



Original Article

# One-year neuropsychological outcome after temporal lobe epilepsy surgery in large Czech sample: Search for factors contributing to memory decline

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## ABSTRACT

**Background:** Assessment of cognitive functions is an integral part of the evaluation the efficacy of temporal resections. We studied postoperative neuropsychological changes and factors contributing to worse memory outcomes in patients who experienced a significant decline using reliable change indices.

**Methods:** We prospectively studied 110 patients in whom we indicated anteromesial temporal resection (AMTR) and 46 patients who underwent selective amygdalohippocampectomy (SAHE). We administered Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised, and the Verbal Fluency Test before and 1 year after the operation.

**Results:** At a group level, we did not observe any statistically significant changes in global, verbal, and visual MQ in either the AMTR or the SAHE group. At an individual level, we found a mean decrease of verbal MQ after left-sided AMTR by -4.43 points ( $P = 0.01$ ). We detected no significant differences between the left and right side of surgery in the SAHE group. In patients with significant postoperative memory decline, we found either pre-existing extrahippocampal deficits/postoperative complications or incomplete hippocampal resection or a combination of these factors.

**Conclusion:** In addition to the side of surgery, structural integrity and functional adequacy of resected hippocampus and volume of resected tissue and preoperative extrahippocampal lesions/postoperative complications also contribute to postoperative memory decline after temporal lobe epilepsy surgery.

**Keywords:** Amygdalohippocampectomy, Anteromesial temporal resection, Intelligence, Memory, Neuropsychology, Temporal lobe epilepsy

## INTRODUCTION

Temporal lobe epilepsy (TLE) is often refractory to anti-seizure medication and is the most common type of partial epilepsy referred for epilepsy surgery.<sup>[8,31,35]</sup> The most frequent cause of TLE is mesiotemporal sclerosis, a lesion affecting the hippocampus and adjacent mesial structures.<sup>[26]</sup>

For many years, anterior temporal lobectomy (anteromesial temporal resection [AMTR]) and selective amygdalohippocampectomy (SAHE) have been the gold standard approach for the

treatment of medically refractory TLE, commonly leading to favorable seizure and neuropsychological outcomes along with minimal postsurgical complications.<sup>[28,42]</sup>

However, concerns for postoperative memory impairment frequently limit the perceived surgical candidacy of some patients, especially if the planned operation involves the speech-dominant side. Indeed, impaired verbal memory has historically been reported after the left temporal resections.<sup>[21]</sup> Nonverbal memory deficits are less consistently found after resections in the nondominant hemisphere.<sup>[3]</sup> The material-specific model is supported by large meta-analysis study that report deterioration of verbal memory in 44% of patients operated on the left and in 20% of patients operated on the right side. Visual memory impairment occurred in 21% of patients operated on the left and 23% of patients operated on the right side. Key aspects of inclusion criteria in this meta-analysis were  $n \geq 20$  and use of reliable change index (RCI) or standardized regression-based change estimates.<sup>[32]</sup> While this simplified model finds frequent employment in presurgical risk evaluation and in aggregate outcomes analyses,<sup>[4]</sup> its performance has frequently been criticized as inconsistent.<sup>[27]</sup>

However, it is important to realize that pharmacoresistant TLE is also associated with progressive memory impairment even in nonsurgical patients. In fact, TLE patients develop long-term memory dysfunction (especially involving declarative memory) early in life. While neuropsychological test performance may predict patients' academic accomplishments and every day function, subjective memory complaints are also often related to psychiatric comorbidities such as depression, which complicates analysis.<sup>[13]</sup> Furthermore, memory deficits can be potentially affected by developmental delay, brain damage, as well as dynamic factors such as prescribed medication and seizure frequency, etc.<sup>[5,30]</sup>

Thus, postoperative neuropsychological outcomes significantly depend on many factors, including the patient's innate characteristics. Previously published studies preoperatively assess the risk of postoperative memory impairment according to (1) preoperative memory function and (2) morphological findings on the hippocampus.

