Very long-term outcome in resected and non-resected patients with temporal lobe epilepsy with medial temporal lobe sclerosis: A multiple case-study

P. Grewe[a,*], R. Schulz[a], F.G. Woermann[a], C. Brandt[a], A. Doll[a,b], M. Hoppe[a],
M. Tomka-Hoffmeister[a], C.G. Bien[a,c]

[a] *Bethel Epilepsy Center, Bielefeld, Germany*
[b] *Department of Psychology, Bielefeld University, Bielefeld, Germany*
[c] *Laboratory Krone, Bad Salzuflen, Germany*

ARTICLE INFO

ABSTRACT

Purpose: To investigate the very long-term (i.e., ≥ 15 years) seizure, cognitive and psycho-social outcomes in resected patients (RP) with TLE compared to control patients not having undergone epilepsy surgery.

Methods: We applied a multiple case-study design including three non-resected patients (NRP) who were compared to a group of six RP. The latter were matched to the NRP according to clinical-demographic data. Outcome measures were various seizure, cognitive, and psycho-social variables.

Results: Patients were 56–72 years old. Seizure and AED outcome was more favourable among RP. RP reported better self-perceived overall health but higher subjective memory complaints. Upon formal neuropsychological testing, RP presented with lower verbal memory scores. Very long-term memory decline was evident in left-sided RP with good baseline memory scores, while RP with lower baseline performance, right-sided RP and NRP remained stable. Seizure-freedom had remarkable effects on the relationship between objective and subjective outcome: seizure-free patients, in general, subjectively reported the best psychosocial and cognitive outcome – irrespective of neuropsychological test results.

Conclusion: Our study suggests positive effects of TLE surgery in the very long-term course of ≥ 15 years postoperatively. Long-term seizure-freedom appears to have the strongest impact on patients' subjectively perceived psycho-social and cognitive outcome and may even outweigh actual memory disturbances and/or decline. Overall, our data do not support the assumption of a generally accelerated cognitive decline in patients with TLE.

1. Introduction

Epilepsy surgery is the most effective treatment option for refractory temporal lobe epilepsy (TLE) with a "good outcome" (i.e., usually seizure-free for at least one year, auras not considered) for about 65% of patients in epilepsy surgery in general [1]. Patients' decisions in favor of or against surgery are based on a complex trade-off between the chances of seizure-freedom and patients' subjective expectations [2], on the one hand, and the risks of postoperative cognitive decline [3,4] and further neurological and surgical complications [5], on the other hand. Ideally, this decision is supported by information about the long-term postoperative prognosis of seizure, cognitive, psychiatric, and psycho-social outcome.

So far, only a limited number of studies report seizure and cognitive outcome at long-term intervals, i.e., > 5 years postoperatively [6]. In spite of recent publications on the very long-term psychosocial [7] and cognitive [8] outcome after epilepsy surgery, the comprehensive very long-term (i.e., ≥ 15 years) assessment including cognitive, seizure, and subjective (i.e., psychosocial and mood) variables after TLE surgery has been broadly neglected in the literature so far. There are two potential hypotheses: Ongoing seizures may trigger an accelerated cognitive decline in the course of a chronic epilepsy, whereas seizure-freedom (or longer seizure-free intervals) may protect from this [9–11]. This concept is empirically supported by studies demonstrating a long-term memory decline for unoperated patients with TLE [12,13].

The alternative (or complementary) idea is that anterior temporal lobe resections (aTLR, but not selective amygdalohippocampectomies) may accelerate memory loss [14] because a reduced postoperative

---

cognitive performance might offer less cognitive reserve against aging-related decline. Recent results corroborated this argument showing that – at least in patients with tau pathology operated on at age 50 and beyond – aTLR led to accelerated cognitive decline twelve months postoperatively [15].

The key challenge is, however, to counsel patients who are evaluated for aTLR around the age of 30 years – the typical population in adult presurgical cohorts [6]. This also holds for the aforementioned studies [8,12,13,16] in which the patients' average age at long-term examination was mostly below the age of 40 years. As physiological cognitive decline will usually not be observed before the fifth decade of life, follow-up intervals of at least 15 years should be considered to examine a potential accelerated cognitive decline in TLE.

The aim of the current study was to examine the course of operated and non-operated patients with TLE who attended to our centre at least 15 years ago. We sought to compare the very long-term seizure, cognitive, and psycho-social outcomes in patients after aTLR compared to non-resected patients with TLE. Facing the fact that prospective randomized trials considering very long-term outcome will presumably not be available in the near future due to recall difficulties [8], we had the chance to evaluate very long-term outcome in a case series of older patients with TLE. This offered the opportunity to comprehensively examine individual long-term outcome and trajectories.

2. Methods

2.1. Patient recruitment

Two groups who had undergone presurgical evaluation at the Bethel epilepsy center [17,18] were included in this study: non-resected patients (NRP) with TLE and matched resected patients (RP) who had undergone aTLR. Data were obtained from the Bethel presurgical/surgical epilepsy database. This database is continuously maintained and updated with the most recent data on presurgical, surgical, and post-surgical data of the patients from the epilepsy surgery program by P.G.

First, we identified the NRP because we expected this to be the smaller and more difficult to recruit group (Fig. 1). We initially examined 4/32 NRP. One of these four patients was excluded post-hoc as recent MRI showed bilateral medial temporal lobe sclerosis (MTS), which confirmed a presurgical suspicion about a bilateral TLE. The final number of NRP included in our study hence was 3/32. A detailed study of the original records for the NRP revealed the following reasons against epilepsy surgery: ID1 opted against an offered left aTLR, probably because the seizure situation improved after presurgical assessment; ID2 was rejected by the team because of uncertainty about the left-sided MTS (although confirmed by retrospective and recent MRI) and because of better Wada memory performance of the epileptogenic side ("failed the Wada" – today's view on both issues wouldn't have excluded her from surgery); ID3 was rejected because he "failed the Wada" (today, the Wada wouldn't have been performed and the patient would have been offered surgery).

