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Pre- and postoperative verbal memory and executive functioning in frontal versus temporal lobe epilepsy

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ABSTRACT

There is accumulating evidence for considerable overlap in preoperatively affected cognitive functions in patients with temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE). The current study investigated whether it is possible to differentiate between patients with FLE and TLE prior to surgery, based on measures of verbal memory and executive functioning. Furthermore, the postoperative cognitive development was compared. Pre- and postoperative data from 109 patients with FLE and 194 patients with TLE were retrospectively analyzed. Preoperatively, there were no differences in verbal memory, and postoperatively, no distinctive cognitive change was found between patients with FLE and TLE. However, patients with FLE performed worse on a cognitive switching task. Notably, irrespective of localization, patients with a presumed epileptogenic area in the language-dominant hemisphere performed worse than patients with seizures that originated in the nonlanguage-dominant hemisphere on measures of verbal memory, both pre- and postoperatively. In sum, the results suggest that verbal memory scores may be less valuable for differentiation between TLE and FLE, while measures of executive functioning may help identify patients with FLE. Additionally, rather than the localization, epilepsy lateralization critically impacts the evaluation of verbal memory functioning in both TLE and FLE. The results are discussed in light of the current frameworks of functional disturbances in epileptic networks.

1. Introduction

Patients with focal epilepsy not only endure disturbing seizures, but they also often suffer from localization-specific cognitive deficits. Seizure frequency reduction can be accomplished by performing epilepsy surgery, a standard treatment option for patients with intractable focal epilepsy. However, despite good chances of seizure freedom, in some cases, epilepsy surgery further affects the cognitive status of patients [1,2]. The pre- and postoperative cognitive outcome is especially well studied in patients with temporal lobe epilepsy (TLE) [3–5]. After temporal lobe resection (TLR), these patients may deteriorate on tasks that are classically associated with temporal lobe functioning (e.g., memory and language) [6,7], but they may also improve on tasks that are linked to frontal lobe functioning (i.e., attention, executive functioning, psychomotor speed, motor coordination, and short-term memory), particularly when they are seizure-free after surgery [7,8].

In the last decades, frontal lobe epilepsy (FLE) has become a more and more frequent indication for resective surgery [9]. Compared with healthy controls and patients with TLE, patients with FLE show impairments in aspects of executive functioning. For instance, these patients are impaired in tasks of concept formation and shifting, response inhibition, verbal and nonverbal fluency, anticipation and planning, and proverb interpretation [5,10–13]. Moreover, patients with FLE show impairments in working memory, cognitive speed, attention, and motor coordination [10,14]. Decline in long-term memory, including story recall, verbal free recall, verbal recognition, and visual reproduction, also occasionally occurs in patients with FLE [15–17]. However, small sample sizes prevent one from drawing firm conclusions about these findings.

There are only a few investigations on the cognitive effects of frontal lobe resection (FLR) in patients with FLE, and the findings are predominantly inconclusive. A study by Sarkis and colleagues [18] found verbal fluency to be impaired after FLR, especially when resection took place in the language-dominant hemisphere. A study by Helmstaedter and colleagues [8] indicated that patients' performance dropped from pre- to postoperative assessment on measures of psychomotor speed, attention, and motor coordination and improved on measures of short-term memory. In contrast to the study by Sarkis and colleagues [18], Helmstaedter and colleagues [8] did not find lateralization effects for left- versus right-operated patients. Other early studies identified a subtle decline in verbal memory [19] and associative learning [20], but

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no decline in visual memory performance [21] after FLR. Interestingly, a recent study from Sweden indicated cognitive stability of patients with FLE on various measures of cognitive functioning two years after resection, findings that suggest minimal effects from this procedure at group level [22].

Given the diversity of and overlap between affected cognitive functions in TLE and FLE, there appears to be neither clear cutoffs for TLE and FLE differentiation prior to surgery nor definite evidence for the cognitive effects of FLR. Some studies identified specific executive functions (e.g., proverb interpretation) that may distinguish FLE from TLE preoperatively [11]. Such tests, however, are typically not included in standard test batteries at epilepsy centers, and norms are rarely available or published [23]. Therefore, the present study investigated whether it is possible to reliably distinguish between patients with FLE and TLE preoperatively, based on widely used neuropsychological tests that assess aspects of verbal memory and executive functioning. Furthermore, we examined the postoperative development of patients with FLE compared with patients with TLE.

We hypothesized that patients with FLE, as compared with patients with TLE, would preoperatively show greater impairment on tests of executive functioning and "frontal" measures of verbal memory (i.e., short-term memory, learning capacity, susceptibility to interference, and tendency to perseverate) but less impairment on "temporal" measures of verbal memory (i.e., long-term retention, long-term recognition, and long-term recall). Based on existing cognitive outcome studies [6–8], we further expected that patients with FLE would deteriorate on frontal measures and improve on temporal measures after FLR. This pattern should be reversed in patients with TLE after TLR. Finally, we expected the abovedescribed effects to be most pronounced in patients with a presumed epileptogenic area or surgery in the language-dominant hemisphere, since our primary outcome measures assessed *verbal* memory performance [18].

