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Factorial validity of a neuropsychological test battery and its ability to discern temporal lobe epilepsy from frontal lobe epilepsy – A retrospective study

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ABSTRACT

Purpose: Firstly, to evaluate the validity of a neuropsychological test battery in epilepsy patients, i.e. whether its tests sufficiently allow the assessment of the required cognitive domains in this specific group. Secondly, to examine its ability to differentiate between cognitive profiles of different subgroups of focal epilepsy.
Methods: The test battery suggested by the German ILAE Chapter was performed on 207 epilepsy patients, and its factor structure was investigated by principal component analysis (PCA). To further examine its accuracy in two matched subgroups of patients with temporal lobe epilepsy (TLE, n = 35) and frontal lobe epilepsy (FLE, n = 35), a discriminant function analysis (DFA) was used.
Results: PCA revealed eleven interpretable factors, accounting for 69.1% of total variance: Divided Attention, Reaction Time, Verbal Learning, Verbal Memory, Contextual Memory, Short-term- and Working Memory, Visuospatial Functioning, Space Perception, Verbal Fluency, Response Monitoring and Cognitive Flexibility. DFA identified six test to be most appropriate to discern TLE from FLE: WMS-IV Logical Memory, recognition; WMS-R Digit Span, backwards; VLMT, repetitions; VOSP Silhouettes; VLMT, delayed recall; and RWT Phonemic verbal fluency. Group membership was correctly predicted for 78.6% of patients using cross-validation.
Conclusions: As neuropsychological assessments are central in clinical decision-making in presurgical work-up of epilepsy patients, the appropriateness of the test battery in use is essential. The majority of cognitive domains are sufficiently measurable by the test battery and it is highly sensitive to differentiate between the cognitive profiles of TLE and FLE. However, the selection of tests assessing nonverbal memory functions requires further improvement.

1. Introduction

1.1. Neuropsychology in epilepsy surgery

In the diagnosis and treatment of epilepsy, neuropsychology makes an important contribution to the comprehensive characterization of patients. Through the administration of standardized psychometric tests, cognitive and behavioral strengths and deficits of patients can be detected and quantified. Neuropsychological assessments not only provide useful information regarding the functionality of affected brain structures and networks, but can also be used to examine psychosocial difficulties of epilepsy patients as well as potential cognitive side effects of antiepileptic drugs [1,2]. In patients considered for epilepsy surgery, neuropsychological assessments are furthermore required to evaluate reserve capacities and predict possible cognitive impairments as well as the necessity of psychiatric or neuropsychological rehabilitation after surgery. Thus, neuropsychological assessments have to meet high requirements, as their results are used to reflect the relation between the risks and benefits of epilepsy surgery on an individual level [3–6].

Therefore, the implementation of a thoroughly compiled neuropsychological test battery including the examination of several domains of cognitive functioning is desirable. Further advantages include the potential to save time and resources by choosing a core test battery that can be extended if necessary, as personnel capacities are usually

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limited. Moreover, for neuropsychologists who are new to the field of epilepsy surgery, the opportunity to rely on the suggestions of experts by using an established test battery could be rather helpful. Lastly, consensus regarding a standard test battery would facilitate the communication between epilepsy centers and multicenter studies could be pursued more easily [7,8].

Despite the agreement on a core set of cognitive domains to assess in accordance with the Neuropsychology Task Force of the International League against Epilepsy (ILAE) [8,9], no consensus regarding the selection of specific psychometric tests has been reached so far on an international level: Vogt et al. [8] identified a variety of 186 different tests used in epilepsy centers across Europe, their choice often based on personal preferences and aspects of availability [10]. On a national level, the Neuropsychological Commission of the German ILAE Chapter collected suggestions regarding a minimum standard neuropsychological test battery to use in presurgical work-up and named specific tests that were found to hold appropriate psychometric properties [7,11].

1.2. Validity and accuracy of the suggested test battery

After using this suggested neuropsychological test battery as a standard for several years, it appeared to be necessary to retrospectively confirm the appropriateness of its use in the context of epilepsy surgery.

Firstly, we were interested in the validity of the suggested test battery in epilepsy patients in general: There is agreement regarding the use of (age- and education-based) normative data for the interpretation of individual test scores, and the construct validity of a psychometric test is commonly reported. However, as normative data for test validation typically emanate from test manuals or non-epilepsy-specific publications, evidence supporting the application of specific tests *in epilepsy patients* only exists in a few cases [8,10]. Therefore, in this study, we assessed the factorial validity of the suggested test battery, i.e. the correspondence between the grouping of test scores and the cognitive domains intended to be assessed by these specific tests, in a large sample of epilepsy patients.