There are several examples of the role of preoperative memory function. For instance, a larger memory deficit can be expected in preoperatively cognitively normal patients than in patients with preoperatively impaired memory abilities.<sup>[13]</sup> The postsurgical memory deficits can be negatively influenced by poor seizure outcome and low mental reserve capacity, while the functional relief due to seizure freedom moderates the negative impact.<sup>[13]</sup>

The concept of structural integrity and functional adequacy of resected hippocampus is a leading theory on which preoperative patients' counseling is based. In other words,

patients with preoperatively morphologically intact hippocampus and preserved memory are at higher risk of postoperative memory decline than those with severely atrophic and sclerotic hippocampus and impaired memory.<sup>[5,12]</sup>

Another factor influencing postoperative cognitive outcomes is the extent and location of the resection, for example, whether or not the parahippocampal gyrus and entorhinal cortex are targeted.<sup>[11,18]</sup> For the past several decades, there has been controversy over what type of resection should be used; specifically, it is unclear whether wider resections are appropriate in light of the higher risk of associated neuropsychological deficits or whether smaller lesions should be created even if there is risk of not achieving permanent freedom from seizures. In practice, the extent of resection usually reflects the neurosurgeon's preference and prior experience.<sup>[42]</sup> Several surgical techniques designed to minimize adverse outcomes are currently employed. First, AMTR was introduced to minimize the resection of neocortical structures; unfortunately, this technique still carries a risk of memory impairment.<sup>[33]</sup> Thus, more selective approaches have been introduced. The SAHE through the gyrus temporalis medius<sup>[22]</sup> and transylvian amygdalohippocampectomy<sup>[40]</sup> being the most limited one<sup>[4,8]</sup> with favorable neuropsychological results.<sup>[28]</sup>

Some studies have reported statistically lower freedom from recurrent seizures after SAHE compared to AMTR.<sup>[14,16]</sup> However, the clinical significance of this difference remains unclear and has not been subjected to the rigors of a well-designed randomized study. In addition, postoperative persistence of seizures may itself worsen cognitive outcomes.<sup>[10]</sup> With respect to cognition, SAHE did not have better results when compared to AMTR,<sup>[14,16]</sup> but some authors found more favorable cognitive results<sup>[7,9,16,24,38,40]</sup> However, our own clinical experience has not always matched these findings, which prompted us to systematically analyze the outcomes in our own patient cohort.

The aim of our descriptive and exploratory study is as follows: (1) to compare the cognitive performance before and 1 year after AMTR and SAHE in a large sample of patients from a tertiary epilepsy center (observation period from 2000 to 2019) and (2) to concentrate on those patients in which memory significantly worsened (using RCI) after the operation and explore additional factors contributing to this deterioration.

## MATERIALS AND METHODS

### Patient selection

We studied a large sample of consecutive patients who underwent AMTR ( $n = 110$ ) and 46 patients who underwent SAHE at the tertiary Epilepsy center at Na Homolce Hospital, Prague, the Czech Republic, during the period from 2000

to 2019. Only those who had been neuropsychologically evaluated and followed at our center were included in the study. Some patients did not complete the entire battery of cognitive tests (sensory, movement or verbal deficits before or postsurgery, insufficient effort, and poor cooperation during neuropsychological assessment).

Demographic data are summarized in Table 1. One hundred and thirty-three patients were right handed, 15 left handed, and 12 were ambidextrous. Patients were evaluated preoperatively by a standard noninvasive evaluation protocol (interictal and ictal scalp video-electroencephalography, magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (FDG-PET), visual field, Wada test, and complex neuropsychological assessment).

After the comprehensive preoperative evaluation, the patients were educated about their treatment options. SAHE was preferred whenever the operation involved the left and dominant hemisphere in the right-handed individuals.

### Surgical technique

AMTR includes resection of the anterior part of temporal neocortex, amygdala, uncus, parahippocampal gyrus, and hippocampus proper. The resection of the anterior temporal neocortex spares a part of the superior temporal gyrus and is 3–4 cm in length on the dominant side and 4–5 cm on the nondominant side according to Spencer.<sup>[33]</sup> If MRI or invasive epileptological monitoring identifies epileptogenic areas beyond this routine neocortical resection, the resection is appropriately extended. The mesial resection starts by the resection of uncus and amygdala. The superomedial resection of amygdala is limited below the line between the inferior choroidal point and limen insulae, thus avoiding injury to the basal ganglia. Later, the parahippocampal gyrus is evacuated followed by subpial removal of the hippocampus itself. The dorsal limit of hippocampal resection is at the level of corpora quadrigemina unless planned differently based on preoperative investigation.