2. Materials and methods

2.1. Participants and procedure

The participants included 303 patients with either FLE ($n = 109$; 61 males/48 females) or TLE ($n = 194$; 96 males/98 females) who all underwent extensive interictal and ictal preoperative video-electroencephalogram (EEG) monitoring and FLR or TLR at the Epilepsy Center Bethel in Bielefeld, Germany [24,25]. Resection side and type of surgical procedure were specified based on neuroradiological findings and scalp or invasive EEG recordings. Patients underwent resection in either the language-dominant (FLE: $n = 48$; TLE: $n = 90$) or nonlanguage-dominant (FLE: $n = 61$; TLE: $n = 104$) hemisphere, as determined by functional magnetic resonance imaging (fMRI) [26]. Patient groups were matched based on education, duration of epilepsy, and age at preoperative neuropsychological assessment by SPSS case–control matching. In this procedure, we defined the patients with FLE as the index group from which patient matches from a larger group of patients with TLE (619 patients) were drawn. Inclusion criteria for patients with FLE were FLE diagnosis based on a comprehensive assessment of seizure semiology, interictal and ictal EEG, MRI findings during presurgical diagnostics performed by experienced epileptologists, participation in neuropsychological assessment, age at preoperative assessment over 16 years, and a clearly indicated language lateralization by fMRI. These criteria resulted in 109 patients with FLE.

Patients from 2003 to 2018 were analyzed retrospectively. Neuropsychological assessment took place during the presurgical evaluation phase at the Epilepsy Monitoring Unit of the Epilepsy Center Bethel in Bielefeld (preoperatively); postoperative assessment was performed six months after surgery. Of the 194 preoperatively tested patients with TLE, data from postoperative assessment on verbal memory and executive functioning variables were available in 194 (100%) and 165 (85.1%) patients, respectively. Of the 109 preoperatively tested patients with FLE, data from postoperative assessment on the verbal memory and executive functioning variables were available in 88 (80.7%) and 76 (69.7%) patients, respectively. Postoperatively, 55.1% of patients with FLE and 72.6% of patients with TLE were seizure-free at the six-month follow-up. Seizure freedom was defined as sustained seizure freedom, with or without aura, six months after surgery (Engel 1A and 1B) [27]. For further medical and demographic characteristics, see Table 1.

2.2. Materials

Since we were interested in differentiation between frontal and temporal lobe functioning on the basis of specific components of a verbal memory test, we examined test results from the Verbal Learning and Memory Test (VLMT) [28], which is the German adaptation of the Rey Auditory Verbal Learning and Memory Test [29]. The VLMT is widely used by epilepsy centers across Europe [23]. It is an episodic verbal memory test that requires learning fifteen unrelated words over five trials with immediate recall after each trial, free recall after verbal interference, and free recall and recognition after a 30-minute delay. Based on the nature of the different components of this test, we postulated four variables that might significantly rely on frontal lobe function and, therefore, possess diagnostic value [15,28,30]:

1. short-term memory (trial 1: number of immediately and freely recalled words from all fifteen words);
2. learning capacity (trial 1 to 5: sum of correctly remembered words throughout trial to trial 5);
3. susceptibility to interference (trial 5–6: number of correctly remembered words on trial 5 minus the number of correctly remembered words after an interference list); and

Table 1
Medical and demographic characteristics of patients with frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE).

Variables		FLE[a] ($n = 109$)	TLE[a] ($n = 194$)
Sex	Female (%)	44.0	50.5
Age at baseline (years)	m (sd)	32.3 (11.7)	33.4 (11.2)
Age at epilepsy onset (years)	m (sd)	13.0 (11.3)	17.1 (11.4)
Duration of epilepsy (years until surgery)	m (sd)	19.8 (12.6)	16.3 (10.2)
Education at baseline:	*n* (%)		
High school graduation		24 (22.3)	42 (21.6)
Secondary school grad. (10 years)		32 (29.4)	64 (33.0)
Secondary school grad. (9 years)		32 (29.4)	60 (30.9)
No graduation		8 (7.5)	10 (5.5)
School for handicapped children		11 (10.3)	15 (8.0)
Still attending school		1 (1.1)	2 (1.0)
Side of surgery	Language-dominant (%)	44.0	46.4
Etiology:	*n* (%)		
Tumor[b]		24 (22.0)	38 (19.6)
MTS			111 (57.2)
MCD		71 (65.1)	5 (2.6)
Phakomatosis			2 (1.0)
Vascular		5 (4.6)	10 (5.2)
Encephalitis		3 (2.8)	3 (1.5)
Scar		4 (3.7)	3 (1.5)
Nonlesional/unspecified		2 (1.8)	22 (11.4)
Seizure outcome	Seizure-free (%)	55.1	72.6

Notes. FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy; m = mean; sd = standard deviation; MTS = mesial temporal sclerosis; MCD = malformations of cortical development.

[a] Patient groups were matched based on education, duration of epilepsy, and age at preoperative neuropsychological assessment.

[b] Including benign tumors, astrocytomas, oligodendrogliomas, gangliogliomas, dysembryoplastic neuroepithelial tumors, low-grade astrocytomas, and angiocentric neuroepithelial tumors.

4. tendency to perseverate (number of word repetitions across all five learning trials).

Moreover, we defined three measures that might rely more on temporal lobe functioning [28,31]:

1. long-term retention (trial 5–7: number of correctly remembered words after trial 5 minus the number of correctly remembered words after a 30-minute delay);
2. long-term recognition (number of correctly recognized words after a 30-minute delay minus the number of false positives); and
3. long-term recall (number of correctly recalled words after a 30-minute delay).

In order to validate the extent to which the different components of the VLMT assess frontal lobe function, we also analyzed data from the Delis–Kaplan Executive Function System Trail Making Test (D-KEFS TMT) [32]. This test has been validated for frontal lobe function and pathology [33–35] and is based on the traditional two-part Trail Making Test by Reitan [36]. The D-KEFS TMT consists of five conditions: visual scanning, number sequencing, letter sequencing, number–letter switching, and motor speed. We concentrated on two of the five conditions, namely:

1. number–letter switching; and
2. motor speed.