RP were matched to the NRP (Supplementary File 1). This resulted in twelve potential patients who had undergone standard aTLR with the histological diagnosis of a MTS. Six patients had to be excluded due to the following reasons: patient deceased ($n = 2$), no current address/telephone number/no response in spite of repeated request ($n = 2$), and participation rejected by patient due to current illness other than epilepsy ($n = 2$). The final number of participants from the resected TLE group was $n = 6$.

Patients of both groups were invited to participate in a comprehensive assessment at the Bethel Epilepsy Center, which lasted one or two days depending on the patient's condition. This included a medical examination and history-taking by senior epileptologists, 3T brain MRI, and a neuropsychological examination.

2.2. Neuropsychological testing

As a German adaptation of the Rey auditory verbal learning test, the "Verbaler Lern- und Merkfähigkeitstest" (VLMT [19]) is a "classical" word-list learning test consisting of five trials of memorizing 15 orally
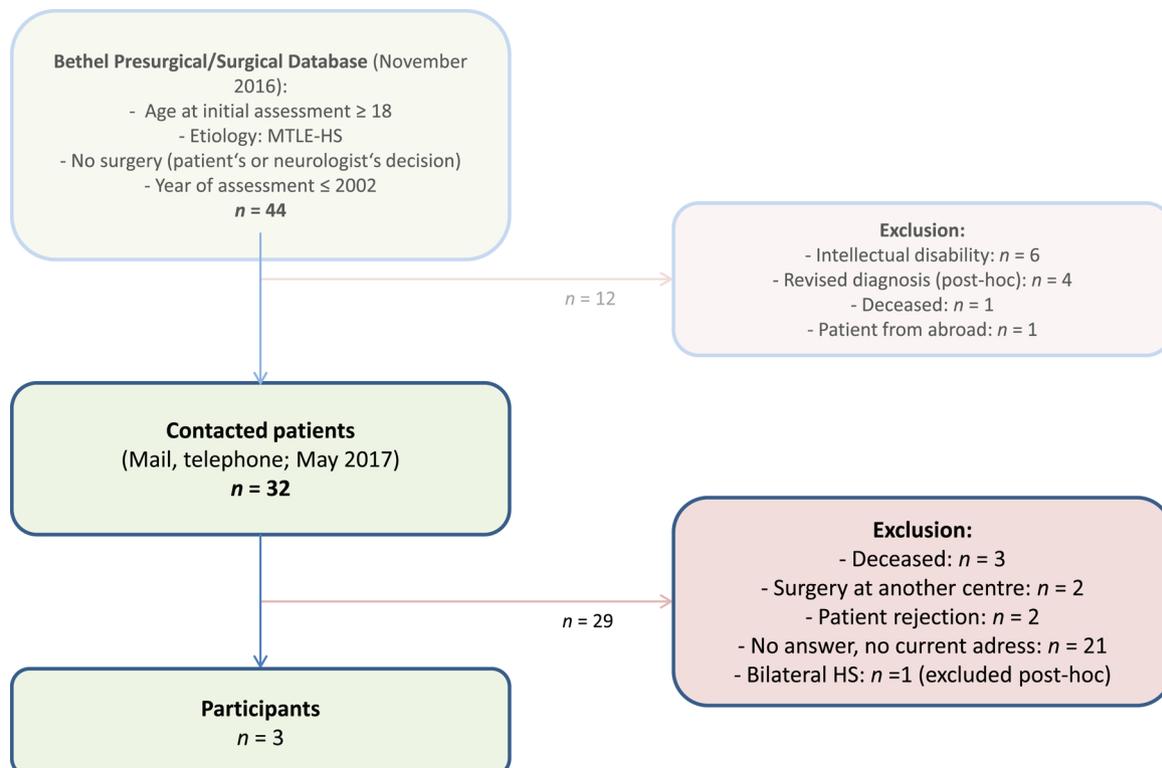

Fig. 1. Recruitment process of the non-resected patient group. MTLE-HS, medial temporal lobe epilepsy with hippocampal sclerosis.

presented words, freely recalling and, finally, recognizing this word list. We considered measures of cumulative learning (i.e., sum of trial 1–5), free delayed recall (i.e., trial 7), forgetting (i.e., trial 5 minus trial 7), and corrected recognition (i.e., hits minus false alarms).

The subtest "Logical Memory" from the Wechsler Memory Scale – revised [20] was taken as a measure of memory for logically connected verbal content. Patients have to reproduce from memory the content of two orally presented prose passages both immediately after presentation (i.e., immediate recall) and after 20–30 min (i.e., delayed recall).

The "Diagnosticum für Cerebralschädigung II" (DCS-II) consists of five consecutive trials of memorizing nine abstract design patterns (i.e., line drawings) which have to be reproduced from memory with wooden sticks. We used the cumulative learning score (i.e., sum of correctly reproduced designs from trial 1 to 5) as a measure of figural learning.

The subtest "number sequencing" of the Trail-Making-Test [21] was taken as a measure of processing and perceptual speed. The subtest "number-letting-switching" [21], which requires the patient to connect numbers and letters in an alternating fashion was taken as a measure of cognitive flexibility.

The "Mehrfachwahl-Wortschatz-Intelligenztest" (MWTB [22]) is a German adaptation of the "National Adult Reading Test" and was applied as a measure of premorbid intelligence. The "Mini Mental State Examination" (MMSE) was employed as a measure of general cognitive impairment and as a screening test for dementia with a cutoff of < 26 [23].

The "Fragebogen zur geistigen Leistungsfähigkeit" (FLei [24]) is a self-report measure of patient's perceived cognitive impairment in everyday situations. We considered the three functional subscales "memory", "executive functions", "attention" and the total score of these subscales.

2.3. Psychosocial assessment

We applied the "Quality of life in Epilepsy-31" (QOLIE-31 [25,26]) to assess self-reported quality of life (QoL) by eight subscales (overall QoL, seizure worry, emotional well-being, energy/fatigue, cognition, medication effects, overall health, and social function) and one total score. Scores may range from 0–100 with higher values indicating better QoL.

