Pre- and Postoperative Verbal Memory and Executive Functioning in Frontal Lobe Epilepsy versus Temporal Lobe Epilepsy

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Abstract

Neuropsychological assessment has become an important tool in evaluating the preoperative cognitive status and the postoperative cognitive outcome after neurosurgery in patients with focal epilepsy. Even though earlier studies predominantly focused on cognitive functioning in patients with temporal lobe epilepsy (TLE), there is evidence for a great overlap in preoperatively affected cognitive functions between patients with TLE and patients with frontal lobe epilepsy (FLE). The current study aimed to investigate whether it is possible to differentiate between FLE and TLE patients prior to surgery based on different measures that assess verbal memory and executive functioning. Furthermore, since it has been proposed that the two groups develop differently after surgery, the postoperative cognitive development of patients was examined. Pre- and postoperative data of 303 patients with either FLE (n = 109) or TLE (n = 194) was retrospectively analyzed. Preoperative results indicate that the patient groups did not differ on measures of verbal memory functioning. In fact, measures of executive functioning may be more valuable in differentiating FLE from TLE patients. Postoperative findings revealed that there is no distinctive development between patients with FLE and TLE on the assessed cognitive functions. Results rather suggest that the lateralization, not the localization of epileptic activity may be the more important variable in evaluating preoperative presentation and postoperative outcome, at least for measures of verbal memory functioning. Results are discussed in the light of generalization concerns and heterogeneity issues pertaining to the patient groups that were included in this study. In conclusion, the present study adds to the knowledge base on the grounds of which patients may be advised for or against epilepsy surgery.

In the past decades, epilepsy surgery has become a standard treatment approach for patients with intractable focal epilepsy. Studies that focus on the effectiveness of epilepsy surgery typically concentrate on seizure outcome as their primary outcome measure. According to a recent Cochrane review that identified 177 studies reporting on seizure outcome after surgery, 65% of more than 16.000 patients with focal epilepsies became seizure free after the surgical procedure. (West et al., 2015; see also Ryvlin & Rheims, 2016). However, despite good chances of seizure freedom, lesser is known about the potential cognitive effects of epilepsy surgery. Importantly, clinicians should be enabled to thoroughly clarify the advantages and disadvantages of surgery not only on the basis of potential seizure control but also on the basis of possible cognitive consequences that may arise after the procedure.

When considering all types of focal epilepsy syndromes, it becomes evident that the focus of scientific attention has been primarily on cognitive functioning in patients with temporal lobe epilepsy (TLE) and after temporal lobe resection (TLR). It has been shown, for example, that patients suffering from TLE exhibit deficits in working memory, long-term memory, attention, visuo-spatial abilities, executive functioning, and intelligence (e.g., Helmstaedter & Kockelmann, 2006; Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; Patrikelis, Angelakis, & Gatzonis, 2009). After surgery, those patients may improve on tasks that are linked to fronal lobe functioning, (i.e., attention, executive functioning, psychomotor speed, motor coordination; Helmstaedter, Gleißner, Zentner, & Elger, 1998; Sherman et al., 2011). Hence, preoperative deficits in these cognitive domains may depend on the propagation of seizure activity through reciprocal connections between the frontal and temporal lobes. In contrast, cognitive functions in TLE patients that are more classically associated with temporal lobe functioning (e.g., memory, language) seem to either remain negatively affected or even deteriorate after surgery (Hamberger & Drake, 2006). Accordingly, the review by Sherman et al. (2011) suggests a decrease of verbal memory performance after left TLR in 44% of operated patients.

With regard to frontal lobe epilepsy (FLE), the second most common type of focal epilepsy, scientific evidence for its cognitive characteristics is more sparse. Existing studies indicate impairments in aspects of executive functioning in patients with FLE, as compared to healthy controls and patients with TLE. For instance, FLE patients show reduced performance in concept formation and shift, response inhibition, verbal and non-verbal fluency, anticipation and planning, and proverb interpretation (Helmstaedter, Kemper & Elger, 1996; McDonald, Delis, Kramer, Tecoma, & Iragui, 2008; McDonald et al., 2005; Patrikelis et al., 2009; Upton & Thompson, 1996). Moreover, FLE patients show impairments in working memory, speed, attention, and motor coordination (Helmstaedter et al., 1996; Patrikelis et al., 2016). Memory decline has also been reported in patients with FLE but generally to a lesser degree than in patients with TLE (Centeno, Thompson, Koepp, Helmstaedter, & Duncan, 2010; Centeno et al., 2012; Exner et al., 2002).

Even less literature can be found on the cognitive effects of frontal lobe resection (FLR) in patients with FLE and findings are predominantly inconclusive. Sarkis et al. (2012) found verbal fluency (as a measure of executive functioning) to be impaired after FLR, especially when resection took place in the language dominant hemisphere. In this study, however, verbal fluency was the only variable that was examined and no comparative groups were included. A study by Helmstaedter et al. (1998) found psychomotor speed, attention, and motor coordination to be more impaired and short-term memory to be improved three months after FLR, as compared to preoperative scores. In contrast to the study by Sarkis et al. (2012), however, Helmstaedter et al. (1998) did not find lateralization effects for left- versus right operated patients, even though this might be explained by the nature of cognitive tests that were applied. Interestingly, a recent study by Ljunggren, Andersson-Roswall, Rydenhag, Samuelsson, and Malmgren (2015) indicated cognitive stability of FLE patients on various measures of cognitive functioning two years after FLR, suggesting little effects of FLR at group level. In sum, studies of cognitive outcome after FLR are sparse and difficult to compare due to a great variety in test intervals, control groups, and neuropsychological methods.