Specifically, the number–letter switching condition, a visual-motor sequencing procedure that is a measure of flexibility of thinking and response inhibition, crucially depends on the integrity of frontal lobe structures [34]. To test whether it is solely the executive component (i.e., flexibility, inhibition) that discriminates between patients with

Table 2
Pre- and postoperative performance and statistical results of frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE) patients on all dependent variables.

Parameter	FLE	TLE	MANOVA			
			Group	Lateralization	Time	Interaction (Lateralization × Time)
VLMT						
Trial 1						
Pre	−0.020 (0.99)	−0.217 (0.94)	$p = 0.057$, $F(1,278) = 3.324$, $eta^2 = 0.013$	$p = 0.054$, $F(1,278) = 3.003$, $eta^2 = 0.012$	$p = 0.701$, $F(1,242) = 0.148$, $eta^2 = 0.001$	**$p = 0.007$**, $F(1,242) = 7.529$,
Post	−0.076 (1.04)	−0.143 (0.97)				$eta^2 = 0.030$
Trial 1 to 5						
Pre	−0.121 (1.14)	−0.307 (1.06)	$p = 0.133$, $F(1,278) = 2.269$, $eta^2 = 0.008$	$p = 0.437$, $F(1,278) = 0.060$, $eta^2 = 0.002$	$p = 0.539$, $F(1,242) = 0.378$, $eta^2 = 0.002$	**$p = 0.008$**, $F(1,242) = 7.231$,
Post	−0.149 (1.17)	−0.201 (1.09)				$eta^2 = 0.029$
Trial 5–6						
Pre	−0.234 (0.94)	−0.459 (0.92)	$p = 0.061$, $F(1,278) = 3.550$, $eta^2 = 0.012$	**$p = 0.016$**, $F(1,278) = 5.898$, $eta^2 = 0.020$, dominant < nondominant	$p = 0.804$, $F(1,242) = 0.062$, $eta^2 = 0.000$	$p = 0.577$, $F(1,242) = 0.313$,
Post	−0.165 (1.04)	−0.424 (0.91)				$eta^2 = 0.001$
PE						
Pre	−0.533 (0.80)	−0.581 (0.79)	$p = 0.729$, $F(1,278) = 0.120$, $eta^2 = 0.000$	$p = 0.361$, $F(1,278) = 0.838$, $eta^2 = 0.003$	$p = 0.125$, $F(1,242) = 2.370$, $eta^2 = 0.010$	$p = 0.298$, $F(1,242) = 1.086$,
Post	−0.537 (0.72)	−0.466 (0.74)				$eta^2 = 0.004$
Trial 5–7						
Pre	−0.265 (0.97)	−0.479 (1.01)	$p = 0.087$, $F(1,278) = 2.949$, $eta^2 = 0.010$	**$p = 0.007$**, $F(1,278) = 7.301$, $eta^2 = 0.025$, dominant < nondominant	$p = 0.460$, $F(1,242) = 0.548$, $eta^2 = 0.002$	$p = 0.280$, $F(1,242) = 1.171$,
Post	−0.504 (0.95)	−0.131 (1.03)				$eta^2 = 0.005$
Recog						
Pre	−0.052 (0.95)	−0.189 (0.97)	$p = 0.044$, $F(1,278) = 4.154$, $eta^2 = 0.015$, FLE > TLE	$p = 0.701$, $F(1,278) = 0.192$, $eta^2 = 0.002$	$p = 0.396$, $F(1,242) = 0.722$, $eta^2 = 0.003$	**$p = 0.025$**, $F(1,242) = 5.102$,
Post	−0.007 (1.00)	−0.275 (1.05)				$eta^2 = 0.021$
Trial 7						
Pre	−0.337 (1.15)	−0.557 (1.11)	$p = 0.089$, $F(1,278) = 2.907$, $eta^2 = 0.010$	$p = 0.437$, $F(1,278) = 0.605$, $eta^2 = 0.002$	$p = 0.242$, $F(1,242) = 1.374$, $eta^2 = 0.006$	$p = 0.263$, $F(1,242) = 1.259$,
Post	−0.268 (1.21)	−0.492 (1.12)				$eta^2 = 0.005$
D-KEFS TMT						
NLS						
Pre	−0.557 (1.19)	−0.273 (1.28)	**$p = 0.047$**, $F(1,238) = 5.211$, $eta^2 = 0.017$ FLE < TLE	$p = 0.327$, $F(1,238) = 0.964$, $eta^2 = 0.004$	$p = 0.221$, $F(1,204) = 1.505$, $eta^2 = 0.007$	$p = 0.782$, $F(1,204) = 0.077$,
Post	−0.583 (1.18)	−0.092 (1.13)				$eta^2 = 0.000$
MS						
Pre	0.592 (0.64)	0.401 (0.92)	$p = 0.147$, $F(1,238) = 2.119$, $eta^2 = 0.009$	$p = 0.906$, $F(1,238) = 0.014$, $eta^2 = 0.000$	$p = 0.194$, $F(1,204) = 1.700$, $eta^2 = 0.008$	$p = 0.940$, $F(1,204) = 0.006$,
Post	0.562 (0.50)	0.593 (0.64)				$eta^2 = 0.000$

Notes. Means and standard deviations are given in standardized *z*-scores. Standard deviations appear in parentheses. Significant post hoc results after significant multivariate tests appear in bold. Significant post hoc results after nonsignificant multivariate tests are presented in italics. VLMT = Verbal Learning and Memory Test; Trial 1 to 5 = sum of trial 1 to trial 5; Trial 5–6 = trial 5 minus trial 6; PE = perseveration errors; Trial 5–7 = trial 5 minus trial 7; Recog = recognition; D-KEFS TMT = Delis–Kaplan Executive Function System Trail Making Test; NLS = number–letter switching; MS = motor speed; Pre = preoperative assessment; Post = postoperative assessment; FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy.