Secondly, the question occurred as to whether the suggested test battery is equally suitable for patients of *different subgroups of focal epilepsy*. The investigation of the behavioral and cognitive profiles of patients with temporal lobe epilepsy (TLE) has been particularly promoted in previous research and impairments in memory functions have been reported as their leading neuropsychological symptom [12–14]. On the contrary, only a limited number of studies have assessed the cognitive profile related to frontal lobe epilepsy (FLE), which seems to include deficits regarding attention, processing speed and executive functioning [15–17]. Consequently, in this study, we examined whether the typical deficits of these most frequent subgroups of focal epilepsy (TLE and FLE) result in measurable group differences and tried to identify specific psychometric tests most appropriate to discern their cognitive profiles.

2. Methods

2.1. Patients

In this retrospective study, a consecutive clinical sample of 224 epilepsy patients of the tertiary Epilepsy Center Frankfurt Rhine-Main was collected. Patients without formal education (n = 8) or with diagnosed psychiatric comorbidities (n = 9) were excluded (7.6%), resulting in a final sample of 207 epilepsy patients (52% women; mean age: 37.85 years, SD = 14.71). The standard neuropsychological test battery was performed as part of presurgical work-up from 2015 to 2019. Syndrome diagnoses were obtained during Video-EGG-Monitoring and the classification of seizure types and epilepsies was based on the definitions proposed by the ILAE [18,19]. Socio-demographic and neuropsychological characteristics of the sample are summarized in Table 1. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [20].

Table 1
Socio-demographic and neuropsychological characteristics of the final sample (n = 207).

	Number	Percent
Gender		
Women	107	51.7%
Men	100	48.3%
Handedness[a]		
Consistently right-handed (EHI ≥ 50)	182	87.9%
Consistently left-handed (EHI ≤ -50)	13	6.3%
Ambidextrous	12	5.8%
Diagnosis[b]		
Temporal lobe epilepsy (TLE)	145	70.0%
Frontal lobe epilepsy (FLE)	35	16.9%
Parietal lobe epilepsy (PLE)	4	1.9%
Occipital lobe epilepsy (OLE)	3	1.4%
Unknown	20	9.8%
Lateralization of the epileptogenic focus[b]		
Left-sided focus	97	46.9%
Right-sided focus	86	41.5%
Bilateral focus	15	7.2%
Unknown	9	4.3%
Etiology[b]		
Structural etiology	142	68.7%
Genetic etiology	5	2.4%
Infectious etiology	6	2.9%
Immune etiology	3	1.4%
Unknown	51	24.6%
Seizure frequency[b]		
≥1 seizures per day	20	9.7%
1–6 seizures per week	56	27.1%
1–3 seizures per month	60	29.0%
1–11 seizures per year	17	8.2%
Unstable	54	26.1%
Secondary generalized tonic-clonic seizures[b]		
Occurred (at least once) before	160	77.3%
Never occurred before	47	22.7%
Education		
≤9 years (German Hauptschulabschluss)	54	26.7%
10–12 years (German Realschulabschluss)	99	49.0%
> 12 years (German Abitur)	49	24.3%
	Mean (Range)	**SD**
Age (years)	37.85 (15–70)	14.71
Age of onset of epilepsy (years)	21.47 (0–65)	14.35
Duration of epilepsy (years)	15.58 (0–63)	13.34
Intelligence		
MWT-B (Verbal IQ)	103.56 (78–145)	13.41
Socio-demographic prediction model (IQ)	101.19(82–131)	11.21
Symptoms of depression[c]		
BDI-II	11.09 (0–28)	7.52

Range = Minimum-maximum; SD = Standard deviation.
[a] Handedness was determined by the Edinburgh Handedness Inventory (EHI).
[b] Syndrome diagnoses were obtained during Video-EGG-Monitoring.
[c] Symptoms of depression were assessed by the Beck Depression Inventory-II (BDI-II).

To differentiate the cognitive profiles of different subgroups of focal epilepsy, in a second step, the group of patients with FLE (n = 35) and a group of age-, gender- and education-matched patients with TLE (n = 35) was defined out of the sample. The socio-demographic and neuropsychological characteristics of the two subgroups are displayed in Table 2. A subdivision of the groups regarding the lateralization of the epileptogenic focus was omitted, as firstly, we rather focused on a *localizational* differentiation between groups, and secondly, a further division would have resulted in a loss of statistical power due to small sample sizes.

