
Total Lifetime GTCs	155	No = 42 Yes = 113	No = 5 Yes = 21	No = 15 Yes = 25	No = 10 Yes = 31	No = 12 Yes = 36	*ns*
Total Episodes of Status	162	0.70 (5.2)	0.31 (0.93)	0.19 (0.71)	1.6 (10.0)	0.57 (1.7)	*ns*
Duration of Seizure Disorder (Yrs)	182	20.7 (13.3)	23.7 (13.8)	20.9 (13.7)	20.0 (14.4)	19.1 (11.7)	*ns*
Abnormal Hippocampal Findings	185	No = 108 Yes = 77	No = 23 Yes = 16	No = 34 Yes = 13	No = 23 Yes = 21	No = 28 Yes = 27	*ns*
Surgery Type	174	None = 18 R_{ATL} = 83 L_{ATL} = 73	None = 4 R_{ATL} = 17 L_{ATL} = 15	None = 6 R_{ATL} = 22 L_{ATL} = 15	None = 6 R_{ATL} = 13 L_{ATL} = 22	None = 2 R_{ATL} = 31 L_{ATL} = 21	*ns*
Wada Language Lateralization	147	67.3 (45.0)	41.9 (62.3)	84.4 (19.7)	59.5 (43.3)	77.6 (37.8)	GL < Low EF/S, GH

Note: Mean (Standard Deviation). GL = Globally Low; Low EF/S = Low Executive Functioning/Speed; Low L/M = Low Language/Memory; GH = Globally High; ATL = anterior temporal lobectomy; R = right; L = left; Cluster differences based on $p < .05$; (*t*) = Trending difference; *ns* = No significant difference.

There were no significant differences between clusters with regard to initial age at seizure onset, number of seizure types, number of seizure medications, lifetime total number of generalized tonic–clonic seizures, total number of episodes of status epileptics, duration of seizure disorder, abnormal hippocampal findings (sclerosis or atrophy), or surgery type (right anterior temporal lobectomy [ATL], left ATL, no surgery).

4. Discussion

Cognitive profiles in TLE are widely varied, with past research highlighting "average" profiles of generalized cognitive dysfunction as well as material-specific deficits associated with epileptogenic localization (e.g., impairments in verbally-mediated tasks in left TLE). Results of the current replication study, in conjunction with the work of Hermann et al. [4], provide further insights into the heterogeneity of cognitive profiles in TLE and identification of specific cognitive phenotypes within this patient population.

The cluster analytic approach applied in the current study produced two clinically meaningful clusters solutions. In both our 3- and 4-cluster solutions, a minimally impaired group emerged, consistent with the findings of Hermann et al. [4]. Interestingly, the clear majority of domain scores across all clusters (including our Globally Low cluster) were within the broadly average range (i.e., generally between a low average score of 80 and an average score of 105). The only exceptions to this were borderline impaired domain scores for language and speed in our Globally Low cluster. While the presence of some degree of cognitive weakness is evidenced by these borderline impairments, it is notable that cognitive functioning overall was relatively preserved in this sample of presurgical candidates seen within a comprehensive epilepsy program. This, too, is consistent with the previous work of Hermann et al. [4], in which the largest cluster of their participants (constituting 47% of the sample) demonstrated generally intact cognition.

While relative weaknesses in certain domains were not in the range of clinical impairment, patterns of specific weaknesses across the different clusters did emerge, producing 4 distinct cognitive phenotypes. As anticipated, a cluster characterized by low language and memory emerged in our cluster analysis. There was a greater proportion of patients with left TLE in this cluster relative to the other 3 clusters, with no differences in the proportions of patients with right TLE across the 4 clusters. This finding supports previous research documenting material-specific deficits in language-based neurocognitive tasks associated with left TLE. This cluster did not differ from the others with regard to language lateralization based on the Wada. Patients in this cluster did tend to be younger (based on age at neuropsychological testing) and have an earlier age at onset of recurrent seizures, particularly in comparison to the Low Executive Functioning/Speed cluster.

The emergence of the Low Executive Functioning/Speed cluster is particularly notable as it demonstrates the consistency of weaknesses in these domains across now two large, distinct samples of patients with TLE (the current study and Hermann et al. [4]). Interestingly, the cluster exhibiting executive functioning and speed weakness in the study by Hermann et al. [4] also exhibited impairments in memory, though only 3 clusters were examined in that study due, at least in part, to small sample sizes in a 4-cluster solution. The larger sample size in the current study allowed for examination of additional cluster solutions, with the extension to a 4-cluster solution being beneficial for further parsing specific cognitive phenotypes. In the current cluster analysis, 91 participants comprised a Middle performance cluster in the 3-cluster solution. When further differentiated in the 4-cluster solution, it was this same group of patients who separated into the Low Language/Memory and Low Executive Function/Speed clusters (Low L/M $n = 44$; Low EF/S $n = 47$). The subjects comprising the Low performance cluster in the 3-cluster solution were identical to those in the Globally Low cluster of the 4-cluster solution and the subjects comprising the High performance cluster in the 3-cluster solution were identical to those in the Globally High cluster of the 4-cluster solution. Thus, the larger sample size and the 4-cluster solution add value by allowing for a better characterization of subjects with intermediate levels of performance.