The SAHE is performed according to Niemeier<sup>[22]</sup> or Olivier<sup>[23]</sup> either transmedial temporal gyrus or through superior temporal sulcus and after reaching of the temporal horn of the lateral ventricle, the medially located resection follows as mentioned for AMTR.

To diminish any possible vascular injury, several steps are followed. In general, the resection is subpial, hence diminishing the probability of injury to Sylvian vessels and to vessels in an optocarotid, ambient, and crural cisterns. Larger cortical temporal arteries that traverse through the resected area to the dorsal temporal neocortex are, if possible, separated and preserved along with any larger draining veins. Any difficulties in finding of temporal horn (in the case of SAHE) are easily overcome using perioperative ultrasound;

this modality is also used to check the extent of resection and to reveal any possible hemorrhage.

### Neuropsychological evaluation

All patients were evaluated preoperatively and 1 year (2- and 5-year follow-ups are not included in this study) after surgery with a comprehensive neuropsychological battery. They were tested during 2 consecutive days; each session took 90–120 min, on average. During the first session, a psychological interview was performed and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was administered. Memory and verbal functions were assessed using the Wechsler Memory Scale-Revised (WMS-R)<sup>[37]</sup> and the Verbal Fluency Test (standardized Czech versions), respectively, during the second session. Verbal Fluency Test and quality of life questionnaire (QOLIE-89) were not involved in this study. Before surgery, hand laterality (test of laterality)<sup>[20]</sup> and language and memory lateralization were evaluated by the WADA test. All patients were informed about the test results at the end of the assessment.

### Statistical analysis

All values are presented as mean and standard deviation (SD) for continuous variables and as the number (percent) of subjects for categorical variables. Wilcoxon *t*-test was used to evaluate differences before and after the surgery and Mann–Whitney tests for differences in cognitive performance between AMTR and SAHE group at baseline and postoperatively (as a change from baseline). We report *P*-values that were uncorrected for multiple comparisons. The effect of age on memory functioning was evaluated using Pearson correlation. Statistical analyses were performed using R (R Core Team, 2020).<sup>[25]</sup>

We estimated the surgery effect at an individual level and employed the RCI classification.<sup>[15]</sup> Patients were divided into groups according to whether they demonstrated significant deterioration, improvement, or no change after the surgery using index of reliability for each test. Test-retest reliability coefficients for each test score were used to derive the

**Table 1:** Basic demographic and surgery data.

	AMTR	SAHE
Sex (M: F)	51:59	20:26
Age	36.34 (12:63)	35.56 (11.33)
Education	11.88 (2.13)	12.02 (1.87)
Laterality R: L: A	92:10:8	37:5:4
Side of surgery R: L	59:51 (54:46%)	19:27 (41:59%)
WADA speech R: L: A (missing)	5:51:2 (53)	4:20:2 (20)
WADA memory R: L: A (missing)	7:37:11 (55)	5:15:5 (21)

standard error (SE) of difference. We used these data to calculate a 95% confidence interval (CI) for the change. Score changes that fell outside the CI represent a statistically reliable change that would occur <2.5% of the time in patients without surgery. The RCI classification is based on the extent of individual performance change, while instrument reliability and general data variance are considered.

## RESULTS

### Surgical results

After AMTR, 68% of patients were classified as Engel I, 13% as Engel II, 12% as Engel III, and 7% as Engel IV. After SAHE, comparable seizure outcomes were found. Engel Class I had 70%, Engel II 15%, Engel III 13%, and Engel IV 2% of patients [Table 2].

The proportion of seizure-free (IA and IB) and nonseizure-free (IC to IV) patients was comparable for both approaches ( $\chi^2(1) = 0.07, P = 0.792$ ).

### Neuropsychological outcomes after AMTR

#### Intellectual outcomes

At the group level, we detected a statistically significant increase in Global and Performance IQ ( $P = 0.018$ , and  $P = 0.003$ , respectively) [Table 3]. At an individual level [Table 4], 14 (13%) patients improved in Full-Scale IQ, 83 (78%) of patients remained unchanged, and 9 (9%) deteriorated. Verbal performance increased in 10 (10%)

patients, 85 (81%) remained stable, and 9 (9%) deteriorated. Performance IQ improved in 9 (9%) patients, in 86 (84%) remained stable, and in 7 (7%) decreased.