FLE and TLE, we included results on the motor speed condition as a control measure.

2.3. Data analysis

Patient performance on the seven outcome variables was transformed into standardized, age-corrected *z*-scores according to the norms of the respective tests. In order to examine preoperative differences at the group level, multivariate analyses of variance (MANOVA) were performed with group (FLE vs. TLE) and side of seizure focus (language-dominant vs. nonlanguage-dominant) as independent variables and performance on the five VLMT and the two D-KEFS TMT conditions as dependent variables. In order to evaluate pre- to postoperative cognitive development, repeated measures ANOVA were computed using group (FLE vs. TLE) and side of surgery (language-dominant vs. nonlanguage-dominant) as between-subject factors and time (pre vs. post) as a within-subject factor. To control for multiple testing, we only interpreted the significant univariate effects of the significant multivariate analyses.

At the individual level, analyses comprised the frequencies of impaired performance at pre- and postoperative assessment as well as the percentages of clinically significant gains and losses from pre- to postoperative assessment for all patient groups. Pre- and postoperative impaired performance scores were defined as *z*-scores that fell less than one standard deviation from the mean (i.e., $z \leq -1$). Significant pre- to postoperative performance changes were calculated with change *z*-scores ($z\text{-score}_{post}$ minus $z\text{-score}_{pre}$) and defined as scores that exceeded one standard deviation from the mean in both directions (i.e., change $z\,\Delta$ post − pre > 1 and <− 1). Typically, analyses of significant individual change are based on reliable change indices (RCIs) [22]. However, RCIs were not available for all VLMT and TMT parameters, and earlier studies showed that results based on the above outlined procedure do not significantly differ from using RCIs with a 90% confidence interval [37]. All analyses were performed by using IBM SPSS Statistics (version 22).

3. Results

In the following section, we report only the significant ($p < 0.05$) main effects and post hoc tests for the preoperative and pre- to postoperative group comparisons and, thereafter, sum up the descriptive individual results. For a full overview of means and standard deviations of all dependent variables at pre- and postoperative assessment as well as the statistical results, the reader is referred to Table 2.

3.1. Preoperative group differences

The MANOVA for preoperative comparisons on the seven VLMT variables yielded a significant "side of seizure focus" main effect ($F(7,274) = 3.741$, $p = 0.001$, $\text{eta}^2 = 0.074$). Post hoc tests indicated that patients with a presumed epileptic focus in the language-dominant hemisphere performed significantly worse than patients with a presumed epileptic focus in the nonlanguage-dominant hemisphere for trial 5–6 ($F(1,278) = 5.898$, $p = 0.016$, $\text{eta}^2 = 0.020$) and trial 5–7 ($F(1,278) = 7.301$, $p = 0.007$, $\text{eta}^2 = 0.025$). Fig. 1 illustrates the preoperative differences for all variables depending on the side of the presumed epileptic focus.

The MANOVA for preoperative comparisons on the two D-KEFS TMT variables revealed a significant "group" main effect ($F(2,237) = 2.262$, $p = 0.042$; $\text{eta}^2 = 0.023$). As revealed by the post hoc analyses, patients with FLE had lower scores than patients with TLE on the number–letter switching condition ($F(1,238) = 5.211$, $p = 0.047$, $\text{eta}^2 = 0.017$).

3.2. Pre- to postoperative group differences

There was no overall effect on the nine outcome variables between seizure-free patients and patients with continuing seizures after surgery ($F(9,172) = 1.187$, $p = 0.446$). Consequently, means of all dependent variable converged, and data from patients with and without continuing seizures were pooled for further analysis. The repeated measures MANOVA that examined pre- to postoperative development of patients' performance on the seven VLMT variables revealed a significant interaction effect between "time" and "side of surgery" ($F(7,238) = 2.053$, $p = 0.050$, $\text{eta}^2 = 0.058$). Post hoc analyses indicated that the performance of patients who underwent surgery in their language-dominant hemisphere deteriorated from pre- to postoperative assessment on trial 1 ($F(1,242) = 7.529$, $p = 0.007$, $\text{eta}^2 = 0.030$), on trial 1 to 5 ($F(1,242) = 7.231$, $p = 0.008$, $\text{eta}^2 = 0.029$), and on recognition ($F(1,242) = 5.102$, $p = 0.025$, $\text{eta}^2 = 0.021$), whereas the performance of patients who underwent surgery in their nonlanguage-dominant hemisphere improved or remained stable over time for those variables. Fig. 2 depicts the pre- to postoperative performance for trial 1, trial 1 to 5, and in recognition memory depending on the side of resection.

The repeated measures MANOVA that examined the pre- to postoperative development of patients' performance on the two D-KEFS TMT variables yielded a significant "group" main effect ($F(2,204) = 5.521$, $p = 0.020$, $\text{eta}^2 = 0.026$). As illustrated in Fig. 3, patients with FLE performed worse on the D-KEFS TMT number–letter switching condition both pre- and postoperatively.