Implicated by the diversity of and the extensive overlap between affected cognitive functions in TLE and FLE, there seem to be neither clear-cut guidelines for the differentiation between TLE and FLE prior to surgery nor definite evidence for the cognitive effects of FLR. Some studies identified specific subfunctions of executive functioning that may distinguish FLE from TLE preoperatively (e.g., McDonald et al., 2008). Such tests, however, are typically not included in standard test batteries at epilepsy centers and norms are rarely available or published (Vogt et al., 2017). Therefore, the present study aims to investigate whether it is possible to reliably distinguish between patients with FLE and TLE preoperatively, based on widely used neuropsychological tests that assess verbal memory and executive functioning. Furthermore, the postoperative development of FLE patients, as compared to TLE patients is examined.

We chose to use measures of verbal memory, since memory dysfunctions are frequently reported in both FLE and TLE patients. Until now, however, most clinical studies only provided one comprised memory score for patients; Individual scores on the different components of implemented tests are usually not examined or provided by the authors. Since the proportions by which the different components of such tests measure, for instance, working memory, short-term memory, or long-term memory, may vary (see Helmstaedter, Lendt, & Lux, 2001), it is likely that some components not only quantify processes associated with the temporal lobes (e.g., long-term memory), but also processes associated with the frontal lobes (e.g., retrieving words after an interference list, short-term recall of words, monitoring processes; Centeno et al., 2010, 2012). Therefore, FLE and TLE patients might show different profiles on memory tests and we do not need highly specific tests of executive functioning to differentiate between FLE and TLE patients. Furthermore, if we can identify different profiles of FLE and TLE patients on verbal memory tests, the dissimilar development between frontal functions after FLR and after TLR (see Helmstaedter et al., 1998) might also be identified. Another reason why we search for 'markers' of frontal lobe functioning in verbal memory tests, is that such tests are among the most frequently used neuropsychological tests in epilepsy centers (Vogt et al., 2017). Hence, clinicians are generally well trained in the assessment and, consequently, much larger sample sizes can be investigated than normally provided in clinical studies.

Based on the nature of the different components of verbal memory tests, we postulated three cognitive processes that might significantly rely on frontal lobe functioning and, therefore, might possess diagnostic value for the differentiation between FLE and TLE. Those processes are: short-term memory, susceptibility to interference, and tendency to perseverate. On the other hand, we identified two measures of verbal memory tests that might rely more on processes associated with temporal lobe functioning. Those processes are: long-term recall and long-term recognition. Neuroscientific studies have consistently shown the former three processes to be crucially dependent on the functionality of frontal lobe structures (for an overview, see Gazzaniga, Ivry, & Mangun, 2014) and the latter two processes to be significantly dependent on the functionality of temporal lobe structures (for an overview, see Gluck, Mercado, Myers, 2016).

Consequently, we hypothesized that patients with FLE, as compared to patients with TLE, are preoperatively more impaired on measures of verbal memory tests that assess short-term memory, susceptibility to interference, and tendency to perseverate. We further hypothesized that FLE patients, as compared to TLE patients, are preoperatively less impaired on measures of verbal long-term memory and recognition. Based on existing cognitive outcome studies in the field (e.g., Hamberger & Drake, 2006; Helmstaedter et al., 1998; Sherman et al., 2011), we also expected that TLE patients improve on the hypothesized measures of frontal lobe functioning (i.e., short-term memory, susceptibility to interference, and tendency to perseverate) and deteriorate on the hypothesized measures of temporal lobe functioning (i.e., long-term memory and recognition) after TLR. This effect should be reversed in patients with FLE after FLR. The expected deterioration in frontal functions after FLR and temporal functions after TLR is based on functional neuroanatomy assuming that the loss of focal cortical integrity (e.g., through surgical ablation of cortical tissue) will lead to localization-specific functional deficits. We additionally expected the above described effects to be most pronounced in patients with epileptic focus or surgery in the speech-dominant hemisphere, since our primary outcome measures assessed *verbal* memory performance (Sarkis et al., 2013).

In order to test the hypotheses, we retrospectively analyzed neuropsychological data of FLE and TLE patients, who were hospitalized in the Epilepsy Center Bethel (Bielefeld, Germany) during the time period between 2003 and 2018. Preoperative neuropsychological assessment was performed during the presurgical evaluation phase at the Epilepsy Monitoring Unit and postoperative assessment was carried out approximately six months after surgery took place. For the purpose of this study, we concentrated on test results from the Verbal Learning and Memory Test (Helmstaedter et al., 2001). As a control measure for our hypotheses, we also included data from the Delis-Kaplan Executive Function System Trail Making Test (Delis, Kaplan, & Kramer, 2001) in our analyses.

Method

Subjects

Subjects consisted of 303 patients with either FLE (n = 109; 61 male/48 female) or TLE (n = 194; 96 male/98 female) who all underwent extensive interictal and ictal preoperative video EEG-monitoring and individually tailored FLR or TLR at the Epilepsy Center Bethel in Bielefeld, Germany. Resection side and type of the surgical procedure were specified based on neuroradiological findings and scalp- or invasive EEG recordings. Patients underwent resection either in the speech-dominant (FLE: n = 48; TLE: n = 90) or non-speech-dominant (FLE: n = 61; TLE: n = 104) hemisphere as determined by fMRI. Patient groups were matched on education, duration of epilepsy, and age at preoperative neuropsychological assessment. Postoperatively, 55.1% of FLE patients and 72.6% of TLE patients were seizure free at the six-month follow-up. Seizure freedom was defined as sustained seizure freedom, with or without aura, since surgery (Engel 1A and 1B; Engel & Rasmussen, 1993). For further medical and demographic characteristics, see Table 1.

Table 1

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

Variables		**FLE patients**[a] (*n* = 109)	**TLE patients**[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 going to school		1 (1.1)	2 (1.0)
Site of surgery	Speech-Dominant (%)	44.0	46.4
Aetiology:	*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)
Non-lesional/ unspecified		2 (1.8)	22 (11.4)
Seizure Outcome	Seizure free (%)	55.1	72.6

Note. FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy; 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, lowgrade astrocytomas, angiocentric neuroepithelial tumors.