Table 2
Socio-demographic and neuropsychological characteristics of the two subgroups.

	patients with TLE (n = 35)		patients with FLE (n = 35)		
	Number	**Percent**	**Number**	**Percent**	**p-value**[e]
Gender					
Women	13	37.1%	13	37.1%	.598
Men	22	62.9%	22	62.9%	
Handedness[a]					
Consistently right-handed (EHI ≥ 50)	28	80.0%	31	88.6%	.601
Consistently left-handed (EHI ≤ -50)	3	8.6%	2	5.7%	
Ambidextrous	4	11.4%	2	5.7%	
Hemispheric language lateralization (HLL)[b]					
Left HLL	24	68.6%	20	57.1%	.229
Right HLL	0	0.0%	0	0.0%	
No lateralization	11	31.4%	15	42.9%	
Lateralization of the epileptogenic focus[c]					
Left-sided focus	23	65.7%	16	45.7%	.089
Right-sided focus	12	34.3%	16	45.7%	
Bilateral focus	0	0.0%	3	8.6%	
Secondary generalized tonic-clonic seizures[c]					
Occurred (at least once) before	28	80.0%	30	85.7%	.376
Never occurred before	7	20.0%	5	14.3%	
Education					
≤9 years (German Hauptschulabschluss)	7	20.0%	12	34.3%	.348
10–12 years (German Realschulabschluss)	20	57.1%	18	51.4%	
> 12 years (German Abitur)	8	22.9%	5	14.3%	
	Mean	**SD**	**Mean**	**SD**	**p-value**[f]
Age (years)	32.11	13.61	32.26	13.68	.965
Age of onset of epilepsy (years)	19.53	13.60	15.65	11.75	.212
Duration of epilepsy (years)	12.56	12.00	15.88	12.15	.260
Intelligence					
MWT-B (Verbal IQ)	97.90	11.14	98.63	10.68	.835
Socio-demographic prediction model (IQ)	102.77	8.65	98.38	10.43	.059
Symptoms of depression[d]					
BDI-II	9.86	6.49	10.26	7.70	.813

[a] Handedness was determined by the Edinburgh Handedness Inventory (EHI).
[b] HLL was assessed by functional transcranial Doppler sonography (fTCD) and functional MRI.
[c] Syndrome diagnoses were obtained during Video-EGG-Monitoring.
[d] Symptoms of depression were assessed by the Beck Depression Inventory-II (BDI-II).
[e] Chi-square-tests and [f]independent samples t-tests, SD = Standard deviation.

2.2. Neuropsychological test battery

The neuropsychological test battery suggested by the German ILAE Chapter [7], used as a standard in presurgical work-up, consists of the following ten standardized psychometric tests that were chosen to assess several domains of cognitive functioning (see Table 3):

(1) For evaluating *attentional functions*, the subtest Divided Attention of the computerized Testbatterie zur Aufmerksamkeitsprüfung (TAP) [21] was applied. This test requires the parallel processing of a visual and an auditory task, operationalized by detecting squares and identical tones by pressing a key. For both tasks, reaction times as well as omissions and commission errors are measured. (2) For the assessment of *verbal learning and memory functions*, a German adaptation of the Rey Auditory Verbal Learning Test, the Verbaler Lern- und Merkfähigkeitstest (VLMT) [22] was used, wherein fifteen words have to be learned within five repetitions. Later, the words have to be recalled after learning a distraction list and after a 30-minute delay. Finally, the words have to be recognized out of fifty words. False positives, repetitions as well as interferences are counted. (3) Furthermore, the subtest Logical Memory of the Wechsler Memory Scale-IV (WMS-IV) [23] was applied, wherein two short stories have to be remembered and freely recalled immediately. After a 30-minute delay, the stories have to be recalled again and fifteen yes/no-questions to each story have to be answered. (4) For evaluating *nonverbal learning and memory functions*, the Diagnosticum für Cerebralschädigung II (DCS-II) [24] was

Table 3
Psychometric tests included in the standard neuropsychological test battery [7], sorted by the cognitive domains they assess.