#### Memory outcomes

At a group level, we did not observe any statistically significant changes in global, verbal, and visual MQ, attention, and delayed recall ( $P = 0.961; 0.610; 0.504; 0.395$ ; and  $0.186$ , respectively).

Using RCI [Table 4], 3 (3%) patients improved in global MQ, 97 (91%) were unchanged and 6 (6%) patients deteriorated. In verbal MQ, 1 patient (1%) improved, 101 (94%) remained unchanged, and 5 (5%) worsened. A total of 5 (5%) patients improved, 97 (91%) remained stable, and 4 (4%) patients experienced a decrease in their visual MQ. A reliable increase in 5 (5%) patients, no change 87 (85%), and deterioration 10 (10%) were detected in attention assessment. Improvement in 4 patients (4%), no change in 85 (84%), and deterioration in 2 patients (2%) were found in delayed recall.

When the relationship between age and memory performance postsurgery was examined using Pearson correlation, we detected a trend toward negative correlation in almost all measures, although this failed to reach statistical significance: WMS MQ ( $r = -0.4, P = 0.67, n = 105$ ), WMS verbal MQ ( $r = -0.7, P = 0.48, n = 106$ ), and WMS visual MQ ( $r = 0.09, P = 0.32, n = 105$ ).

#### Comparison of cognitive performance according to the side of AMTR

Using a (unpaired) Mann-Whitney U-test, we compared changes in pre- and postoperative performance according to the side of AMTR for all measures. We detected significant difference between the left and right side of surgery only in verbal MQ. Mean decrease of verbal MQ after the left-sided surgery was  $-4.43$  points; mean increase of verbal MQ after the right-sided surgery was  $1.81$  points, ( $P = 0.013$ ).

**Table 2:** Engel classification.

Engel class	AMTR (%)	SAHE (%)
IA, IB, IC, D	62, 8, 4, 1 (56, 7, 4, 1)	25, 6, 0, 1 (55, 13, 0, 2)
IIA, IIB	12, 2 (11, 2)	6, 1 (13, 2)
IIIA	13 (12)	6 (13)
IVA, IVB, IVC	5, 2, 1 (4, 2, 1)	0, 0, 1 (0, 0, 2)

**Table 3:** The WAIS-R and WMS-R scores before and after AMTR and SAHE.

Test	AMTR						SAHE						baseline_p	change_p
	n	m0	sd0	m1	sd1	p	n	m0	sd0	m1	sd1	p		
WAIS-R FS IQ	106	89.2	11.9	90.6	12.3	0.018	44	90.1	11.4	92.2	12.5	0.027	0.550	0.433
WAIS-R PIQ	102	90.4	12.2	92.6	12.0	0.003	45	90.4	12.7	94.1	14.6	0.008	0.633	0.429
WAIS-R VIQ	104	89.6	11.3	89.5	14.2	0.179	44	91.0	12.1	92.4	13.1	0.104	0.629	0.636
WMS-R MQ	106	92.4	17.9	91.9	18.8	0.961	44	86.5	18.1	85.7	18.1	0.655	0.144	0.752
WMS-R DR	91	93.0	18.1	91.5	20.8	0.186	38	88.2	15.3	87.5	14.6	0.892	0.076	0.454
WMS-R Attention	102	81.0	16.2	79.7	16.5	0.395	42	87.2	19.2	83.6	19.4	0.105	0.032	0.443
WMS-R Verbal	107	93.4	15.9	92.3	17.0	0.610	43	88.6	18.0	87.5	17.6	0.650	0.161	0.852
WMS-R Visual	106	95.3	17.9	96.1	18.8	0.504	43	86.9	15.0	88.7	12.5	0.308	0.007	0.747

FS IQ: Full-scale intelligence quotient; VIQ: Verbal intelligence quotient, PIQ: Performance intelligence quotient, MQ: Memory quotient, DR: Delayed recall



Differences in all other measures were not statistically significant.

## Neuropsychological outcomes after SAHE

### Intellectual outcomes

In the whole patient cohort, we observed a small, but significant improvement in global and performance IQ ( $P = 0.027$  and  $P = 0.008$ , respectively) after SAHE [Table 3]. At the individual level [Table 5], global IQ improved in 8 (18%) patients, 34 (77%) patients remained stable, and 2 (5%) deteriorated. Verbal IQ improved in 4 (9%) patients and 40 (91%) remained unchanged. Performance IQ improved in 7 (16%) patients, remained stable in 36 (80%) patients, and in 2 (4%), deterioration was detected.