Procedure and Material

Neuropsychological assessment took place during the presurgical evaluation phase at the Epilepsy Monitoring Unit (EMU) of the Epilepsy Center Bethel in Bielefeld (preoperatively) and approximately six months after surgery was performed (postoperatively). Data was collected between 2003 and 2018 and was analyzed retrospectively. The goal of the presurgical evaluation phase is to localize the epileptogenic zone in order to define the focus for the potential surgical resection. Patients typically remained at the EMU for one week to establish a reliable diagnosis by means of long-term EEG measurements, video recordings, neuroimaging, and neuropsychological assessment. Six months after resection took place, patients returned to the EMU for the postoperative neuropsychological examination in which the individual cognitive development and outcome was monitored.

Usually, pre- and postoperative neuropsychological assessment involves several standardized cognitive tests that cover most cognitive functions. For the purpose of the present study, however, we only analyzed a fraction of the data that was collected during the above mentioned time period, since we were interested in the differentiation between frontal and temporal lobe functioning on the basis of specific components of a verbal memory test.

As our primary outcome measure, we examined test results from the Verbal Learning and Memory Test (VLMT; Helmstaedter et al., 2001), which is the German adaptation of the Rey Auditory Verbal Learning and Memory Test (Schmidt, 1996). The VLMT is widely used by epilepsy centers across Europe (Vogt et al., 2016). It is an episodic verbal memory test that requires learning 15 unrelated words over five trials with immediate recall, free recall after interference, free recall after 30 minutes delay, and cued long-delay recognition. The VLMT also specifies the type of errors subjects make. Based on the nature of the different components of this test, we postulated three variables that might significantly rely on frontal lobe functioning and, therefore, might possess diagnostic value (Helmstaedter et al., 2001; see also Centeno et al., 2010; Gazzaniga et al., 2014). Those variables are:

1. short-term memory (Trial 1: immediate free recall of the 15 words);
2. susceptibility to interference (Trial 5-6: number of correctly remembered words after trial 5 minus the number of correctly remembered words after an interference list);
3. tendency to perseverate (number of perseveration errors).

As a comparison, we identified two measures that might rely more on temporal lobe functioning (Gluck et al., 2016; Helmstaedter et al., 2001). Those variables are:

4. long-term memory (Trial 5-7: number of correctly remembered words after trial 5 minus the number of correctly remembered words after a 30 minutes delay);
5. long-term recognition (number of correctly recognized words after a 30 minutes delay minus the number of false positives).

In order to validate the extent to which the different components of the VLMT assess frontal lobe functioning, we also analyzed data from the Delis-Kaplan Executive Function System Trail Making Test (D-KEFS TMT; Delis et al., 2001) as a control measure. This test has been validated in regard to frontal lobe function and pathology (e.g., Ghawami, Sadeghi, Raghibi, & Rahimi-Movaghar, 2017; Yochim, Baldo Nelson, & Delis, 2007; see also Delis, Kramer, Kaplan, & Holdnack, 2004) and is based on the traditional two-part Trail Making

Test by Reitan (1992). 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;
2. motor speed.

Specifically, the number-letter switching condition, a visual-motor sequencing procedure, which is a measure of flexibility of thinking and response inhibition, crucially depends on the integrity of frontal lobe structures (e.g., Yochim et al., 2007). We included results on the motor speed condition as a comparison. Thus, in total, we analyzed test results from the five components of the VLMT plus the two conditions of the D-KEFS TMT as dependent variables in the present study.

Data analysis

Performance of patients on the seven outcome variables was transformed into standardized z-scores. Percentage of missing data and sample sizes on which analyses are based, are reported in Table 2. In order to examine preoperative differences on group level, multivariate analyses of variance were performed with Group (FLE, TLE) and Site of seizure focus (speech-dominant, non speech-dominant) as independent variables and performance on the five conditions of the VLMT and the two conditions of the D-KEFS TMT as dependent variables. In order to evaluate pre- to postoperative cognitive development of FLE and TLE patients on those dependent variables, repeated measures analyses of variance were computed using Group (FLE, TLE) and Site of surgery (speech-dominant, non speech-dominant) as between-subject factors and Time (pre, post) as a within-subject factor. For all analyses post hoc tests were adjusted for multiple comparisons with a Bonferroni correction ($\alpha = .05$).

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 falling below one standard deviation from the mean (i.e., $z \leq 1$). Significant pre- to postoperative changes of performance were calculated by use of change z-scores (post minus pre) and defined as scores exceeding one standard deviation from the mean in both directions (i.e., $z \leq 1$ and $z \geq 1$). Typically, analyses of significant individual change are based on reliable change indices (RCI; e.g., see Ljunggren et al., 2015). However, no RCIs are provided for the VLMT and earlier studies showed that results based on the above outlined procedure do not significantly differ from using RCIs with a confidence interval of 90% (Baxendale & Thompson, 2005). All analyses were performed by using IBM SPSS statistics (version 21).

Table 2

Pre- and postoperative sample sizes of TLE and FLE patients per test and condition

Variables	Preoperative		Postoperative	
	n **FLE**	***n*** **TLE**	***n*** **FLE**	***n*** **TLE**
VLMT:				
Trial 1	107	194	88	194
Trial 5-6	107	192	88	192
PE	107	185	84	191
Trial 5-7	107	194	87	189
Recog	102	189	85	184
% missing	1.57	2.83	20.73	2.11
D-KEFS TMT:				
NLS	85	158	72	161
MS	92	161	76	165
% missing	18.81	17.78	31.19	15.98

Note. VLMT = Verbal Learning and Memory Test; 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; FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy.