"Beck's Depression Inventory II" (BDI-II [27]) reflects the self-reported degree of current depressive symptoms (scores ≥13 indicating increased depressive mood). We also employed an exploratory questionnaire on psycho-social variables such as driver's license, or occupational status.

2.4. Presurgical assessment

To evaluate individual patients' cognitive long-term trajectories, we compared preoperative with long-term verbal memory scores for the "logical memory" (see above). In addition, long-term scores of the VLMT were compared with presurgical scores of the California Verbal Learning Task (CVLT [28]) as VLMT scores were not available from the presurgical dataset. The CVLT is a word-list learning paradigm comparable to the VLMT. However, the word list consists of 16 instead of 15 words and words can be clustered according to four semantic categories. For reasons of comparability, we used current test norms [20,28] for conversion of both presurgical and long-term raw scores into age-corrected standardized scores.

2.5. Statistical analyses

Due to the small sample size, we did not perform inferential statistics for between-group comparisons but discussed results on a descriptive level. Raw scores of the neuropsychological tests were transformed into standardized scores according to the normative scores given in the respective test manuals. Neuropsychological impairment

was defined as z-scores < -1.5 (i.e., < 1.5 SD below the mean) based on the respective normative scores.

2.6. Ethics and patient consent

The study was approved by the local ethics committee (Münster, Germany; 2016-048-f-S). All patients gave written informed consent for participation and received an allowance of 100€ for participation.

3. Results and discussion

A key experience of our study was that it is extremely difficult to recruit patients from a presurgical cohort studied approximately 20 years ago, especially if they were not operated on. Based on the decreasing number of patients with MTS [18,29,30], future studies will presumably not offer large-scale prospective data of RP and NRP with MTS focussing on an age range of approximately 60 years. This underlines our study's relevance – particularly for the NRP. Our proportion of included NRP (10%) is similar to that of a comparable recent questionnaire study without need for the patients to travel to the epilepsy center (21% [7]). Of note, our follow-up period was longer (16–21 years as compared to 9–17 years [5]). This may increase the probability that patients' addresses could not be identified or that patients may have deceased. Of note, among the patients with available data, 4/23 NRP and 2/10 of the RP had died which confirms previous observations of an increased mortality among patients with epilepsy [31,32].

3.1. Clinical-demographical variables

Clinical-demographical data are given in Table 1. All patients were in between 56 and 73 years (median 58) and had comparable follow-up times after initial presurgical evaluation (17 years, range 16–21). Recent MRI studies confirmed the original diagnoses of MTS for the NRP and the extent of surgery in the RP.

3.2. Seizure and AED outcome

A more favourable very long-term seizure outcome was observed among the RP (Engel class I: RP: 5/6 vs. NRP: 1/3) with 3/6 of the RP but none of the NRP reaching complete seizure-freedom (i.e., Engel IA). In addition, RP clearly had longer seizure-free periods and a longer time since the last seizure. Moreover, the number of AEDs (polytherapy/ monotherapy/off AEDs: resected, 2/2/2 and non-resected, 3/0/0) and the AED drug load was lower for the RP (median defined daily doses: resected: .3, non-resected: 2.3).

Seizure-freedom rates in this small cohort are comparable to the long-term outcome rates from other larger epilepsy surgery series [33]. Our marginally higher numbers may result from the highly selective sample with MTS and our strict exclusion criteria. Moreover, methodological issues (personal interviews with experienced epileptologists in our study vs. mailed questionnaires in earlier studies) may explain diverging outcome rates. Notwithstanding, the high rates of seizure-freedom clearly argue in favour of the efficacy of aTLR as a treatment for medial TLE – even in the very long-term course.

3.3. Quality of life, subjective memory and depression

As a key finding, we observed higher rates of cognitive complaints among the RP in both the QOLIE-32 and the FLei (Fig. 2A,B; Table 2). In detail, the highest rates of cognitive complaints were found in RP for the memory subscale of the FLei, while the remaining two scales (i.e., executive functions, attention) did not substantially differ between groups. In addition, RP reported a better overall health in the QOLIE-32. Besides these differences, comparable scores of the QOLIE were found for the remaining subscales across both patient groups (Fig. 2A;

Table 1
Clinical-demographical data of the resected and the NRP.

	Non-surgical			Surgical					
Patient ID	1	2	3	4	5	6	7	8	9
Age at long-term Follow-up	58.1	73.3	57.5	56.5	63.5	57.3	60.6	72.6	57.7
Md		58.1					59.1		
Age at epilepsy onset	2	34	20	12	19	1	13	31	1
Md		20					12.5		
Follow-Up (Years)	16.8	21.6	17.3	19.3	21.3	15.9	16.8	19.8	16.2
Md		17.3					18.0		
Age at initial presurgical assessment	41.3	51.8	40.4	37.2	42.2	41.3	43.8	52.8	41.5
Md		41.3					41.8		
Gender	f	f	m	m	m	f	m	f	f
Handedness	right	right	right	right	right	right	right	right	right
Lateralisation of epilepsy focus	left	left	left	right	left	left	right	left	left
Seizure outcome (Engel class)	IIC	IIIA	IC	IIB	IC	IB	IA	IA	IA
Time since last seizure (Months)	0	1	72	15	0	0	203	227	187
longest seizure-free period (Years)	2	.5	6	13	13	4	17	19	15.5
Current number of AEDs	3	2	2	1	2	2	1	0	0
		2					1		
Defined Daily Doses (AEDs)	3.1	2.3	1.7	.3	3.3	1.4	.3	.0	.0
Md		2.3					.3		

Md, median; Handedness: assessed with the Modified Edinburgh Handedness Inventory (Salmaso, D. and Longoni, A.M. Problems in the assessment of hand reference. *Cortex* 1985; 21: 533-549.); defined daily doses correspond to the doses defined by the World Health Organization. AED, antiepileptic drug.