Presented visually in Fig. 1C, the clusters representing the low and high performers in both cluster solutions have been removed and the remaining graphs depict the 91 participants who were clustered differently across the two cluster solutions. While this group was averaged together in the 3-cluster solution and variations across cognitive domains followed the same general patterns of the other clusters, the nuanced variability in their cognitive profiles can be appreciated at the level of the 4-cluster solution where the Low Language/Memory and Low Executive Functioning/Speed clusters clearly emerged. This speaks to the complications of focusing on the "average" cognitive profile in groups of patients with TLE when cognitive functioning in these patients is more heterogeneous.

In both the current study and Hermann et al. [4], the clusters demonstrating executive functioning and speed impairments were older. We also found that this cluster (Low EF/S) had a later age of recurrent seizures, and Hermann et al. [4] showed a more protracted duration of seizures in their comparable cluster. Additionally, relative to the minimally impaired and memory impaired clusters examined previously, the memory, executive, and speed impaired cluster in Hermann and colleagues' study was found to have a more adverse cognitive course over a 4-year follow-up period. Moreover, that cluster demonstrated the most pronounced and widespread neuroanatomical changes, including the most significant cortical thinning across 14 bilateral brain regions and volume reductions in the corpus callosum, left and right thalamus, right cerebellum, and left hippocampus [4,33].

Beyond demonstrating the presence of these distinct clusters, it is of course important to consider their broader meaning. Given the relatively minimal differences in clinical seizure variables across clusters in the current study, it seems unlikely that the clusters represent distinct TLE disease entities. Perhaps more likely is that they represent different aspects of disease progression, such as progression as a function of severity and/or progression as a function of time (i.e., as it relates to onset and age). The overall poorer cognition of the Globally Low cluster appears indicative of a more severe disease process among individuals in this cluster, with the findings of less left-lateralized language in this group likely signifying more diffuse pathology and potential reorganization of function. Other demographic and seizure variable differences seemed to particularly differentiate the Low Executive Functioning/Speed cluster, which was significantly older and had a later age of recurrent seizures than other clusters. This cluster also demonstrated a tendency toward greater seizure frequency. Thus, advanced age and increased seizure frequency may signify other aspects of disease stage or progression that are particularly related to deficits in executive functioning and speed. Considered along with Hermann et al.'s findings [4] of more extensive neuroanatomical changes in their memory, executive, and speed impaired cluster, these executive and speed deficits may also be associated with severity related to particular neuroanatomical changes.

5. Limitations and directions for future research

Several limitations of the current study should be recognized. First, the cognitive domains were intentionally defined to match those of Hermann et al. [4], given our intention to replicate that cluster analysis in a larger, independent sample. While these domains produced clinically meaningful and now replicated clusters, we recognize that alternate methods for defining cognitive domains could be explored, potentially resulting in different clusters or phenotypes. For example, in the current study and Hermann et al. [4], memory tests were divided into immediate and delayed memory domains. It could be argued that the domains would be better structured by separating memory scores into visual and verbal memory domains, given material-specific memory deficits in TLE [34]. This was not pursued in the current study given concerns about collapsing immediate and delayed memory measures and otherwise having only 1 test comprising various domains (e.g., verbal delayed memory). Additionally, we acknowledge that many of the neuropsychological measures are not pure measures of one specific construct of interest, thereby complicating their placement in certain cognitive domains. For example, letter fluency is a language-based task that was included in the Language domain, but adequate performance also relies upon executive functioning (e.g., self-monitoring, strategic lexical retrieval) and speed of information processing. Given that these neuropsychological tests are potentially capturing neuropsychological processes beyond the cognitive domain in which they were placed, it is possible that certain domain-specific effects were less apparent (e.g., language effects related to the Boston Naming Test (BNT) may have been washed out by confounding executive effects of verbal fluency in the Language domain). An additional limitation regarding the cognitive domains is the assumption of normal distributions across the tests that were averaged to compute the domain scores, while patients may show ceiling effects on certain measures (e.g., BNT, WCST). Future research assessing alternative approaches for defining cognitive domains and exploring the degree to which such differences impact resulting clusters would be beneficial.