Results

Preoperative group differences

Means and standard deviations for all dependent variables and all groups at pre- and postoperative assessment are reported in Table 3. The MANOVA for preoperative comparisons on the five dependent variables of the VLMT yielded no significant interaction effect between Group and Site of seizure focus ($F(5,274) = 0.109$, $p = .990$) and no significant main effect of Group ($F(5,274) = 1.291$, $p = .268$). However, a significant main effect of Site of seizure focus was found ($F(5,274) = 2.571$, $p = .027$, eta^2 = .045). Post hoc tests indicated that patients with epileptic focus in the speech-dominant hemisphere performed significantly worse than patients with epileptic focus in the non speech-dominant hemisphere on Trial 5-6 ($F(1,278) = 4.031$, $p = .046$, eta^2 = .014) and on Trial 5-7 ($F(1,278) = 5.192$, $p = .023$, eta^2 = .018). No significant differences were found between those groups on the dependent variables Trial 1, perseveration errors, and recognition (p-values ≥ .079). Figure 1 illustrates preoperative differences between patients on all variables depending on the site of the epileptic focus.

The MANOVA for preoperative comparisons on the two dependent variables of the D-KEFS TMT revealed neither a main effect of Site of epileptic focus ($F(2,237) = 0.634$, $p = .531$), nor an interaction effect between Group and Site of epileptic focus ($F(2,237) = 2.690$, $p = .070$). However, a significant main effect of Group was found ($F(2,237) = 2.262$, $p = .042$; eta² = .023); As revealed by the post hoc analyses, FLE patients performed below TLE patients on the number-letter switching condition ($F(1,238) = 5.211$, $p = .047$, eta² = .017). No differences were found on the motor speed condition ($p = .147$).

Table 3

Averaged pre- and postoperative performance of the patient groups on all dependent variables

Variables	**FLE**		**TLE**		**Total**	
	speech-dominant	**non speech-dominant**	**speech-dominant**	**non speech-dominant**	**speech-dominant**	**non speech-dominant**
VLMT:						
Trial 1						
Pre	.131 (0.96)	-.140 (1.02)	-.139 (0.98)	-.289 (0.90)	-.046 (0.98)	-.233 (0.95)
Post	-.032 (0.98)	-.115 (1.11)	-.330 (1.02)	.030 (0.90)	-.238 (1.02)	-.017 (0.97)
Trial 5-6						
Pre	-.326 (1.05)	-.160 (0.85)	-.613 (0.94)	-.318 (0.88)	-.514 (0.98)	-.258 (0.87)
Post	-.012 (1.02)	-.296 (1.06)	-.676 (0.94)	-.190 (0.83)	-.471 (1.01)	-.224 (0.91)
PE						
Pre	-.568 (0.83)	-.506 (0.78)	-.619 (0.78)	-.547 (0.79)	-.602 (0.79)	-.532 (0.79)
Post	-.603 (0.74)	-.481 (0.71)	-.360 (0.73)	-.566 (0.75)	-.435 (0.74)	-.538 (0.73)
Trial 5-7						
Pre	-.389 (1.04)	-.166 (0.91)	-.657 (0.99)	-.317 (1.02)	-.565 (1.01)	-.260 (0.98)
Post	.060 (0.97)	-.294 (1.08)	-.784 (0.89)	-.245 (0.94)	-.525 (0.99)	-.261 (0.98)
Recog						
Pre	.065 (0.90)	.042 (0.99)	-.254 (0.99)	-.129 (0.95)	-.145 (0.97)	-.064 (0.97)
Post	.064 (0.93)	-.042 (1.07)	-.586 (1.07)	.014 (0.96)	-.386 (1.07)	-.004 (0.99)
D-KEFS TMT:						
NLS						
Pre	-.452 (1.12)	-.638 (1.26)	-.198 (1.20)	-.333 (1.21)	-.276 (1.17)	-.428 (1.23)
Post	-.524 (1.28)	-.629 (1.12)	.067 (1.03)	-.221 (1.19)	-.113 (1.14)	-.347 (1.18)
MS						
Pre	.474 (0.81)	.689 (0.47)	.537 (0.74)	.296 (1.05)	.515 (0.76)	.432 (0.91)
Post	.512 (0.56)	.602 (0.46)	.677 (0.63)	.525 (0.66)	.627 (0.61)	.549 (0.61)

Note. Means and standard deviations are given in standardized z-scores. Standard deviations appear in parentheses. VLMT = Verbal Learning and Memory Test; 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.