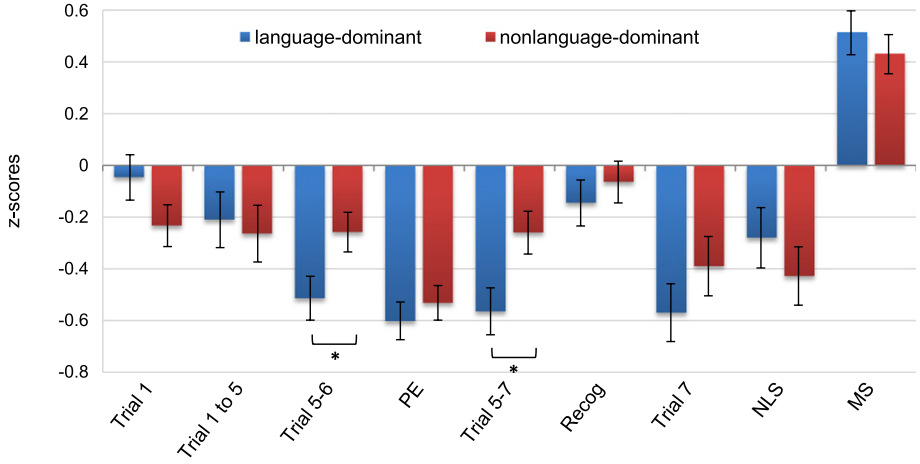

Fig. 1. Preoperative differences for all outcome variables between patients with a language-dominant or nonlanguage-dominant side of presumed epileptic focus. Bars represent mean ± 1 standard error. Dependent variables of the verbal learning and memory test are as follows: Trial 1, Trial 5–6, perseveration errors (PE), Trial 5–7, and recognition (Recog). Dependent variables of the Delis–Kaplan Executive Function System Trail Making Test are as follows: number–letter switching (NLS) and motor speed (MS). *p < 0.05. **p < 0.025.

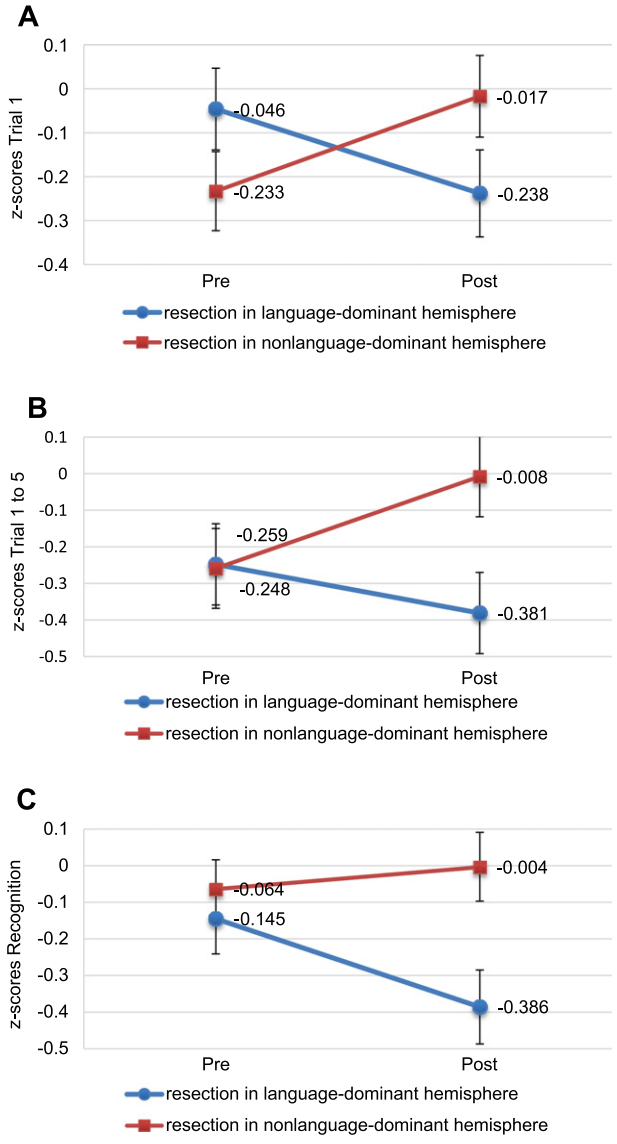

Fig. 2. Pre- to postoperative performance on the Verbal Learning and Memory Test for Trial 1 (A) and in recognition memory (B) depending on the side of resection. Bars represent mean ± 1 standard error. Abbreviations: Pre = preoperative assessment; Post = postoperative assessment.

3.3. Individual level analyses

Table 3 depicts the frequencies of impairment before and after surgery and the percentages of significant individual losses and gains from pre- to postoperative assessment per group and side of epileptic focus or surgery, respectively. In contrast to our group results, when comparing patients with FLE with patients with TLE with a presumed epileptic focus in their language-dominant hemisphere, it becomes clear that for all VLMT variables, a slightly higher percentage of patients with TLE were impaired prior to surgery. This phenomenon also held true when considering the entire group with TLE. In accordance with these findings, the language-dominant hemisphere-resected patients with TLE showed slightly higher percentages of significant deterioration from pre- to postoperative assessment on almost all VLMT variables compared with language-dominant hemisphere-resected patients with FLE. Both of these findings were not observed when comparing patients with FLE with patients with TLE with a presumed epileptic focus or resection in their nonlanguage-dominant hemisphere.

When considering the individual results on the D-KEFS TMT number–letter switching condition, roughly the same percentage of patients with FLE and TLE were clinically impaired before surgery (29% vs. 27%, respectively). However, in contrast to our group analyses, postoperatively, more patients with FLE compared with patients with TLE were clinically impaired (39% vs. 17%, respectively).