Table 2). A recent study by Edelvik et al. [7] reported higher scores for several facets of QoL in resected patients 14 years after epilepsy surgery. This could not be replicated for all patients in our case-study. Inspecting our individual patient's data revealed that in general, higher QoL-scores for the RP as compared to the NRP were found for the subgroup of the seizure-free patients (ID 7,8,9). In contrast, non-seizure-free RP (ID 4,5,6) had comparable or even lower QoL-scores than the NRP. Comparable moderating effects of seizure-freedom on QoL were evident for patients' levels of depression, which were lowest among the seizure-free RP (Fig. 2C). Likewise, cognitive complaints in the FLei (and the QOLIE-32) were particularly low for the seizure-free RP (ID 7,8,9) who also demonstrated the lowest scores in almost all remaining subscales of the QOLIE-32. Conflicting results between our and Edelvik et al.'s study may emerge from methodological differences. While Edelvik et al. included different epilepsy syndromes, we focussed solely on older patients with unilateral MTS. Also, instead of using the SF-36, we applied the QOLIE-32 and the BDI-II to assess patient's QoL and mood. The SF-36 does not contain items on cognitive functions, is a non-epilepsy-specific questionnaire (as compared to the QOLIE-32), and assesses depressive symptoms in a different manner (as compared to the BDI-II). These differences may restrict a direct comparison between both studies and might explain the seemingly diverging results.

In sum, RP in general presented with a better overall health, but complained more frequently about cognitive-mnemonic disturbances. Seizure-freedom had a critical moderating impact on the subjective very long-term psychosocial outcome seeing that outcome was best among seizure-free RP, while subjective outcome of non-seizure-free RP was as low as – or even lower than – the NRP's.

3.4. Neuropsychological variables

According to the higher rates of memory complaints among the RP, objective memory scores were more frequently diminished in this group (Table 2). Particularly, measures of verbal memory consolidation (i.e., forgetting rate) were impaired in 3/6 of the RP, but only 1/3 of NRP (Fig. 2D). In the remaining variables, there were no marked differences between both groups with neither substantial median group-differences nor – on an individual level – diverging frequencies of scores below the clinical cut-off. RP and NRP, thus, presented with comparable levels of objective cognitive scores in the very long-term course, except for a difference in verbal memory (consolidation) measures. On an individual level, lowest verbal memory performances were observed in RP after left-sided surgery (ID 5,6,8,9; Figs. 2D and 3 lower panel); right-sided RP (ID 4,7), on the other hand, achieved average verbal memory scores. From a clinical perspective, this confirms the validity of measures of verbal memory consolidation as a measure of (left-sided) medial temporal functioning [34]. Remarkably, the differences in memory scores did not fully explain the subjective memory complaints and psychosocial outcome among the RP, as 3/6 RP (ID 7,8,9) presented with memory complaints and QoL comparable to the NRP (Fig. 2A,B) in spite of the lower "objective" memory scores (Fig. 2D). Thoroughly inspecting patients' individual profiles, we found that the discordances between subjective perception and objective test scores could be explained by moderating effects of seizure-freedom. Splitting the RP into seizure-free and non-seizure-free patients revealed remarkable differences. Particularly, the aforementioned RP with good subjective outcome in spite of lowered "objective" verbal memory scores (ID 7,8,9) were exactly those who achieved complete seizure-freedom. In line with this explanation, all of the remaining RP (ID 4,5,6), who had the lowest subjective outcomes in memory, depression, and most facets of QoL, in fact were not seizure-free. It may thus be assumed that the positive effects of long-term seizure-freedom may compensate for actual objective memory disturbances. Therefore, our single case-based observations offer a potential explanation for the discordance between postoperative memory scores and subjective memory complaints which has already been reported by Baxendale et al. [4]. Notably, in spite of diminished scores in single cognitive functions none of the patients in our study fell under the cut-off indicative of dementia in the MMSE. This is in line with the conclusion of a current study that TLE patients are not at an elevated risk for accelerated cognitive decline [8,see discussion below].