Cognitive Domain		Psychometric tests
Attention	(1)	Testbatterie zur Aufmerksamkeitsprüfung (TAP), Divided Attention
Learning and Memory	(2)	Verbaler Lern- und Merkfähigkeitstest (VLMT)
	(3)	Wechsler Memory Scale-IV (WMS-IV), Logical Memory
	(4)	Diagnosticum für Cerebralschädigung II (DCS-II)
	(5)	Rey-Osterrieth Complex Figure Test (ROCFT), Delayed Recall
	(6)	Wechsler Memory Scale-Revised (WMS-R), Digit Span and Visual Memory Span
Visuospatial Functioning	(7)	Rey-Osterrieth Complex Figure Test (ROCFT), Copy
	(8)	Visual Object and Space Perception Battery (VOSP), Silhouettes and Position Discrimination
Language	(9)	Regensburger Wortflüssigkeitstest (RWT), Phonemic Verbal Fluency and Semantic Verbal Fluency
Executive Functioning	(10)	Testbatterie zur Aufmerksamkeitsprüfung (TAP), Flexibility

performed, wherein nine figures have to be remembered and freely recalled by building them with five wooden sticks within a maximum of six repetitions. (5) Additionally, the Rey-Osterrieth Complex Figure Test (ROCFT) [25,26] was used, wherein a complex figure has to be copied and freely recalled after a 30-minute delay. (6) For measuring *short-term memory and working memory*, the subtests Digit Span and Visual Memory Span of the Wechsler Memory Scale-Revised (WMS-R) [27] were used, wherein sequences of digits and block positions in ascending length have to be recalled forwards and backwards. (7) *Visuospatial functioning* was measured by the completeness of the copy of the complex figure mentioned before (ROCFT). (8) Moreover, the subtests Silhouettes and Position Discrimination of the Visual Object and Space Perception Battery (VOSP) [28] were performed, wherein thirty silhouettes of animals and objects have to be recognized and twenty positions of dots inside of squares have to be discriminated. (9) *Language functions* were assessed by the subtests Phonemic verbal fluency and Semantic verbal fluency of the Regensburger Wortflüssigkeitstest (RWT) [29], whereby as many words as possible have to be generated within one minute, either starting with a certain letter respectively one of two alternating letters (phonemic) or fitting into a certain category respectively one of two alternating categories (semantic). (10) For the assessment of an aspect of *executive functioning*, the subtest Flexibility of the before mentioned TAP was used. In this test, a letter and a number are simultaneously presented on screen. The task is to press the left or right key according to whether the target stimulus (alternating between letter and number from trial to trial) appears to the left or right side. Reaction times as well as mistakes are measured.

The neuropsychological assessments were carried out in a standardized fashion by trained neuropsychologists. The total assessment lasted about three hours. All patients included in the final sample received polytherapy with a combination of antiepileptic drugs. It was ensured that patients were not currently treated with topiramate or zonisamide and that they had no seizures or status epilepticus within a period of 24 h before the examination.

2.3. Other variables

Handedness was determined by the Edinburgh Handedness Inventory [30]. Intelligence was assessed by a multiple-choice vocabulary test measuring verbal IQ (Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B) [31] as well as a complex regression equation, estimating the level of premorbid global cognitive functioning on the basis of socio-demographic characteristics, such as education, musical ability and occupation [32]. Symptoms of depression were measured by the Beck Depression Inventory-II (BDI-II) [33].

2.4. Statistical analysis

To investigate the factor structure of the neuropsychological test battery, an exploratory factor analysis (EFA) on the resulting test scores of all 207 assessments was used. Prior to factor extraction, the Bartlett's Test of Sphericity (BTS) and the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) were applied to confirm the suitability of the data characteristics for this operation. As the extraction method, principal component factoring was used. Missing values for each test score were replaced by the mean of the test score in the sample. For a better interpretation of the extracted factors, a varimax rotation was performed.

The subgroups (patients with TLE and patients with FLE) were compared with independent samples t-tests for numerical data and chi-square-tests for categorical data. Where applicable, the conservative Bonferroni correction was used [34], which sets the critical p-value for each comparison by dividing the alpha value (α) by the number of all n comparisons (within one factor as revealed by the EFA), in order to adjust the family-wise error rate when performing multiple comparisons. A stepwise discriminant function analysis (DFA) was run on all the resulting test scores, to identify the psychometric tests most suitable to discriminate between the cognitive profiles of patients with TLE and patients with FLE.

Data are displayed as mean (M) and standard deviation (SD) if not labeled otherwise. Analyses were carried out in IBM SPSS Statistics 22 (IBM Corporation, Armonk, New York, USA).

3. Results

3.1. Principal component analysis (PCA)

Kaiser-Meyer-Olkin analysis revealed an index of 0.805 and BTS analysis (Chi-Square(595) = 1818.17; $p < .000$) was highly significant; both indicating that the psychometric criteria for the performance of valid factor analyses were met sufficiently.