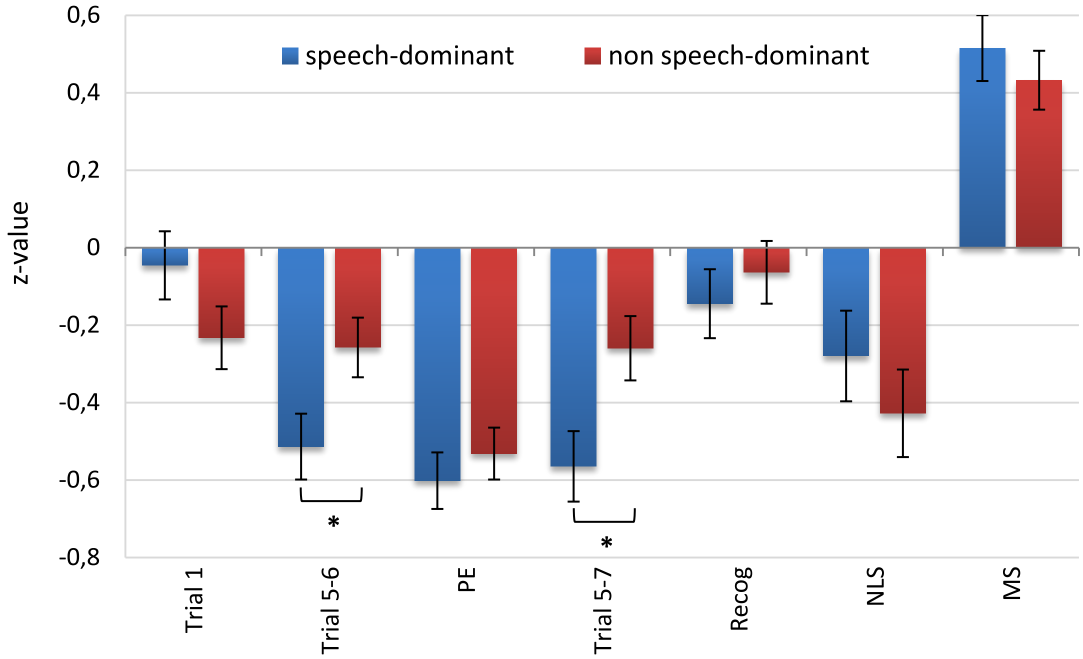

Figure 1. Preoperative differences on all outcome variables between patients with speech-dominant and non speech-dominant site of epileptic focus. Error bars represent standard errors. Dependent variables of the Verbal Learning and Memory Test are: Trial 1, Trial 5-6, perseverations errors (PE), Trial 5-7, recognition (Recog). Dependent variables of the Delis-Kaplan Executive Function System Trail Making Test are: number-letter switching (NLS), motor speed (MS).

* $p < .05$.

Pre- to postoperative group differences

There was no effect found between seizure free patients and patients with continuing seizures after surgery (F(7,172) = 1.162, p = .327). Consequently, means of all dependent variables converged and data of patients with and without continuing seizures were pooled for further analysis. The repeated measures MANOVA examining pre- to postoperative development of patient's performance on the five dependent variables of the VLMT revealed neither main effects of Group and Site of surgery, nor an interaction effect between those two variables (p = .071; p = .509; p = .183, respectively). Furthermore, the analysis yielded no main effect of Time, no interaction effect between Time and Group and no three-way interaction between Time, Group and Site of surgery (p = .481; p = .768; p = .051, respectively). However, an interaction effect between Time and Site of surgery was found (F(5,238) = 2.700, p = .021, eta^2 = .054). Post hoc analyses showed that the performance of patients undergoing surgery in their speech-dominant hemisphere deteriorated from pre- to postoperative assessment on Trial 1 (F(1,242) = 6.850, p = .009, eta^2 = .028) and on recognition (F(1,242) = 5.152, p = .024, eta^2 = .021), whereas the performance of patients undergoing surgery in their non speech-dominant hemisphere improved over time on those two variables (see Table 3; all other variables: $p \geq .268$). Figure 2 depicts pre- to postoperative performance on Trial 1 and in recognition memory depending on the site of the resection.

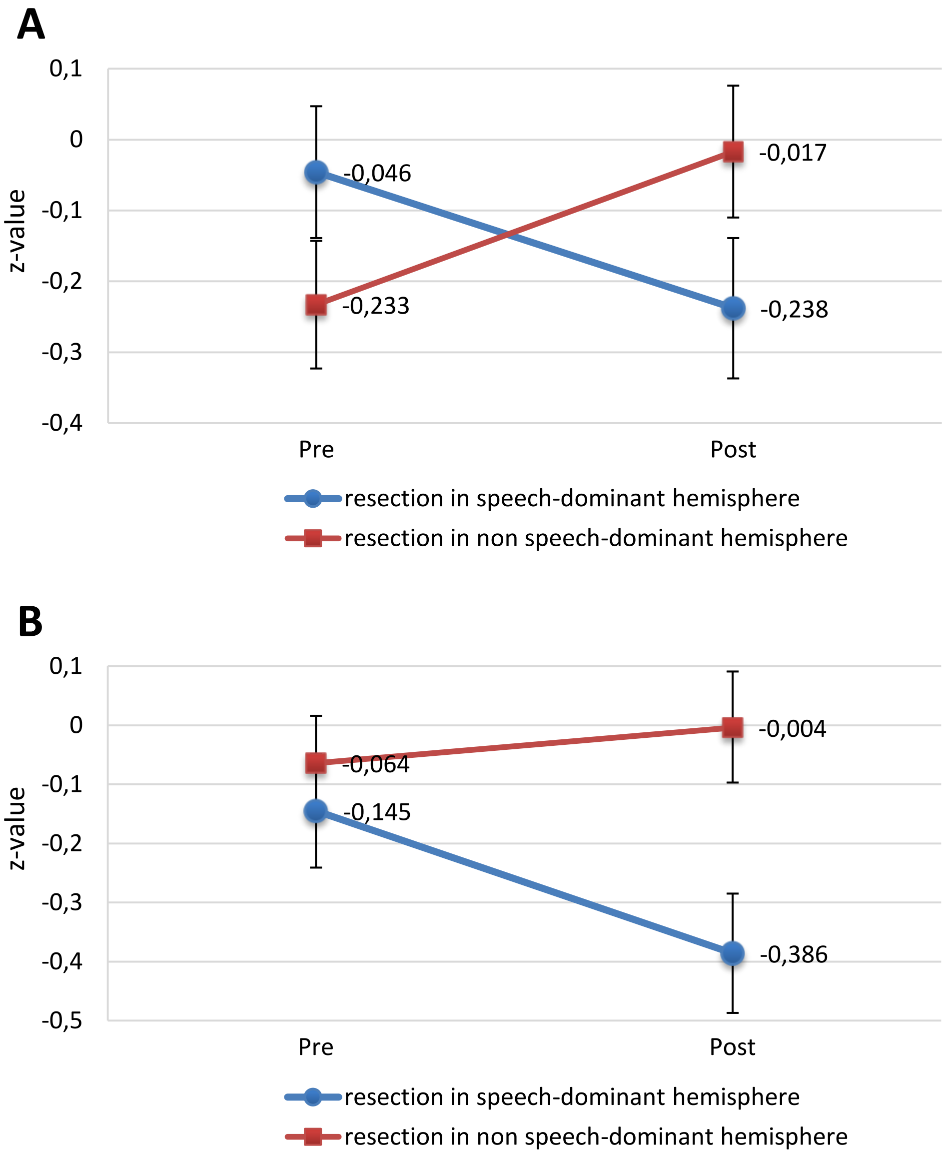

Figure 2. Pre- to postoperative performance on the Verbal Learning and Memory Test on Trial 1 (A) and in recognition memory (B) depending on the site of the resection. Error bars represent standard errors. Pre = preoperative assessment; Post = postoperative assessment.