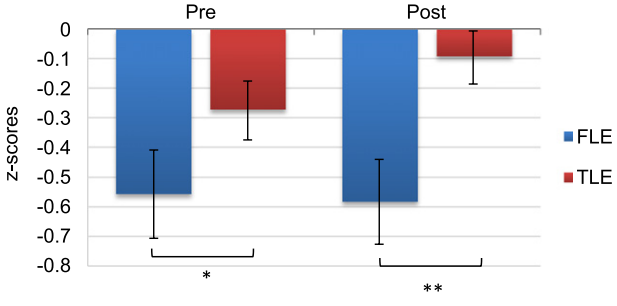

Fig. 3. Pre- and postoperative group differences in the number–letter switching condition of the Delis–Kaplan Executive Function System Trail Making Test. Bars represent mean ± 1 standard error. Abbreviations: Pre = preoperative assessment; Post = postoperative assessment; FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy. *$p < 0.05$. **$p < 0.025$.

4. Discussion

Differentiation between patients with FLE and TLE based on neuropsychological profiles is challenging because of a great overlap in affected cognitive functions. Furthermore, while the cognitive outcome after temporal lobe surgery in patients with TLE has been studied extensively, there is less evidence for the cognitive effects of FLR in patients with FLE. The goal of the present study was to identify 'cognitive markers' of frontal lobe dysfunction in order to differentiate between patients with FLE and TLE by examining test results from the VLMT and the D-KEFS TMT. Moreover, the current study investigated the pre- to postoperative cognitive development of patients with FLE compared with patients with TLE.

4.1. Preoperative verbal memory

Preoperatively, patients with a presumed seizure focus in their language-dominant hemisphere were more impaired in verbal long-term retention and susceptibility to interference than patients with a presumed seizure focus in their nonlanguage-dominant hemisphere. This finding suggests, concurrently with the notion by Upton and Thompson [13], that lateralization—and not localization—of the presumed epileptic focus accounts for preoperative impairments in verbal memory function. Lateralization effects of verbal long-term memory performance are consistently reported for patients with TLE [3,5,38–40]. Evidence for such effects in patients with FLE is less conclusive [5,8,15]. Our results seem to support the idea that preoperative lateralization effects on verbal memory exist in both patients with TLE and FLE.

Preoperative group analyses indicated that patients with FLE and TLE could not be clearly differentiated based on the pattern of verbal memory performance. We only found a trend, as revealed by our individual analyses, that a consistently greater proportion of patients with TLE were clinically impaired on all measures of verbal memory function, but statistical comparisons at the group level did not reveal significant differences. Therefore, we did not find evidence for our first hypothesis that measures of verbal short-term memory, learning capacity, susceptibility to interference, and tendency to perseverate are sensitive to frontal lobe dysfunction in patients with FLE. Nevertheless, our results fit well into well-documented memory deficits in both patients with FLE and TLE [14–17].

One possible explanation for the abovementioned findings could be the complexity of verbal memory, which draws upon a wide-ranging intrahemispheric network of mainly frontal and temporal neural structures [41]. Disruptions at various nodes in either frontal or temporal regions of this wider memory network may be sufficient to cause verbal

Table 3
Frequencies of impairment before and after surgery and percentage of significant individual changes from pre- to postoperative assessment per group and side of epilepsy focus/surgery.

	VLMT							D-KEFS TMT	
	Trial 1	Trial 1 to 5	Trial 5–6	PE	Trial 5–7	Recog	Trial 7	NLS	MS
FLE language-dominant									
Impaired at T1 (T2)	10% (15%)	26% (30%)	25% (18%)	35% (33%)	25% (15%)	20% (18%)	29% (26%)	31% (38%)	14% (6%)
Change T1 → T2	25% ↓ 10% ↑	18%↓ 10% ↑	13% ↓ 35% ↑	10% ↓ 8% ↑	8% ↓ 26% ↑	17% ↓ 11% ↑	13%↓ 8% ↑	10% ↓ 14% ↑	3% ↓ 6% ↑
FLE nonlanguage-dominant									
Impaired at T1 (T2)	19% (25%)	34% (41%)	14% (33%)	25% (18%)	14% (19%)	25% (26%)	28% (38%)	28% (40%)	2% (3%)
Change T1 → T2	13% ↓ 13% ↑	13%↓ 19% ↑	23% ↓ 21% ↑	9% ↓ 14% ↑	21% ↓ 26% ↑	15% ↓ 4% ↑	15%↓ 19% ↑	14% ↓ 14% ↑	5% ↓ 5% ↑
TLE language-dominant									
Impaired at T1 (T2)	20% (30%)	36% (41%)	40% (42%)	36% (21%)	33% (39%)	26% (39%)	42% (45%)	25% (14%)	6% (4%)
Change T1 → T2	26% ↓ 14% ↑	18%↓ 13% ↑	21% ↓ 23% ↑	10% ↓ 17% ↑	22% ↓ 17% ↑	23% ↓ 6% ↑	15%↓ 18% ↑	5% ↓ 12% ↑	2% ↓ 6% ↑
TLE nonlanguage-dominant									
Impaired at T1 (T2)	20% (15%)	30% (24%)	25% (16%)	28% (31%)	23% (13%)	23% (19%)	29% (20%)	28% (20%)	11% (4%)
Change T1 → T2	8% ↓ 30% ↑	7%↓ 25% ↑	16% ↓ 24% ↑	13% ↓ 9% ↑	13% ↓ 26% ↑	13% ↓ 20% ↑	15%↓ 24% ↑	14% ↓ 17% ↑	7% ↓ 11% ↑
FLE total									
Impaired at T1 (T2)	15% (21%)	30% (36%)	19% (26%)	30% (25%)	19% (17%)	23% (22%)	29% (32%)	29% (39%)	8% (4%)
Change T1 → T2	18% ↓ 12% ↑	15%↓ 15% ↑	18% ↓ 28% ↑	10% ↓ 11% ↑	15% ↓ 26% ↑	16% ↓ 7% ↑	14%↓ 14% ↑	12% ↓ 14% ↑	4% ↓ 6% ↑
TLE total									
Impaired at T1 (T2)	20% (22%)	33% (32%)	32% (28%)	32% (26%)	28% (25%)	24% (28%)	35% (32%)	27% (17%)	9% (4%)
Change T1 → T2	16% ↓ 23% ↑	12%↓ 20% ↑	18% ↓ 24% ↑	12% ↓ 13% ↑	17% ↓ 22% ↑	18% ↓ 14% ↑	15%↓ 21% ↑	10% ↓ 15% ↑	5% ↓ 9% ↑