Using principal component analysis (PCA), eleven factors with eigenvalues greater than 1.0 were extracted (see Table 4). On the basis of theoretical considerations regarding the interpretability of the factors, this eleven-factor solution accounting for 69.1% of total variance was considered most appropriate:

(1) *Divided Attention*: The first factor consisted of factor loadings of test scores for missed auditory stimuli and mistakes in the TAP subtest Divided Attention. (2) *Reaction Time*: The second factor was built by factor loadings of test scores for reaction times to auditory stimuli in the TAP subtest Divided Attention. (3) *Verbal Learning*: Test scores for learning words (in the first, fifth and in all repetitions as well as the distraction list of the VLMT), together with scores for delayed recalling and recognizing words of the VLMT, were loaded on the third factor. (4) *Verbal Memory*: Negative factor loadings of test scores for forgetting words after distraction or delay, together with positive factor loadings of scores for delayed recalling words of the VLMT, formed the fourth factor. (5) *Contextual Memory*: The fifth factor was built by factor loadings of test scores for immediately and delayed recalling, together with scores for recognizing details of two short stories (WMS-IV subtest Logical Memory). (6) *Short-term- and Working Memory*: Test scores for recalling digits forwards and backwards (WMS-R subtest Digit Span) loaded on the sixth factor. (7) *Visuospatial Functioning*: Test scores for recalling block positions forwards and backwards (WMS-R subtest Visual Memory Span), together with scores for learning figures (in the first and in all repetitions of the DCS-II) and scores for identifying silhouettes of the VOSP, were loaded on the seventh factor. (8) *Space Perception*: Negative factor loadings of test scores for missed visual stimuli in the TAP subtest Divided Attention, together with positive loadings of scores for correct identifications of the VOSP subtest Position Discrimination, built the eighth factor. (9) *Verbal Fluency*: The ninth factor consisted of factor loadings of test scores for simple and complex phonemic and semantic verbal fluency (RWT). (10) *Response Monitoring*: Test scores for false positive words and repetitions in the VLMT loaded on the tenth factor. (11) *Cognitive Flexibility*: The eleventh factor consisted of factor loadings of test scores for reaction times and mistakes in the TAP subtest Flexibility.

3.2. Discriminant function analysis (DFA)

Independent samples t-tests and chi-square-tests showed no significant differences between the two subgroups (patients with TLE and patients with FLE) concerning gender, handedness, hemispheric language lateralization, lateralization of the epileptogenic focus, occurrence of secondary generalized tonic-clonic seizures, education, age, age of onset of epilepsy, duration of epilepsy, intelligence or symptoms of depression (see Table 2).

The cognitive profiles of the two subgroups, analyzed with Bonferroni corrected independent samples t-tests, revealed significantly poorer performances (M ± SD) of patients with FLE relative to patients with TLE (FLE vs. TLE) in the following factors (see Table 5): Contextual Memory (WMS-IV, delayed recall; 24.26 ± 6.31 vs. 28.52 ± 6.25; $p = .006$ and WMS-IV, recognition; 25.05 ± 1.58 vs. 26.62 ± 1.42; $p =$

Table 4
Factor loadings of the test scores of all 207 assessments with the standard neuropsychological test battery.[a]

	Divided Attention	Reaction Time	Verbal Learning	Verbal Memory	Contextual Memory	Short-term- and Working Memory	Visuospatial Functioning	Space Perception	Verbal Fluency	Response Monitoring	Cognitive Flexibility
TAP Divided Attention, auditory (omissions)	.777										
TAP Divided Attention (mistakes)	.618										
TAP Divided Attention, auditory (RT)		.808									
VLMT, first repetition (LW)			.692								
VLMT, fifth repetition (LW)			.827								
VLMT, all repetitions (LW)			.862								
VLMT, distraction list (LW)			.594								
VLMT, recognition discriminability			.654								
VLMT, delayed recall			.654	.625							
VLMT, recall after distraction (FW)				−.769							
VLMT, delayed recall (FW)				−.848							
WMS-IV Logical Memory, immediate recall					.844						
WMS-IV Logical Memory, delayed recall					.832						
WMS-IV Logical Memory, recognition					.628						
WMS-R Digit Span, forwards						.763					
WMS-R Digit Span, backwards						.686					
WMS-R Visual Memory Span, forwards							.516				
WMS-R Visual Memory Span, backwards							.701				
DCS-II, first repetition (LF)							.634				
DCS-II, all repetitions (LF)							.694				
VOSP Silhouettes							.519				
TAP Divided Attention, visual (omissions)								−.744			
VOSP Position Discrimination								.792			
RWT Phonemic fluency, one letter									.781		
RWT Phonemic fluency, two letters									.779		
RWT Semantic fluency, one category									.759		
RWT Semantic fluency, two categories									.732		
VLMT, false positives										.687	
VLMT, repetitions										.644	
TAP Flexibility (RT)											.594
TAP Flexibility (mistakes)											.719

RT = Reaction times, LW = Learned words, FW = Forgotten words, LF = Learned figures.
No groupings of test scores found for TAP Divided Attention, visual stimuli (reaction times); VLMT interferences; ROCFT copy; and ROCFT delayed recall.
[a] Extraction method: principal component factoring; rotation method: varimax with Kaiser normalization. Coefficient absolute values below 0.5 not displayed.