3.5. Cognitive long-term trajectories

Marked deteriorations over time on several measures of verbal memory (i.e., learning and free recall of both word lists and prose passages) were seen in two left-sided RP with postoperative seizure-freedom (ID 8,9, Fig. 3). In the remaining cases, memory was relatively stable with only slight deteriorations and some improvements without showing a consistent pattern over patients and memory parameters. In accordance with the intact very long-term verbal memory scores among the two right-sided RP (ID 4,7), no marked deteriorations in verbal
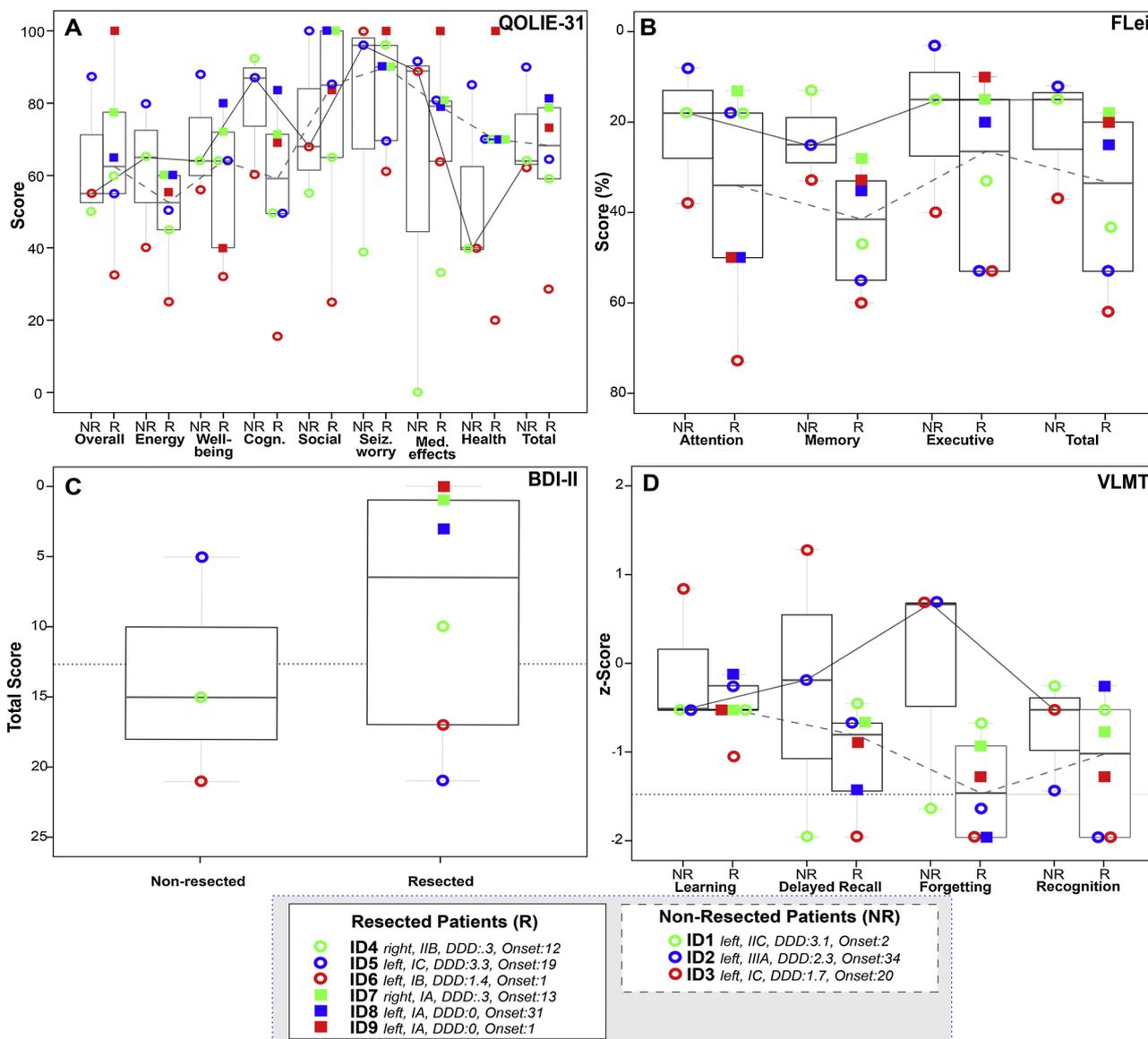
Fig. 2. Median very long-term cognitive and psycho-social outcome in resected (R, dashed lines) and non-resected patients (NR, solid lines). Circles and squares indicate individual patient's test scores. Filled squares represent seizure-free patients, open circles represent non-seizure-free patients. Green data points represent right sided patients; dashed horizontal lines indicate cut-offs for below average scores. In part B and C, higher scores represent higher levels of depression and higher levels of subjective cognitive complaints, respectively; for reasons of comparability, the y-axes in these parts of the Figure have been inverted. Scores of the FLei in part B are given as % of the maximum score of the respective scale for reasons of comparability. DDD, defined daily dose of AEDs taken at long-term follow-up; Onset, age at seizure onset in years; QOLIE-31, quality of Life in Epilepsy (31-item version); Cogn., cognition; Seiz. Worry, seizure worry; Med. effects, medication effects; FLei, Fragebogen zur Geistigen Leistungsfähigkeit (Questionnaire for Complaints of Cognitive Performance); BDI-II, Becks Depression Inventory II; VLMT, Verbaler Lern- und Merkfähigkeitstest (German Version of the Auditory Verbal Learning Test).

memory were observed for these two patients as could be expected. Interestingly, the two cases with the consistent memory deteriorations (ID 8,9) did not strongly complain about cognitive disturbances, and reported relatively high QoL and low levels of depression. Again, as argued above, long-term seizure-freedom may have moderated the individual patient's subjective experience by "covering" an actual memory decline up. We assume that the positive effects of long-term seizure-freedom might have compensated for declined memory – presumably because of positive effects of postoperatively withdrawn AEDs. In fact, both of the aforementioned RP (ID 8,9) were off AEDs and, accordingly, reported the best scores among the RP in the Subscale "Medication Effects" of the QOLIE-32 (Fig. 2A). This suggests that postoperative omission of AEDs may positively affect QoL and the perception of actual cognitive decline. In addition to these results, our case-study design allowed to examine objective and subjective outcome

data separately. This observation revealed that objective testing may not always represent patients' subjective experience. More importantly, patients' subjectively perceived long-term outcome may be determined by an interplay of several clinical factors.

Identifying potential risk factors for very long-term memory decline, the best single factor that could explain the functional very long-term memory loss was the baseline memory performance. In detail, both patients showing a memory drop over time (ID 8,9) had relatively intact preoperative memory functions, which have posed them at a higher risk of losing cognitive functions [35]. Later age at epilepsy onset and later age at epilepsy surgery – critical risk factors for postoperative cognitive decline [35,36] – may also have contributed to the cognitive decline in patient 8 who had an age at epilepsy onset at the age of 31 and epilepsy surgery at the age of 52. However, these factors may not explain the decline in patient 9, who in fact had a very early onset at the age of 1;

Table 2
Neuropsychological and results of the resected and non-resected patients.