Notes. Percentages of pre- (T1) and postoperative impairment (T2) are given per group and side of epilepsy/surgery. Percentages of significant individual changes from pre- (T1) to postoperative assessment (T2) are indicated by arrows pointing downward (decline) and upward (improvement). FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy; VLMT = Verbal Learning and Memory Test; D-KEFS TMT = Delis–Kaplan Executive Function System Trail Making Test; Trial 1 to 5 = sum trial 1 throughout trial 5; Trial 5–6 = trial 5 minus trial 6; PE = perseveration errors; Trial 5–7 = trial 5 minus trial 7; Recog = recognition; NLS = number–letter sequencing; MS = motor speed.

memory deficits in TLE and FLE and, thus, account for the comparable extent of memory deficits in TLE and FLE in our sample. This idea is supported by studies demonstrating that focal lesions might produce focal functional loss of the epileptogenic structure as well as affect long-range network alterations that promote more complex cognitive disturbances (e.g., memory dysfunctions) [42]. Additionally, the overlapping memory deficits in FLE and TLE may be explained by seizure activity that propagates from temporal to frontal areas (or vice versa) and causes cognitive symptoms to arise that do not exclusively reflect the presumed epileptogenic area. As a result, patients with FLE might show an impairment pattern that is normally associated with temporal lobe dysfunction. In line with this idea, several studies found wide-ranging connectivity changes between frontotemporal networks due to either interictal or ictal spread of epileptic activity [43–45]. Another explanation for the difficulty of differentiating patients with FLE and TLE could be that differences between those patients may appear rather on a qualitative level and may not be detected in our quantitative data analyses. In other words, patients with FLE as compared with patients with TLE might adopt distinct task approaches that could be indicated by occurrences of certain kinds of perseveration errors, confabulations, intrusions, a plateau phenomenon [46], or pronounced primacy or recency effects during learning and recall.

4.2. Preoperative executive functioning

When further examining the preoperative results, we found that patients with FLE performed worse than patients with TLE on the D-KEFS TMT number–letter switching condition. This finding matches the results of Upton and Thompson [13], who stated that patients with FLE, as compared with patients with TLE, are impaired on executive measures. However, it contradicts the results by Patrikelis and colleagues, who did not find differences between the two groups on the traditional two-part TMT [14]. This discrepancy might be explained by a lower percentage of patients with nonlesional FLE in our sample (our study: 1.80% vs. Patrikelis et al.: 29.41% [14]), since it is proposed that patients with nonlesional epilepsy are cognitively less impaired than MRI-positive patients [46]. Further, we replicated previous findings that claimed patients with FLE and TLE do not differ in motor speed and that proposed the specificity of impairments in set shifting to patients with FLE compared with patients with TLE and healthy controls [10,14,47]. In sum, our data add to the findings that measures of executive functioning (i.e., flexibility of thinking/response inhibition) possess diagnostic value for the differentiation between patients with FLE and TLE. Therefore, executive functioning measures appear to constitute a valid marker of cognitive functioning in FLE.

4.3. Postoperative change in verbal memory and executive functioning

When focusing on the results of the pre- to postoperative cognitive development, it is apparent that, similar to our preoperative findings, the lateralization, and not localization, of epileptic activity may be the more important variable in evaluating verbal memory outcome. Our results suggest that patients who underwent surgery in their language-dominant hemisphere, as compared with patients who underwent surgery in their nonlanguage-dominant hemisphere, deteriorated on verbal short-term memory, verbal learning capacity, and recognition memory. These data match earlier findings that showed a decline in language function after surgery in the language-dominant hemisphere for both patients with FLE [18,47] and TLE [6,7]. From a theoretical perspective, our results are in line with traditional neuropsychological conceptualizations of Luria who already proposed a hemispheric specialization rather than a strict functional localization approach to cognitive functioning [48]. He also suggested that there seems to be no definite evidence regarding a clear dissociation between temporal and frontal patients based on memory deficits, which is in line with our findings. He further points out that disturbances in goal-directed or monitoring processes in frontal patients could eventually lead to the reported mnestic deficits [49].