Table 5
Group comparisons between the cognitive profiles of patients with TLE and patients with FLE.[a].

	patients with TLE (n = 35)		patients with FLE (n = 35)		
	Mean	**SD**	**Mean**	**SD**	**p-value**[a]
Divided Attention					
TAP Divided Attention, auditory (omissions)	0.63	0.92	1.07	1.24	.103
TAP Divided Attention (mistakes)	2.29	2.61	2.59	2.76	.638
Reaction Time					
TAP Divided Attention, auditory (RT)	599.13	81.69	605.52	102.41	.774
Verbal Learning					
VLMT, first repetition (LW)	7.14	1.63	6.81	2.23	.473
VLMT, fifth repetition (LW)	12.32	2.26	12.10	2.15	.668
VLMT, all repetitions (LW)	51.74	9.20	51.36	10.46	.872
VLMT, distraction list (LW)	6.94	2.40	6.16	2.00	.144
VLMT, recognition discriminability	12.09	3.31	11.50	3.14	.448
Verbal Memory					
VLMT, delayed recall	9.23	3.82	10.20	3.68	.283
VLMT, recall after distraction (FW)	2.38	1.88	1.87	1.95	.268
VLMT, delayed recall (FW)	3.09	2.25	1.90	2.15	.027
Contextual Memory					
WMS-IV Logical Memory, immediate recall	28.52	6.25	24.26	6.31	.006*
WMS-IV Logical Memory, delayed recall	23.04	6.30	20.91	5.70	.141
WMS-IV Logical Memory, recognition	26.62	1.42	25.05	1.58	.000***
Short-term- and Working Memory					
WMS-R Digit Span, forwards	7.28	2.02	6.21	1.73	.020*
WMS-R Digit Span, backwards	6.53	1.94	5.27	1.61	.004**
Visuospatial Functioning					
WMS-R Visual Memory Span, forwards	7.44	2.17	7.62	2.40	.137
WMS-R Visual Memory Span, backwards	8.00	2.10	7.18	1.95	.094
DCS-II, first repetition (LF)	3.00	1.75	2.14	1.62	.037
DCS-II, all repetitions (LF)	5.09	2.24	4.20	1.83	.072
VOSP Silhouettes	19.15	3.22	20.19	3.24	.186
Space Perception					
TAP Divided Attention, visual (omissions)	0.35	1.47	1.29	1.59	.337
VOSP Position Discrimination	19.92	0.23	19.82	0.42	.218
Verbal Fluency					
RWT Phonemic fluency, one letter	12.63	3.90	10.79	4.36	.067
RWT Phonemic fluency, two letters	11.61	3.70	9.89	4.28	.077
RWT Semantic fluency, one category	20.14	6.24	18.45	6.51	.272
RWT Semantic fluency, two categories	14.62	3.89	12.76	3.56	.041
Response Monitoring					
VLMT, false positives	1.39	2.04	1.21	1.65	.673
VLMT, repetitions	4.82	3.46	7.30	4.53	.012*
Cognitive Flexibility					
TAP Flexibility (RT)	750.79	146.82	871.93	264.58	.022*
TAP Flexibility (mistakes)	2.61	2.51	3.23	2.49	.300

SD = Standard deviation, RT = Reaction times, LW = Learned words, FW = Forgotten words, LF = Learned figures.
[a] Bonferroni corrected independent samples t-tests, *p < .05/n, **p < .01/n, ***p < .001/n.

.000); Cognitive Flexibility (TAP Flexibility, reaction times; 871.93 ± 264.58 vs. 750.79 ± 146.82; p = .022); Short-term- and Working Memory (WMS-R Digit Span, forwards; 6.21 ± 1.73 vs. 7.28 ± 2.02; p = .020 and WMS-R Digit Span, backwards; 5.27 ± 1.61 vs. 6.53 ± 1.94; p = .004) and Response Monitoring (VLMT, repetitions; 7.30 ± 4.53 vs. 4.82 ± 3.46; p = .012).