The repeated measures MANOVA examining the pre- to postoperative development of patient's performance on the two dependent variables of the D-KEFS TMT yielded no main effect of Site of surgery and no interaction effect between Group and Site of surgery (p = .512; p = .061, respectively) but a significant main effect of Group (F(2,203) = 4.647, p = .011, eta² = .044). As illustrated in Figure 3, FLE patients performed worse on the number-letter switching condition of the D-KEFS TMT, both pre- and postoperatively (F(1,204) = 5.521, p = .020, eta² = .026). No significant differences were found between those groups on the motor speed condition (p = .790). Furthermore, no main effect of Time, no interaction effect between Time and Group, no interaction effect between Time and Site of surgery, and no three-way interaction between Time, Group, and Site of surgery was found for the D-KEFS TMT variables (all p-values ≥ .109).

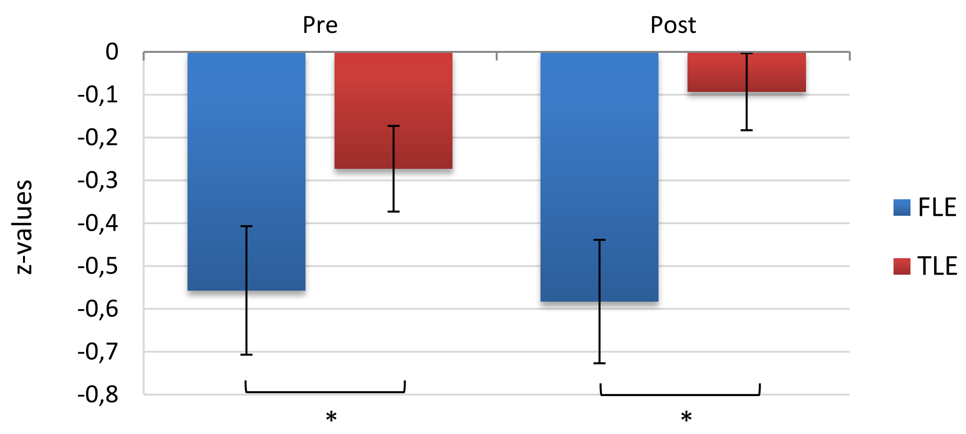

Figure 3. Pre- and postoperative group differences on the number-letter switching condition of the Delis-Kaplan Executive Function System Trail Making Test. Error bars represent standard errors. Pre = preoperative assessment; Post = postoperative assessment; FLE = frontal lobe epilepsy; TLE = temporal lobe epilepsy.
* p < .05.

Individual level analyses

Table 4 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 site of epilepsy focus/ surgery. Preoperatively, FLE patients with epileptic focus in their speech-dominant hemisphere and FLE patients with epileptic focus in their non speech-dominant hemisphere showed significant impairments on the 'frontal measures' of the VLMT (i.e., Trial 1; Trial 5-6; perseveration errors) in 10%, 25%, and 35% versus 19%, 14%, and 25%, respectively. Performance on those variables dropped significantly in 10-25% of

FLE patients who underwent surgery in their speech-dominant hemisphere and in 9-23% of FLE patients who underwent surgery in the non speech-dominant hemisphere. Furthermore, prior to surgery, FLE patients with epileptic focus in the speech-dominant hemisphere and FLE patients with epileptic focus in the non speech-dominant hemisphere showed significant impairments on the 'temporal measures' (i.e., Trial 5-7; recognition) in 25% and 20% versus 14% and 25%, respectively. After surgery, 8% and 17% of speech-dominantly operated FLE patients versus 21% and 15% of non speech-dominantly operated FLE patients significantly deteriorated on those variables.

On the other hand, TLE patients with epileptic focus in their speech-dominant hemisphere and TLE patients with epileptic focus in their non speech-dominant hemisphere showed significant preoperative impairments on the three 'frontal measures' of the VLMT in 20%, 40%, and 36% versus 20%, 25%, and 28%, respectively. Performance on those variables dropped significantly in 10-26% of speech-dominantly operated TLE patients and in 8-13% of non speech-dominantly operated TLE patients. Moreover, prior to surgery, TLE patients with speech-dominant epileptic focus and TLE patients with non speech-dominant epileptic focus showed significant impairments on the two 'temporal measures' in 33% and 26% versus 23% and 23%, respectively. After surgery, 22% and 23% of all speech-dominantly operated TLE patients versus 13% and 13% of all non speech-dominantly operated TLE patients significantly worsened on those variables.

When comparing FLE and TLE patients with epileptic focus in their speech-dominant hemisphere, it becomes clear that, on all variables of the VLMT, a slightly higher percentage of patients in the TLE group was impaired prior to surgery. In accordance with this finding, TLE patients who underwent surgery in their speech-dominant hemisphere showed slightly higher percentages of significant deterioration from pre- to postoperative assessment on all VLMT variables. Both of these findings are not observed when comparing FLE and TLE patients with epileptic focus in their non speech-dominant hemisphere. Furthermore, when comparing all TLE patients with all FLE patients on all dependent measures of the VLMT, preoperative percentages of impairment are consistently higher in the TLE group.

Finally, FLE patients and TLE patients showed preoperatively significant deficits on the number-letter switching condition and the motor speed condition of the D-KEFS TMT in 29% and 8% versus 27% and 9%, respectively. Performance on the two variables dropped significantly from pre- to postoperative assessment in 12% and 4% of FLE patients and in 10% and 5% of TLE patients. After surgery, 39% of FLE and 17% of TLE patients were significantly impaired on the number-letter switching condition.

Table 4

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

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

Note. Percentages of pre- (T1) and postoperative impairment (T2) are given per group and site 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 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.