Our individual analyses indicated that there is also a considerable chance of clinically significant improvement in verbal memory functioning after surgery. This potential benefit was particularly true for patients with FLE and nonlanguage-dominant hemisphere-operated patients with TLE; almost two-thirds of these latter patients significantly improved from pre- to postoperative assessment on verbal short-term and long-term memory. However, even in the language-dominant hemisphere-operated group with TLE, a substantial number of patients showed significant verbal memory gains after surgery. This trend was observed previously, albeit generally to a lesser degree [7]. Our results indicate postsurgical verbal memory stability in about 54–81% of patients with FLE and 58–75% of patients with TLE. Overall, these findings imply that, for most patients, surgery might not result in clinically significant losses of verbal memory functioning.

Remarkably, we found the cognitive outcome in both patient groups to be independent of seizure outcome. Cognitive performance in seizure-free patients did not differ from cognitive performance in patients with continuing seizures; this finding has been reported occasionally [50].

Our group analyses did not suggest that patients with TLE ameliorate on frontal measures after TLR, nor that patients with FLE ameliorate on temporal measures after FLR. However, in our individual analyses, we found a trend for a smaller proportion of patients with TLE, as compared with patients with FLE, to be postoperatively impaired in a classical frontal measure (i.e., the D-KEFS TMT number–letter switching condition). Thus, the previous finding of improvement in frontal functions after TLR [8], based on our data, remains somewhat unclear. Additionally, earlier findings of decline in motor speed after FLR [8] were not replicated in the present study. One explanation for this discrepancy may lie in the different applied test intervals. Helmstaedter and colleagues [8] tested patients three months after surgery when they may still have suffered from postoperative fatigue. Consequently, motor speed measures at that time might be biased by this effect, whereas surgery-related fatigue may recede by six months after the surgical procedure. In line with this supposition, an interesting study by Ljunggren and colleagues [22], who examined patients two years after surgery, also did not find a decline in motor speed after FLR. Inconsistencies between findings of other studies and ours might also be explained by differences in the applied neuropsychological tests, sample sizes, control groups, and methodological variance (e.g., matching of demographic variables).

4.4. Limitations and outlook

This study has some limitations. First, we did not include some clinical factor data, including seizure frequency, number of antiepileptic drugs, or presence of comorbid conditions. Hence, the impact of these variables on the pre- or postoperative cognitive status of our patient sample remains unclear. Second, we did not perform analyses for different subgroups of patients with FLE and TLE because there is no general agreement upon how subgroups should be categorized. Since our rationale was to identify cognitive markers of TLE vs. FLE, comparisons of anatomical subgroups were beyond the scope of this work. Third, since we were particularly interested in identifying 'frontal markers' in a verbal memory test, we mainly focused on pre- and postsurgical *verbal* memory performance. Thus, it might be difficult to compare the results to other studies performed in the field, which have also applied different measures of nonverbal memory. Finally, we cannot exclude the possibility that the relatively high proportion of missing data (especially for the DKEFS-TMT in the group with FLE) may have influenced our results in a systematic way. In a supplementary data analysis, we thus reperformed all main ANOVAs excluding all patients, which had at least one pre- or postoperative missing value in the DKEFS-TMT. Supporting the conclusion that these missing data did not strongly affect our results, we did not find differences between these reanalyses and our original analyses. A strength of the present study is that patient groups were matched based on demographic and clinical variables, including education, duration of epilepsy, and age at preoperative neuropsychological assessment. This design allowed us to control for confounding variables and interactions between cognitive performance and preoperative characteristics that were identified elsewhere [14]. The large sample size is another advantage with regard to statistical power. Further, we computed the level of clinically significant impairment and the percentages of reliable and meaningful change from pre- to postoperative assessment in order to identify patients that showed individual cognitive gains or losses after surgery. Indeed, differential results between individual and group analyses, as those that were described above, were also found elsewhere and underline the relevance of the idea that individual trajectories may sometimes not be clearly detected in group analyses [51,52].

Ongoing research aims to further disentangle the findings regarding the preoperative cognitive presentation of patients with FLE and TLE. In order to do so, future research should strive to find or develop markers of memory functions, which may be more specifically related to "frontal" or "temporal" aspects of verbal memory functions. Pertaining to this, we advise a more qualitative, theory-guided neuropsychological perspective in evaluating cognitive functioning in patients with epilepsy; future studies should include qualitative measures (e.g., sequence of word learning, description of type of errors) that may shed light on the distinct cognitive processes that may exist among patients of those two groups. Moreover, they should also include subjective measurements of cognitive ability status in order to shed light on the discrepancies that have been shown to exist between cognitive outcome as perceived by the patients and objective measurements [7,53]. It would be intriguing to examine to what extent deficits in social cognition or self-reflection, which are observed in FLE, might affect the subjective perception of memory performance.

5. Conclusion

The main finding of the present study is that the side and not the site of the epileptic focus appears to be most important in the evaluation of pre- and postoperative verbal memory performance in patients with TLE and FLE. This finding suggests that verbal memory functioning in patients with epilepsy might be affected by wide-ranging dysfunctional intrahemispheric temporofrontal networks in the language-dominant hemisphere. Measures of executive functioning may be valuable for the differentiation between TLE and FLE. With regard to the individual postoperative cognitive status of patients, our data suggest satisfactory clinical and cognitive outcomes in both patients with TLE and FLE, especially when resection did not affect the language-dominant hemisphere. Our results at both the group and individual levels further indicate that, despite considerable chances of becoming seizure-free after surgery, there is a substantial chance for patients to stabilize or even improve in certain cognitive functions. The findings from the current study, therefore, contribute to more nuanced knowledge that may help clinicians clarify the possible advantages and disadvantages of epilepsy surgery. Hence, the present results may be useful for the individual cost–benefit consideration that precedes a patient's decision about whether or not to undergo epilepsy surgery.

Declaration of competing interest

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