		Non-resected			Resected					
Patient ID		1	2	3	4	5	6	7	8	9
Seizure outcome (Engel class)		IIC	IIIA	IC	IIB	IC	IB	IA	IA	IA
VLMT learning		-.52	-.52	.84	-.52	-.25	-1.04	-.52	-.13	-.52
	Md		-.52					-.52		
VLMT delayed recall		**-1.96**	-.19	1.28	-.45	-.67	**-1.96**	-.67	-1.44	-.93
	Md		-.19					-.80		
VLMT forgetting		**-1.64**	.67	.67	-.67	**-1.64**	**-1.96**	-.93	**-1.96**	-1.28
	Md		.67					-1.46		
VLMT Recognition		-.25	-1.44	-.52	-.52	**-1.96**	**-1.96**	-.76	-.25	-1.28
	Md		-.52					-1.02		
DCS-II learning		-1.23	-1.28	-.61	-1.34	.25	**-2.33**	**-1.88**	-.61	-.55
	Md		-1.23					-.98		
TMT number sequencing		.33	.67	.67	.69	1.00	-1.00	.00	1.37	1
	Md		.69					.85		
TMT number-letter switching		.67	-.33	.00	.33	**-1.67**	-.33	.67	.00	1.33
	Md		.17					.00		
Word fluency		-.99	-.02	.58	-.32	-.80	-.02	-.31	1.04	.28
	Md		-.31					-.15		
Flei	*Md (Min-Max)*									
Attention			7 (3-15)				13.5 (5-29)			
Memory			10 (5-13)				16.5 (11-24)			
Executive Functions			6 (1-16)				10.5 (4-21)			
Total score			18 (14-44)				40.5 (22-74)			
MMSE		30	30	29	26	30	28	30	29	29
	Md		30					29		
MWTB		1.18	.30	.55	1.18	-.28	.30	1.90	.30	.50
	Md		.55					.40		
BDI-II total score		15	5	21	10	21	17	1	3	0
	Md		18.00					6.5		
QOLIE-31	*Md (Min-Max)*									
Overall			55 (50-88)				62.5 (33-100)			
Energy			65 (40-80)				52.5 (25-60)			
Well-being			64 (56-88)				64 (32-80)			
Cognition			86.95 (60-93)				59.17 (16-84)			
Social Function			68 (55-100)				85 (25-100)			
Seizure worry			96 (39-100)				90 (61-100)			
Medication			88.9 (0-92)				79.17 (33-100)			
Overall health			40.0 (40-85)				70 (20-100)			
Total		64	90	62	59	63	29	79	81	74
	Md		64.02					68.27		

Md, median; VLMT, Verbaler Lern- und Merkfähigkeitstest (German Version of the Auditory Verbal Learning Test); DCS-II, Diagnosticum für Cerebral-schädigung II (Figural design learning test); TMT, trail making test; FLei, Fragebogen zur Geistigen Leistungsfähigkeit (Questionnaire for Complaints of Cognitive Performance); *Min*, minimum; *Max*, maximum; MMSE, mini mental status examination; MWTB, Mehrfachwahl-Wortschatzt-Intelligenztest (Vocubulary Intelligence Test); BDI-II, Becks Depression Inventory II; QOLIE-31, quality of Life in epilepsy (31-item version); values printed in bold indicate below average performance (see Section 2 for further details on test descriptions) See text version of Table 2 here.

also patient 9's age at surgery (i.e., 41 years) was comparable to that of the remaining RP (Median: 41). Case-control matching in our study resulted in rather homogenous scores on clinical-demographic scores among our patients. This may have hampered identification of relevant risk factors. However, it seems justified to conclude that a combination

of relatively high baseline memory performance and left-sided surgery may presumably have led to the very long-term decline in these patients [37].

Our case study is not congruent with earlier assumptions of an ac-celerated cognitive decline in patients with TLE [9,12,38], but goes in
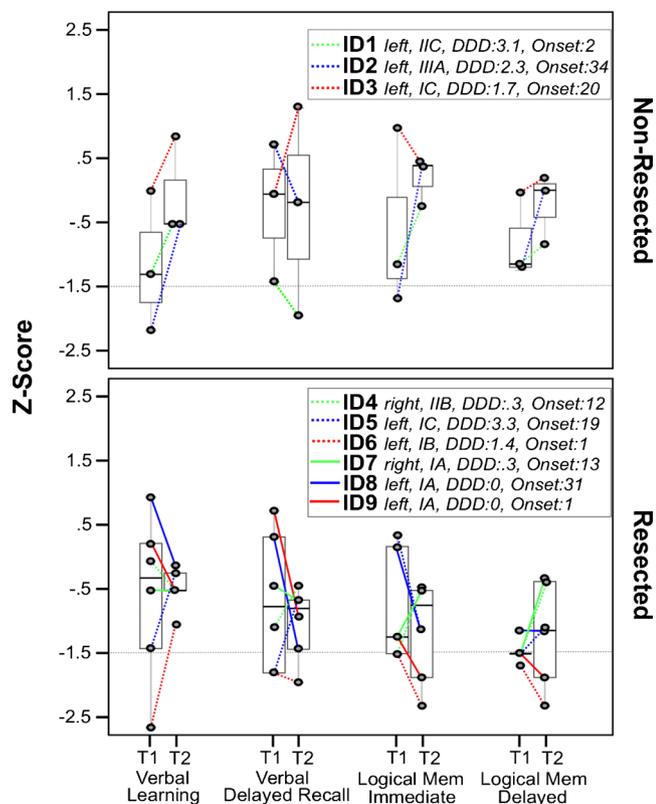
Fig. 3. Verbal memory performance at baseline (T1) and very long-term follow-up (T2) for the non-resected (upper panel) and resected patients (lower panel). Circles indicate individual patient's test scores. Solid lines represent seizure-free patients, dashed lines represent non-seizure-free patients. Green lines represent right sided patients; dashed horizontal lines indicate cut-offs for below average scores. Dashed horizontal lines indicate cut-offs for below average scores. DDD, defined daily dose of AEDs taken at long-term follow-up; Onset, age at seizure onset in years; Logical Mem, logical memory; verbal learning and verbal delayed recall refer to scores of the California Verbal Learning test at T1 and the Auditory Verbal Learning Test at T2 (see Section 2).

line with a current long-term follow-up study [8]. As a novelty, our study replicates these findings by specifically focussing on the very long-term postoperative phase (follow-up of approx. 20 years) in older patients (approx. 60 years and older). Results of this patient group, which has so far been neglected in earlier studies, adds to earlier results, as physiologically, decline of cognitive functions can usually not be observed before the fifth decade of life.

3.6. Social outcome

Two of three NRP possessed a driver's license and independently drove a car during the last 12 months, while this was the case for 4/6 RP. Concerning the occupational status, among the NRP, 1/3 had a reduction in earning capacity, 1/3 was retired on a pension, and 1/3 was fully employed; among the RP, 2/6 had a reduction in earning capacity, 2/6 were fully employed, 1/6 was unemployed, and 1/6 was working as a housewife.