Entering all neuropsychological test scores into the analysis, DFA revealed that six psychometric test scores were most appropriate to discern patients with TLE from patients with FLE: (1) WMS-IV Logical Memory, recognition (Wilk's lambda = 0.781; F = 19.035; df = 68; p < .000), (2) WMS-R Digit Span, backwards (Wilk's lambda = 0.715; F = 13.364; df = 68; p < .000), (3) VLMT, repetitions (Wilk's lambda = 0.637; F = 12.542; df = 68; p < .000), (4) VOSP Silhouettes (Wilk's lambda = 0.589; F = 11.341; df = 68; p < .000), (5) VLMT, delayed recall (Wilk's lambda = 0.548; F = 10.553; df = 68; p < .000) and (6) RWT Phonemic verbal fluency, one letter (Wilk's lambda = 0.512; F = 10.020; df = 68; p < .000). One canonical discriminant function was produced, which discriminated the TLE group from the FLE group. As revealed by the cross-validated classification results (see Fig. 1), 78.6% of patients were correctly classified to one of the two subgroups. TLE group membership was predicted with a sensitivity of 80.0% and a specificity of 77.1% (vice versa for FLE group membership).

4. Discussion

Given the important contribution of neuropsychology to the characterization of epilepsy patients in clinical routine, as well as its relevance for balancing out the risks and benefits of epilepsy surgery, the validity and accuracy of the test battery used is essential. Accordingly, we firstly evaluated whether and to what extent the neuropsychological test battery suggested by the German ILAE Chapter [7] is valid for the use in epilepsy patients in general and, secondly, investigated its suitability to discern the two most relevant subgroups of focal epilepsy.

Regarding the *factorial validity* of the suggested test battery, for the majority of factors the grouping of test scores revealed by the PCA corresponded very well to the cognitive domains to be assessed. Thus, the use of this test battery in the group of epilepsy patients was indeed appropriate to evaluate the examined cognitive domains of attention, verbal learning, verbal memory functions, visuospatial functioning, language, and executive functioning.

Only the cognitive domain of nonverbal learning and memory functions was less adequately measurable: Surprisingly, test scores of the DCS-II showed no groupings to a Nonverbal Memory factor, but were assigned to the factor Visuospatial Functioning. As requirements of visuospatial and executive skills, including concept formation and spatial perception, seemed to be the central demand for the

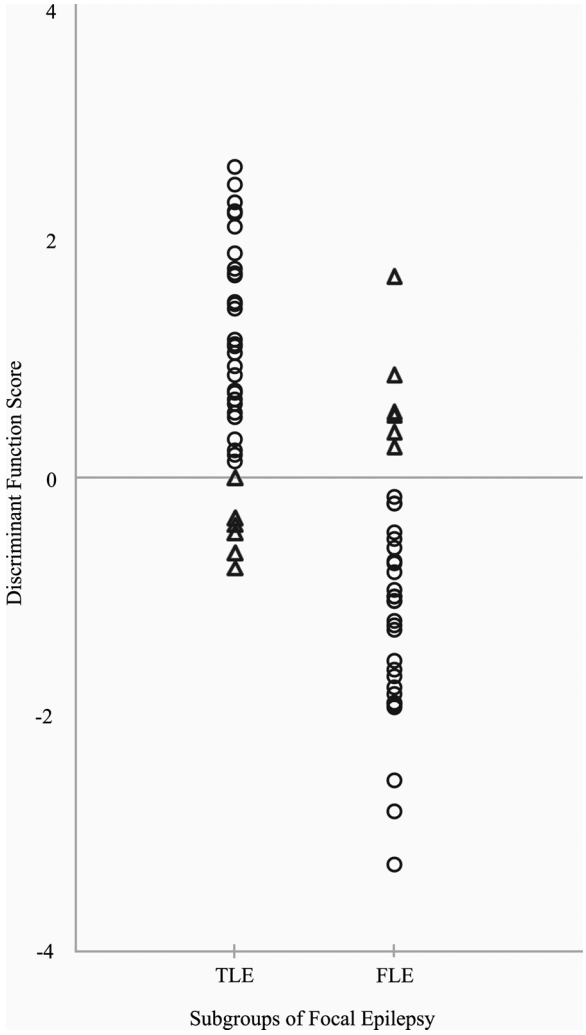

Fig. 1. Scores of the standardized discriminant function (DF) plotted for the two subgroups (patients with TLE and patients with FLE). Correctly classified patients = dots; misclassified patients = triangles.
Discriminant cutting point for classifying cases = 0 (TLE group centroid = 0.963; FLE group centroid = -0.963).
DF = -11.575 - (0.158*VLMT, delayed recall) - (0.089*VLMT, repetitions) + (0.293*WMS-R Digit Span, backwards) + (0.531*WMS-IV Logical Memory, recognition) - (0.154*VOSP Silhouettes) + (0.104*RWT Phonemic verbal fluency, one letter).

performance in this test, while nonverbal learning and memory functions were less important, the DCS-II appeared to have portrayed other cognitive domains than originally intended. Likewise, the ROCFT failed to assess nonverbal memory functions adequately, as neither scores for the copy nor for the delayed recall of the complex figure showed groupings to interpretable factors in the PCA.