Discussion

The differentiation between FLE and TLE patients based on neuropsychological profiles is challenging due to a great overlap in affected cognitive functions. Furthermore, while the cognitive outcome after temporal lobe surgery in TLE patients has been studied extensively, there is less evidence for the cognitive effects of frontal lobe resection in patients with FLE. The goal of the present study was to identify 'markers' of frontal lobe functioning in order to differentiate between FLE and TLE patients by means of examining test results from the Verbal Learning and Memory Test (VLMT) and the Delis-Kaplan Executive Function System Trail Making Test (D-KEFS TMT). Moreover, the current study aimed to investigate the pre- to postoperative cognitive development of patients with FLE compared to patients with TLE.

Preoperative group analyses indicated that FLE and TLE patients could not be differentiated based on the pattern of verbal memory performance. Preoperative individual analyses revealed that, when comparing the percentages of impairment between these patient groups, a consistently greater proportion of TLE patients was found to be impaired on all measures of verbal memory functioning. Therefore, we did not find evidence for our first hypothesis that measures of verbal short-term memory, susceptibility to interference, and tendency to perseverate, are sensitive to frontal lobe dysfunction in FLE patients; Our hypothesized 'frontal measures' of the VLMT do not reliably distinguish between FLE and TLE patients. As such, our results fit well into a body of literature stating that memory deficits are a well documented finding in both FLE and TLE patients (e.g., Centeno et al., 2010, 2012; Exner et al., 2002; Patrikelis et al., 2016).

There are several possible explanations for these findings. Firstly, it is possible that our 'frontal measures' of the VLMT simply lack the sensitivity to distinguish between FLE and TLE patients and rather assess comparable aspects to other variables of verbal memory functioning. Another explanation for the overlapping deficits that has been proposed elsewhere (Patrikelis et al., 2009; Sarkis et al., 2013) states that verbal memory deficits in FLE patients reflect word fluency rather than semantic memory deficits and that most verbal memory tests are not sensitive to differentiate between those two possibilities. However, it is unlikely that this interpretation accounts for our findings. If this would be the case, measures that are less dependent on word fluency (e.g., perseveration tendency or cued recognition memory), which were especially included in the present study, should have been relatively spared from impaired performance of FLE patients. Finally, the overlapping deficits in FLE and TLE may be explained by reciprocally interacting neural networks between frontal and temporal areas; Through seizure propagation from temporal to frontal areas (or vice versa), atypical cognitive symptoms may arise that do not necessarily reflect the focus of seizure onset. As a result, FLE patients might show a pattern of impairment that is normally associated with temporal lobe dysfunction. This might be due to interictal EEG abnormalities in areas not closely related to the zone of epileptogenesis. In line with this, a study by Lieb, Dasheiff, and Engel (1991) found evidence for the spread of temporal seizures to the ipsilateral frontal lobe. The latter explanation seems to provide the best account for our findings, since many studies found (verbal) memory deficits in both FLE and TLE patients. Conclusively, our findings so far suggest that different measures of verbal memory performance lack the sensitivity to discriminate and, therefore, are not of diagnostic value for the differentiation between FLE and TLE patients.

Concurrently with the study by Upton and Thompson (1996), results rather suggest that not the localization but the lateralization of the epileptic focus accounts for preoperative impairments in verbal memory functioning. This is partially in line with our last hypothesis. We found patients with seizure focus in their speech-dominant hemisphere preoperatively to be more impaired on verbal long-term memory and susceptibility to interference than patients with seizure focus in their non speech-dominant hemisphere. Lateralization effects of verbal long-term memory performance have been consistently reported for TLE patients (e.g., Giovagnoli & Avanzini, 1999; Helmstaedter, Gielen, & Witt, 2018; Helmstaedter & Kockelmann, 2006; Weintrob, Saling, Berkovic, Berlangieri, & Reutens, 2002; Patrikelis et al., 2009). Evidence for such effects in FLE patients is inconclusive (e.g., Helmstaedter et al., 1998; for a discussion, see Patrikelis et al., 2009). Our results seem to support the notion that preoperative lateralization effects of verbal memory exist in both TLE and FLE patients, although this effect may be smaller for the FLE group.

When examining the preoperative results further, we found that FLE patients did worse than TLE patients on the number-letter switching condition of the D-KEFS TMT. This finding matches the results of Upton and Thompson (1996) who stated that FLE patients, as compared to TLE patients, are impaired on a number of executive measures. However, it contradicts the results by Patrikelis et al. (2016) who did not find differences between the performance of FLE and TLE patients on the traditional two-part TMT. This discrepancy might be explained by the different scoring procedures between the two versions of the TMT, since performance on part two of the traditional TMT depends on the patient's motor speed in part one. This is not the case in the D-KEFS TMT and, therefore, our results on the number-letter switching condition might be less influenced by the patient's motor speed. Furthermore, we replicated the findings published by Patrikelis et al. (2016) and Helmstaedter et al. (1996), who claimed that FLE and TLE patients did not differ in motor speed. In sum, our data adds to the notion that measures of executive functioning (i.e., flexibility of thinking/ response inhibition) possess diagnostic value for the differentiation between patients with TLE and FLE.

When focusing on the results of pre- to postoperative cognitive development, it becomes clear that, similar to our preoperative findings, the lateralization, not the localization of epileptic activity may be the more important variable in evaluating post surgical verbal memory outcome. Our results suggest that patients who underwent surgery in their speech dominant hemisphere, as compared to patients who underwent surgery in their non-speech dominant hemisphere, deteriorated on verbal short-term memory and recognition memory. This matches earlier findings from studies also showing a decline in language functioning after surgery in the speech-dominant hemisphere for both FLE (Risse, 2013; Sarkis et al., 2013) and TLE patients (Hamberger & Drake, 2006; Sherman et al., 2011). Interestingly, we found 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 - a finding that has been reported occasionally (e.g., Alpherts, Vermeulen, Van Rijen, Lopes da Silva, & Van Veelen, 2006).