Further exploration of cognitive trajectories and neuroanatomical correlates associated with the clusters identified in the current sample will also be a key area of future research to more fully understand that implications of these cognitive phenotypes. While decades of research have emphasized the role of preoperative memory and language performances in predicting cognitive decline following temporal lobectomy [11,35–37], less is known about the value of executive function and speed performance as predictors of decline and the degree to which the importance of these domains may differ across cognitive phenotypes. The longstanding and predominant focus on memory and language has been imperative given the role of the temporal lobes in these functions; however, examination of baseline executive function and speed as they relate to risk for decline across all cognitive domains postoperatively and over the general disease course may elucidate more nuanced differences between TLE clusters. Such examination may also be beneficial for evaluating aspects of decline that are more inherent to surgical interventions (e.g., verbal memory decline following left temporal lobectomy) versus effects of the disease process itself (e.g., more insidious executive functioning changes related to ongoing seizures). Given that these weaknesses in executive functioning and speed among patients with TLE have now been replicated across multiple studies, further research in this area certainly appears warranted. Examination of cognitive phenotypes in other epilepsy groups (e.g., patients with frontal lobe epilepsy or generalized epilepsy) may also be beneficial.

6. Conclusions

This replication study examining cognitive phenotypes in TLE revealed 4 clusters of patients with TLE characterized by Globally Low cognitive performance, Low Executive Function/Speed, Low Language/Memory, and Globally High cognitive performance. These cognitive phenotypes are largely comparable to those demonstrated by Hermann et al. [4], who similarly described a minimally impaired group as well as those characterized by memory impairment and by memory, executive, and speed impairments. Additionally, the current study adds to previous literature on cognitive functioning in TLE by demonstrating that the "average" cognitive profile in TLE often results from an amalgamation of significantly more heterogeneous cognitive profiles. Taken together, these findings suggest that cognitive domains such as language and memory, which have historically been primary domains of focus in TLE, are not the only domains warranting examination and that greater focus on executive and speed domains may be valuable. Additionally, these clusters may have utility for predicting cognitive trajectories, determining likelihood for seizure freedom after surgical intervention, and informing treatment decisions within the highly heterogeneous group of patients with TLE.

Conflict of interest

The authors have no conflicts of interest to report.

References

[1] Snowden JS, Stopford CL, Julien CL, Thompson JC, Davidson Y, Gibbons L, et al. Cognitive phenotypes in Alzheimer's disease and genetic risk. Cortex 2007;43(7):835–45. https://doi.org/10.1016/S0010-9452(08)70683-X.

[2] Langenecker SA, Saunders EFH, Kade AM, Ransom MT, McInnis MG. Intermediate: cognitive phenotypes in bipolar disorder. J Affect Disord 2010;122(3):285–93. https://doi.org/10.1016/j.jad.2009.08.018.

[3] Charman T, Jones CRG, Pickles A, Simonoff E, Baird G, Happé F. Defining the cognitive phenotype of autism. Brain Res 2011;1380:10–21. https://doi.org/10.1016/j.brainres.2010.10.075.

[4] Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy. J Int Neuropsychol Soc 2007;13(01). https://doi.org/10.1017/S135561770707004X.

[5] Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol 2011;7(3):154–64. https://doi.org/10.1038/nrneurol.2011.3.

[6] Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 1997;54(4):369–76. https://doi.org/10.1001/archneur.1997.00550160019010.

[7] Hermann BP, Seidenberg M, Haltiner A, Wyler AR. Adequacy of language function and verbal memory performance in unilateral temporal lobe epilepsy. Cortex 1992;28(3):423–33. https://doi.org/10.1016/S0010-9452(13)80152-9.

[8] Helmstaedter C, Pohl C, Hufnagel A, Elger CE. Visual learning deficits in nonresected patients with right temporal lobe epilepsy. Cortex 1991;27(4):547–55. https://doi.org/10.1016/S0010-9452(13)80004-4.