### Memory outcomes

At the group level, we did not detect any statistically significant changes in global, verbal, and visual MQ, attention, and delayed recall ( $P = 0.655$ ;  $0.650$ ;  $0.308$ ;  $0.105$ ; and  $0.892$ , respectively) after SAHE. Using RCI at the individual level [Table 5], global memory performance improved in 1 (2%) patient, was unchanged in 42 (96%) patients, and decreased in 1 (2%) patient. None of the patients exhibited a change in verbal memory performance. Three (7%) patients improved, 39 (91%) remained unchanged, and 1 (2%) patient showed deterioration in visual MQ. In attention, 41 (98%) showed no change and 1 (2%) patient deteriorated. In delayed recall, improvement was noted in 1 patient (3%), no change in 35 (92%), and deterioration was seen in 2 patients (5%).

Negative but nonsignificant Pearson correlations between age and memory performance in all measures postsurgery were found: WMS MQ ( $r = -0.15$ ,  $P = 0.35$ ,  $n = 41$ ), WMS verbal MQ ( $r = -0.18$ ,  $P = 0.24$ ,  $n = 41$ ), and WMS visual MQ ( $r = -0.02$ ,  $P = 0.9$ ,  $n = 41$ ).

**Table 4:** Intraindividual changes according to reliable change indices in AMTR group.

	Improvement, <i>n</i> (%)	No change, <i>n</i> (%)	Deterioration, <i>n</i> (%)
WMS-R			
Global MQ	3 (3)	97 (91)	6 (6)
Verbal MQ	1 (1)	101 (94)	5 (5)
Visual MQ	5 (5)	97 (91)	4 (4)
Attention	5 (5)	87 (85)	10 (10)
Delayed recall	4 (4)	85 (84)	2 (2)
WAIS-R			
Full-Scale IQ	14 (13)	83 (78)	9 (9)
Verbal IQ	10 (10)	85 (81)	9 (9)
Performance IQ	9 (9)	86 (84)	7 (7)

\*Some patients did not complete all subtests preoperatively or postoperatively. MQ: Memory quotient, IQ: Intelligence quotient

## Comparison of cognitive performance according to the side of SAHE

Using (unpaired) Mann–Whitney U-test, we compared changes in pre- and postoperative performance according to the side of SAHE for all measures. We detected no significant differences between the left and right side of surgery.

## Comparison of neuropsychological changes between AMTR and SAHE procedure

We compared mean postoperative change in all memory and intelligence quotients between AMTR and SAHE. We did not detect any significant differences in postoperative performance between these two procedures [Table 3].

## Data of patients in whom we found postoperative memory decline

[Table 6] lists data specific only to patients with postoperative memory decline. In most of these cases, we found either extrahippocampal MRI lesions or postoperative complications. Furthermore, an incomplete resection of the posterior parts of hippocampus was evident on MRI in a high proportion of these patients [Figures 1 and 2].

## DISCUSSION

This descriptive and exploratory study focuses on postoperative neurocognitive performance after AMTR and SAHE in a large sample of patients from a tertiary epilepsy center (observation period from 2000 to 2019). We also targeted on patients with significant memory decline postsurgery (using RCI) and explored epileptological and MRI findings contributing to this deterioration.

At the group level, we did not observe any statistically significant deterioration in memory and intelligence quotients measured

**Table 5:** Intraindividual changes according to reliable change indices in SAHE group.

	Improvement <i>n</i> (%)	No change <i>n</i> (%)	Deterioration <i>n</i> (%)
WMS-R			
Global MQ	1 (2)	42 (96)	1 (2)
Verbal MQ	0 (0)	43 (100)	0 (0)
Visual MQ	3 (7)	39 (91)	1 (2)
Attention	0 (0)	41 (98)	1 (2)
Delayed recall	1 (3)	35 (92)	2 (5)
WAIS-R			
Full-Scale IQ	8 (18)	34 (77)	2 (5)
Verbal IQ	4 (9)	40 (91)	0 (0)
Performance IQ	7 (16)	36 (80)	2 (4)