Furthermore, we did not find evidence for the hypothesis that TLE patients ameliorate on frontal measures after TLR, nor do our results suggest that FLE patients ameliorate on temporal measures after FLR. We did neither observe such an effect for the verbal memory measures, nor for the more classical frontal measures (i.e., the number-letter switching and motor speed condition of the D-KEFS TMT). TLE patients only slightly but not significantly improved from pre- to postoperative assessment on the D-KEFS TMT and FLE patients did not show any changes at all. Thus, the previous findings of improvement in 'frontal functions' after TLR (Helmstaedter et al., 1998) could not be replicated in our study. However, it should be noted that our data contained a high percentage of missing values for the postoperative assessment of the D-KEFS TMT. This was particularly the case for the FLE group. Unfortunately, we cannot trace back the cause for that missing data due to the retrospective design of our study. It may be that patients discontinued testing autonomously or that the assessment was discontinued by the clinician due to poor performance on previous tests. Consequently, one might speculate that the missing data represents test results of patients, who would have performed worse than the average in the FLE group. As a result, the effect of improvement in frontal functions after TLR might be dispersed by that.

Analogically, earlier findings of decline in motor speed after FLR (Helmstaedter et al., 1998) could not be replicated in the present study. One explanation for this discrepancy may be the difference in test intervals between pre- and postoperative assessment in that study and ours. Helmstaedter and colleagues (1998) tested patients three months after surgery when patients might still have suffered from the immediate consequences of surgery, for instance from postoperative fatigue. Consequently, measures of motor speed three months after surgery might be biased by this effect, whereas surgery-related fatigue may be resolved six months after the surgical procedure. In line with this, Ljunggren et al. (2015), who examined patients two years after surgery, also failed to replicate the finding of motor speed decline after FLR. It should be noted that it is generally difficult to compare the outcomes from previous studies with those from the present study because of the great variety in applied neuropsychological tests and methods, test intervals, analyzed subgroups, and included control groups.

Results from our group analyses revealed a decline in some aspects of verbal memory, especially when resection took place in the language-dominant hemisphere. However, individual analyses indicated that there is also a considerable chance of individual and clinically significant improvement after surgery. This was particularly the case for FLE patients and non speech-dominantly operated TLE patients. Results showed, for instance, that almost two thirds of all non speech-dominantly operated TLE patients significantly improved from pre- to postoperative assessment on verbal short-term and long-term memory. However, even in the speech-dominantly operated TLE group, there was a substantial amount of patients that showed significant verbal memory gains after surgery. This trend has been observed earlier, but generally to a lesser degree (Sherman et al., 2011). Moreover, when considering the whole TLE group, we found that, on all verbal memory variables except for recognition, more patients improved than deteriorated after surgery. Interestingly, results generally indicated higher percentages of meaningful improvement in aspects of verbal memory functioning (VLMT) than in executive functioning (D-KEFS TMT). Furthermore, our results indicate verbal memory stability after surgery in about 54-81% of FLE and 58-75% of TLE patients. In sum, these findings imply that, for most patients, surgery might not lead to clinically significant losses of verbal memory functioning.

A strength of the present study is that patient groups were matched based on demographical and clinical variables, such as education, duration of epilepsy, and age at preoperative neuropsychological assessment. By means of this, we controlled for confounds and interactions between cognitive performance and preoperative characteristics of patients that have been identified in previous studies (e.g., Patrikelis et al., 2016). The large sample size of this study is another advantage. Furthermore, 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.

This study also has some limitations. First of all, due to an incomplete set of data pertaining to the precise epileptogenic zone or resection side, we did not perform analyses for different subgroups of FLE and TLE patients. Consequently, our patient samples were quite heterogeneous in terms of affected anatomical regions. Since earlier studies suggested that preoperative differences in memory and differences in postoperative cognitive development in FLE patients might be caused by the specific location of the epileptic focus and the precise resection side (Centeno et al., 2010; Helmstaedter et al., 1998; Ljunggren et al., 2015), one might argue that this could explain why some of the expected effects were not found. However, it should also be noted that there is no general agreement upon which bases such subgroups should be categorized. As a result, studies that include subgroup analyses will always be challenging to compare. Secondly, we did not include data of clinical factors, such as seizure frequency, number of anti-epileptic drugs, or presence of comorbid conditions. Hence, we could not examine whether such variables influenced the pre- or postoperative cognitive status. Thirdly, as our particular interest in the current study was to identify 'frontal markers' in a verbal memory test, our study mainly focused on pre- and post-surgical *verbal* memory performance. Thus, it might be difficult to compare its results to other studies performed in the field.

It is the topic of ongoing research to further disentangle the findings regarding the preoperative cognitive presentation of FLE patients, as compared to TLE patients. In order to do so and in order to reduce heterogeneity in examined patient groups, future research should strive to develop common anatomical subgroup classifications on the basis of which patients can be categorized. As a consequence, the controversial results pertaining to the differential development between FLE and TLE patients may be unraveled. Using common anatomical subgroup classifications may also help to pinpoint the question of lateralization effects in FLE. Moreover, future studies should 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 (e.g., Sawrie et al., 1999; for an overview, see Sherman et al., 2011).

The main finding of the present study that not the side but rather the site of the epileptic focus seems most important in preoperative cognitive presentation and postoperative cognitive development, matches earlier reports (Upton & Thompson, 1996; Patrikelis et al., 2009; Sherman et al., 2011). Consequently, we did not find evidence for the diagnostic value of verbal memory measures in differentiating FLE from TLE patients. Measures of executive functioning may be more valuable in this diagnostic process. With regard to the postoperative cognitive status of patients, our data suggest satisfactory clinical and cognitive outcomes in both TLE and FLE patients, especially when resection did not affect the speech-dominant hemisphere. Our results, both at group and individual level 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, on the grounds of which clinicians are able to 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.

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