[9] Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004;62(10):1736–42. https://doi.org/10.1212/01.WNL.0000125186.04867.34.
[10] Hermann B, Seidenberg M, Bell B, Rutecki P, Sheth R, Ruggles K, et al. The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. Epilepsia 2002;43(9):1062–71. https://doi.org/10.1046/j.1528-1157.2002.49901.x.
[11] Hermann BP, Seidenberg M, Haltiner A, Wyler AR. Relationship of age at onset, chronologic age, and adequacy of preoperative performance to verbal memory change after anterior temporal lobectomy. Epilepsia 1995;36(2):137–45. https://doi.org/10.1111/j.1528-1157.1995.tb00972.x.
[12] Stretton J, Thompson PJ. Frontal lobe function in temporal lobe epilepsy. Epilepsy Res 2012;98(1):1–13. https://doi.org/10.1016/j.eplepsyres.2011.10.009.
[13] Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G. The Wisconsin Card Sorting Test manual: revised and expanded. Odessa, FL: Psychological Assessment Resources; 1993.
[14] Hermann B, Seidenberg M. Executive system dysfunction in temporal lobe epilepsy: effects of nociferous cortex versus hippocampal pathology. J Clin Exp Neuropsychol 1995;17(6):809–19. https://doi.org/10.1080/01688639508402430.
[15] Horner MD, Flashman LA, Freides D, Epstein CM, Bakay RAE. Temporal lobe epilepsy and performance on the Wisconsin Card Sorting Test. J Clin Exp Neuropsychol 1996;18(2):310–3. https://doi.org/10.1080/01688639608408285.
[16] Strauss E, Hunter M, Wada J. Wisconsin card sorting performance: effects of age of onset of damage and laterality of dysfunction. J Clin Exp Neuropsychol 1993;15(6):896–902. https://doi.org/10.1080/01688639308402606.
[17] Hermann BP, Seidenberg M, Haltiner A, Wyler AR. Mood state in unilateral temporal lobe epilepsy. Biol Psychiatry 1991;30(12):1205–18. https://doi.org/10.1016/0006-3223(91)90157-H.
[18] Kim CH, Lee SA, Yoo HJ, Kang JK, Lee JK. Executive performance on the Wisconsin card sorting test in mesial temporal lobe epilepsy. Eur Neurol 2007;57(1):39–46. https://doi.org/10.1159/000097009.
[19] Labudda K, Frigge K, Horstmann S, Aengenendt J, Woermann FG, Ebner A, et al. Decision making in patients with temporal lobe epilepsy. Neuropsychologia 2009;47(1):50–8. https://doi.org/10.1016/j.neuropsychologia.2008.08.014.
[20] Yamano M, Akamatsu N, Tsuji S, Kobayakawa M, Kawamura M. Decision-making in temporal lobe epilepsy examined with the Iowa gambling task. Epilepsy Res 2011;93(1):33–8. https://doi.org/10.1016/j.eplepsyres.2010.10.009.
[21] Zamarian L, Trinka E, Bonatti E, Kuchukhidze G, Bodner T, Benke T, et al. Executive functions in chronic mesial temporal lobe epilepsy. Epilepsy Res Treat 2011;2011:1–11. https://doi.org/10.1155/2011/596174.
[22] Benton A, Hamsher K, Sivan A. Multilingual aphasia examination. Iowa City, IA: AJA Associates; 1994.
[23] Benton AL, Sivan AB, Hamsher K, Varney NR, Spreen O. Contributions to neuropsychological assessment: a clinical manual. . 2nd ed.New York: Oxford University Press; 1994.
[24] Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974;24(11):1019–25.
[25] Heaton RK, Miller SW, Taylor MJ, Grant I. Revised comprehensive norms for an expanded Halstead-Reitan battery: demographically adjusted neuropsychological norms for African American and Caucasian adults. Lutz, FL: Psychological Assessment Resources; 2004.
[26] Kaplan EF, Goodglass H, Weintraub S. The Boston naming test. . 2nd ed.Philadephia, PA: Lea & Febiger; 1983.
[27] Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery: theory and clinical applications. . 2nd ed.Tucson, AZ: Neuropsychology Press; 1993.
[28] Wechsler D. WAIS-III administration and scoring manual. San Antonio, TX: The Psychological Corporation; 1997.
[29] Wechsler D. Wechsler memory scale. . 3rd ed.San Antonio, TX: The Psychological Corporation; 1997.
[30] Wechsler D. WAIS-IV: Administration and scoring manual. New York, NY: The Psychological Corporation; 2008.
[31] Wechsler D. Wechsler memory scale. . 4th ed.San Antonio, TX: Pearson; 2008.
[32] Berven NL, Hubert LJ. Complete-link clustering as a complement to factor analysis: a comparison to factor analysis used alone. J Vocat Behav 1977;10(1):69–81. https://doi.org/10.1016/0001-8791(77)90043-4.
[33] Dabbs K, Jones J, Seidenberg M, Hermann B. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009;15(4):445–51. https://doi.org/10.1016/j.yebeh.2009.05.012.
[34] Willment KC, Golby A. Hemispheric lateralization interrupted: material-specific memory deficits in temporal lobe epilepsy. Front Hum Neurosci 2013;7(546). https://doi.org/10.3389/fnhum.2013.00546.
[35] Baxendale S, Thompson P, Harkness W, Duncan J. Predicting memory decline following epilepsy surgery: a multivariate approach. Epilepsia 2006;47(11):1887–94. https://doi.org/10.1111/j.1528-1167.2006.00810.x.
[36] Binder JR, Sabsevitz DS, Swanson SJ, Hammeke TA, Raghavan M, Mueller WM. Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. Epilepsia 2008;49(8):1377–94. https://doi.org/10.1111/j.1528-1167.2008.01625.x.
[37] Chelune GJ, Naugle RI, Luders H, Awad IA. Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. Neurology 1991;41(3):399–404. https://doi.org/10.1212/WNL.41.3.399.