3.7. Limitations

One of the main limitations of our study is the small sample size. We could not identify a current address or did not receive any response in spite of all efforts to contact the patients for about two thirds of the patients. We tried to take the small sample size into account by applying rather strict criteria for definition of cognitive impairment (i.e., −1.5 *SD*) and reporting single patients' data for the main results and

results of the group comparisons on a descriptive level. Our results should nevertheless be interpreted as preliminary findings and generalization of our findings to the population of TLE surgery cases without further replication should be drawn with caution. Following our experiences, we advise that very long-term studies would benefit from regular contacts and frequent updating of contact information for all patients having undergone presurgical assessment.

The NRP might be regarded suboptimal controls because 2/3 were rejected by the neurologists. However, none of the NRP would have been rejected from surgery today. Therefore, the NRP are not fundamentally different from RP, at least in later years. Comparison of baseline and long-term memory scores (i.e., word-list paradigms) may be restricted because the tests (i.e., baseline: CVLT, follow-up: VLMT) were similar but not identical [39]. To account for this, we considered an additional measure of verbal memory (i.e., logical memory), which was identically used at baseline and follow-up; this revealed results broadly comparable to those of the word-list paradigms.

In sum, our study should be understood as a first attempt to capture the very long-term outcome on a variety of variables and their case-specific interplay of subjective perception, neurocognitive outcome, and clinical variables in patients with TLE. In spite of its drawbacks, it offers valuable first insights into the very long-term postoperative courses of older patients with TLE on an individual level. This can be understood as an advantage over earlier studies as results of group studies may sometimes mask individually relevant cognitive deterioration [40]. Also, the close case-control-matching allowed us to minimize the influence of demographic and disease-related variables (e.g., age at onset, disease duration) which are known to influence cognitive [35,41,42] and seizure outcome [43]. As a further advantage, we applied a "quasi-prospective" study design and addressed all non-operated patients with TLE from our centre of a given time period. Previous studies included patients who repeatedly visited the respective centre but were not specifically invited with the purpose of participation in a study [8]. Finally, the selection process of our study (Fig. 1) also offers interesting epidemiological information about the long-term course of TLE patients (e.g., the apparently high mortality).

4. Conclusion

This preliminary case study of a highly selective sample of older patients takes the existing long-term outcome investigations in RP and NRP with TLE even further. Our patients had been studied ≥ 15 years after presurgical investigations and were 56–72 years old, i.e., in an age vulnerable to cognitive, emotional, and psycho-social deficits because of lower reserve capacities. RP still had a more favourable seizure outcome and took fewer AEDs. Yet, RP subjectively complained more frequently about cognitive-mnemonic deficits, had lower verbal memory scores, but reported a better overall health. Very long-term memory trajectories revealed relatively stable (and partly improved) memory scores for the NRP and the right-sided RP. Very long-term memory decline was evident in two cases with left-sided surgery and a relatively good presurgical baseline memory performance. However, our study also demonstrates that subjective perception of surgical outcome may differ from objective test scores and, critically, post-operative seizure-freedom may mediate the relationship between objective scores and subjective perception. It seems justified to conclude that the positive effects of the more favourable seizure outcome (i.e., better QoL and mood) outweigh potential cognitive impairment or decline. This calls for complete seizure-freedom and, hence, post-operative withdrawal of AEDs, as the main aim in epilepsy surgery. Finally, our results do not argue in favour of a general elevated risk for accelerated cognitive decline in patients with TLE, regardless if operated on or not. Future studies with ideally larger sample sizes will be needed to replicate our preliminary results.

Conflict of interest

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.02.015.

References

[1] West S, Nolan SJ, Newton R. Surgery for epilepsy: a systematic review of current evidence. Epileptic Disord 2016;18:113–21.

[2] Ozanne A, Graneheim UH, Ekstedt G, Malmgren K. Patients' expectations and experiences of epilepsy surgery — a population-based long-term qualitative study. Epilepsia 2016;57:605–11.

[3] Mathon B, Bielle F, Samson S, Plaisant O, Dupont S, Bertrand A, et al. Predictive factors of long-term outcomes of surgery for mesial temporal lobe epilepsy associated with hippocampal sclerosis. Epilepsia 2017;58:1473–85.

[4] Baxendale S, Thompson P. Defining meaningful postoperative change in epilepsy surgery patients: measuring the unmeasurable? Epilepsy Behav 2005;6:207–11.

[5] Behrens E, Schramm J, Zentner J, König R. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. Neurosurgery 1997;41:1–10.

[6] Baxendale S. Long-term cognitive outcomes after epilepsy surgery in adults. Long-term outcomes of epilepsy surgery in adults and children. Springer; 2015. p. 71–83.

[7] Edelvik A, Taft C, Ekstedt G, Malmgren K. Health-related quality of life and emotional well-being after epilepsy surgery: a prospective, controlled, long-term follow-up. Epilepsia 2017;58:1706–15.

[8] Helmstaedter C, Elger CE, Vogt VL. Cognitive outcomes more than 5 years after temporal lobe epilepsy surgery: remarkable functional recovery when seizures are controlled. Seizure – Eur J Epilepsy 2018;62:116–23.

[9] Jokeit H, Ebner A. Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. J Neurol Neurosurg Psychiatry 1999;67:44–50.

[10] Stefan H, Pauli E. Progressive cognitive decline in epilepsy: an indication of ongoing plasticity. Progress in brain research. Elsevier; 2002. pp. 409–417.

[11] Helmstaedter C. Effects of chronic epilepsy on declarative memory systems. Progress in brain research. Elsevier; 2002. pp. 439–453.

[12] Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003;54:425–32.

[13] Rausch R, Kraemer S, Pietras CJ, Le M, Vickrey BG, Passaro EA. Early and late cognitive changes following temporal lobe surgery for epilepsy. Neurology 2003;60:951–9.

[14] Helmstaedter C, Reuber M, Elger CC. Interaction of cognitive aging and memory deficits related to epilepsy surgery. Ann Neurol 2002;52:89–94.

[15] Tai XY, Koepp M, Duncan JS, Fox N, Thompson P, Baxendale S, et al. Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections. Brain 2016;139:2441–55.