Previous research reported nonverbal memory networks to be organized in a more widespread way compared to verbal memory functions, leading to less consistent results regarding the association of nonverbal memory and the temporal-lobe of the non-dominant hemisphere [35–37]. Due to the general complexity of the construct, difficulties regarding its assessment are not immanent to the specific cohort of epilepsy patients, but occurred in research on other neurological and psychiatric diseases as well [38,39]. As many psychometric tests measuring nonverbal memory functions consist of visual learning material which is easily verbalizable, or contain strong components of attentional and executive functioning, their results can certainly be influenced by impairments in other cognitive domains.

Based on the results of former studies on *cognitive profiles* of different subgroups of focal epilepsy [13–16], we anticipated that TLE was mostly associated with impairments in long-term memory functions, whereas FLE was rather related to deficits in attentional and executive functioning, including working memory. In line with our expectations, we found measurable group differences regarding these typical deficits resulting in lower performances of patients with FLE compared to patients with TLE in the factors Cognitive Flexibility, Short-term- and Working Memory and Response Monitoring. The unexpected finding of poorer performance of patients with FLE in the WMS-IV subtest Logical Memory could be explained by the tests' high requirements of executive skills, including structuring of information and logical reasoning, which can be impaired in patients with FLE [15,16]. Another possible explanation might be associated with differences between patients with TLE and patients with FLE regarding epilepsy related factors (such as disease severity, seizure frequency, age of onset or medication) having an impact on the patients' cognitive functioning [40].

Concerning the differentiation between the two subgroups, the DFA revealed six psychometric test scores to be most sensitive for the aspects causing cognitive impairments in epilepsy and, thus, appropriate to discern patients with TLE from patients with FLE. As group membership was correctly predicted for 78.6% of patients using cross-validation, the suggested test battery was indeed equally suitable for patients of *different subgroups of focal epilepsy*.

The slightly diverse results concerning the psychometric test scores showing significant group differences and those identified by the DFA to be most adequate for group distinction might be due to the stepwise procedure of the DFA, which enables the detection of less dominant but still relevant dissimilarities in the cognitive profiles of the two subgroups.

5. Conclusion

Our findings not only confirm that the majority of examined cognitive domains are *indeed* sufficiently assessable by the neuropsychological test battery investigated, but also show that the test battery allows appropriate cross-validated differentiation between cognitive profiles of TLE and FLE for 78.6% of patients.

As the identification of variables to discriminate between groups is not the only purpose of the DFA, it will be desirable to apply the discriminant function derived from the model finalized in this study *to new data*, in order to verify its utility and further use it to predictively classify new cases. Furthermore, the informative value of our findings could be improved by taking epilepsy related factors, such as disease severity or medication, into consideration, as their impact on the patients' cognitive functioning is already well established. Moreover, an extension of the research focus of this study by additionally incorporating the dimension of *lateralization* into the analysis could be a promising objective for further studies with great value for clinical routine. Together with our findings, examining the ability of the test battery to discern patients with focal epilepsy in the dominant hemisphere from patients with focal epilepsy in the non-dominant hemisphere might not only be interesting for future research, but could also facilitate the predictive classification of ambiguous patients in clinical routine.

In accordance with previous research, we emphasize the necessity to further improve the assessment of the cognitive domain of nonverbal learning and memory functions. As Vogt et al. [8] detected ten different psychometric tests used in epilepsy centers across Europe to measure nonverbal memory, it will be the subject of future research to examine their availability and to provide evidence supporting their application in epilepsy.

Besides this very important goal of improving the informative value of the psychometric tests applied in clinical routine, promoting international consensus regarding a standard neuropsychological test battery to use would be desirable as well and could be encouraged by internationally adapting the German test battery investigated in this

study and examining its appropriateness in other cultural environments.

F. Rosenow and A. Hermsen hold a trademark (Implicit HeRo™) regarding a test-system for implicit memory, which was however not included into this study. Otherwise, none of the authors has any conflict of interest to disclose with respect to this study.

Declaration of Competing Interest

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