[16] Piazzini A, Turner K, Chifari R, Morabito A, Canger R, Canevini MP. Attention and psychomotor speed decline in patients with temporal lobe epilepsy: a longitudinal study. Epilepsy Res 2006;72:89–96.

[17] Grewe P, Siedersleben C, Bien CG. Epilepsy Center Bethel, Bielefeld, Germany. Epilepsy Behav 2017;76:S17–20.

[18] Cloppenborg T, May TW, Blümcke I, Grewe P, Hopf LJ, Kalbhenn T, et al. Trends in epilepsy surgery: stable surgical numbers despite increasing presurgical volumes. J Neurol Neurosurg Psychiatry 2016. https://doi.org/10.1136/jnnp-2016-313831.

[19] Helmstaedter C, Lendt M, Lux S. Verbaler Lern-und Merkfähigkeitstest. Beltz-Test; 2001.

[20] Härting C, Markowitsch HJ, Neufeld H, Calabrese P, Deisinger K, Kessler J. WMS-R Wechsler Gedächtnistest—Revidierte Fassung. Hogrefe & Huber; 2000.

[21] Delis D, Kaplan E, Kramer J. D-KEFS examiner's manual. San Antonio, TX: The Psychological Corporation; 2001.

[22] Lehrl S. Mehrfachwahl-Wortschatz-Intelligenztest MWT-B. Erlangen: Perimed Verlag Dr. Straube; 1977.

[23] Monsch A, Foldi N, Ermini-Fünfschilling D, Berres M, Taylor K, Seifritz E, et al. Improving the diagnostic accuracy of the Mini-Mental State Examination. Acta Neurol Scand 1995;92:145–50.

[24] Beblo T, Kunz M, Brokate B, Scheurich A, Weber B, Albert A, et al. Entwicklung eines Fragebogens zur subjektiven Einschätzung der geistigen Leistungsfähigkeit (FLei) bei Patienten mit psychischen Störungen [Construction of a questionnaire for complaints of cognitive disturbances in patients with mental disorders]. Z Neuropsychol 2010;21:143–51.

[25] May T, Pfäfflin M, Cramer J. Psychometric properties of the German translation of the QOLIE-31. Epilepsy Behav 2001;2:106–14.

[26] Vickrey B, Perrine K, Hays R, Hermann B, Cramer J, Gordon J, et al. Scoring manual for the quality of life in epilepsy inventory-89 (QOLIE-89). Santa Monica, CA: Rand; 1993.

[27] Hautzinger M, Keller F, Kühner C. Beck Depressions-Inventar (BDI-II). Harcourt Test Services; 2006.

[28] Niemann H, Sturm W, Thöne-Otto A, Willmes K. CVLT – California verbal learning test – Deutsche Adaptation. Frankfurt: Pearson; 2008.

[29] Jehi L, Friedman D, Carlson C, Cascino G, Dewar S, Elger C, et al. The evolution of epilepsy surgery between 1991 and 2011 in nine major epilepsy centers across the United States, Germany, and Australia. Epilepsia 2015;56:1526–33.

[30] Kaiboriboon K, Malkhachroum AM, Zrik A, Daif A, Schiltz NM, Labiner DM, et al. Epilepsy surgery in the United States: analysis of data from the National Association of Epilepsy Centers. Epilepsy Res 2015;116:105–9.

[31] Thurman DJ, Logroscino G, Beghi E, Hauser WA, Hesdorffer DC, Newton CR, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia 2017;58:17–26.

[32] Vickrey BG, Hays RD, Rausch R, Engel Jr. J, Visscher BR, Ary CM, et al. Outcomes in 248 patients who had diagnostic evaluations for epilepsy surgery. Lancet 1995;346:1445–9.

[33] Malmgren K, Edelvik A, Duncan JS. Long-term seizure and antiepileptic drug outcomes after epilepsy surgery in adults. Long-term outcomes of epilepsy surgery in adults and children. Springer; 2015. pp. 19–41.

[34] Witt JA, Coras R, Schramm J, Becker AJ, Elger CE, Blümcke I, et al. The overall pathological status of the left hippocampus determines preoperative verbal memory performance in left mesial temporal lobe epilepsy. Hippocampus 2014;24:446–54.

[35] Baxendale S, Thompson P, Harkness W, Duncan J. Predicting memory decline following epilepsy surgery: a multivariate approach. Epilepsia 2006;47:1887–94.

[36] Saykin AJ, Gur RC, Sussman NM, O'Connor MJ, Gur RE. Memory deficits before and after temporal lobectomy: effect of laterality and age of onset. Brain Cogn 1989;9:191–200.

[37] Baxendale S, Thompson P, Harkness W, Duncan J. The role of the intracarotid amobarbital procedure in predicting verbal memory decline after temporal lobe resection. Epilepsia 2007;48:546–52.

[38] Dodrill CB. Progressive cognitive decline in adolescents and adults with epilepsy. Prog Brain Res 2002;135:399–407.

[39] Helmstaedter C, Wietzke J, Lutz MT. Unique and shared validity of the "Wechsler logical memory test", the "California verbal learning test", and the "verbal learning and memory test" in patients with epilepsy. Epilepsy Res 2009;87:203–12.

[40] Baxendale S, Thompson PJ, Duncan JS. Neuropsychological function in patients who have had epilepsy surgery: a long-term follow-up. Epilepsy Behav 2012;23:24–9.

[41] Helmstaedter C, Elger C. Cognitive consequences of two-thirds anterior temporal lobectomy on verbal memory in 144 patients: a three-month follow-up study. Epilepsia 1996;37:171–80.

[42] Hermann BP, Seidenberg M, Haltiner A, Wyler AR. Relationship of age at onset, chronologic age, and adequacy of preoperative performance to verbal memory change after anterior temporal lobectomy. Epilepsia 1995;36:137–45.

[43] Janszky J, Janszky I, Schulz R, Hoppe M, Behne F, Pannek HW, et al. Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. Brain 2005;128:395–404.