\*Some patients did not complete all subtests preoperatively or postoperatively. MQ: Memory quotient, IQ: Intelligence quotient

**Table 6:** Data on patients in whom memory declined after temporal lobe resection.

Patient	Side of surgery	Engel score	Type of surgery	Decline			Delayed Recall	Pre-existing deficits/complications	Hippocampal remnants
				Global MQ	Verbal MQ	Visual MQ			
1	L	Ia	AMTR	Y	N	N	N	Postoperative ischemia temporodorsal from resection on MRI, moderate expressive aphasia, and mild central paresis of the right hand	N
2	R	Ia	AMTR	Y	Y	N	N	Temporal stem lesion and frontal pole gliosis	Y
3	L	Ib	AMTR	Y	Y	N	N	White matter gliosis after previous radiosurgery	Y
4	L	Ia	AMTR	Y	Y	N	N	Preoperative leukoaraiosis and brain atrophy. Postoperative gliotic changes in the temporal stem	N
5	L	Ia	AMTR	Y	Y	N	N	Opercular and insular gliotic changes	N
6	R	IIa	AMTR	Y	Y	N	N	Gliotic changes in the inferior temporal gyrus, temporal neocortex, and posterior to the postresection cavity	N
7	L	Ia	SAHE	Y	N	N	N	Nothing	Y
8	R	IIIa	SAHE	N	N	N	Y	Nothing <sup>1</sup>	Y
9	L	IIIa	SAHE	N	N	N	Y	Nothing <sup>2</sup>	N

Y=yes, N=no, L=left, R=right, <sup>1</sup>: In this patient, we performed only temporal pole resection given the risk of visual field deficit in light of the fact that he had his right eye enucleated as a child (due to an infection). <sup>2</sup>: This is the only patient in this group who had not had any pre-existing deficit/complication and his left hippocampus was completely resected. However, he was right handed and left hemisphere speech dominant and had a morphologically intact left hippocampus. Furthermore, he is not seizure free after the operation

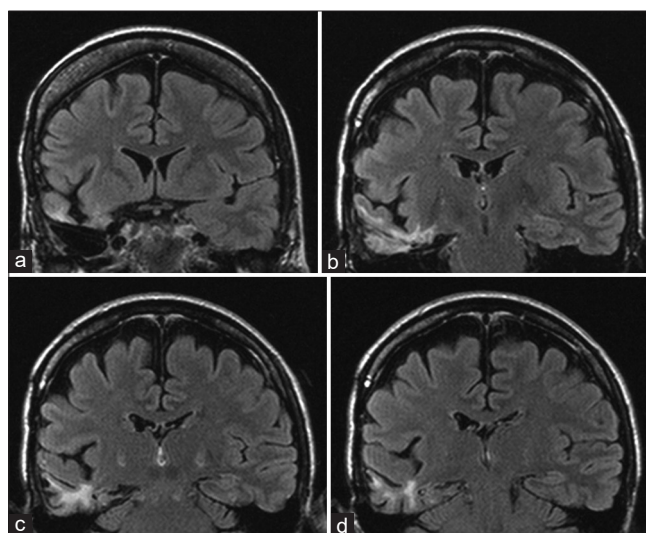
by WAIS-R and WMS-R after AMTR and SAHE. Neuropsychological and epileptological results were satisfactory in our patients and comparable with previously published studies.<sup>[28,42]</sup>

We analyzed the possible causes of memory deterioration in both subgroups in addition to what those that have already been published. We detected two subgroups of patients with significant memory decline: (1) individuals with clinically manifested surgical complications or with large postoperative gliosis and (2) patients with residues of resected left hippocampus.

At the individual level, 6 (6%) patients deteriorated in global MQ, 5 (5%) in verbal MQ, 4 (4%) in visual MQ, 10 (10%) in attention, and 2 patients (2%) in delayed recall after AMTR.

Those patients that deteriorated in global and verbal memory were operated on the left side (four patients) and on the right side (two patients). One patient suffered from moderate expressive aphasia, mild paresis of his right hand, and temporodorsal ischemia from resection, as confirmed by an MRI (Engel Class 1A). One patient suffered from transient phatic disorder and prosopagnosia (Engel Class 1A). Gliotic changes were detected in all patients. In one patient, there was ischemia, and in two patients, there was remnant hippocampus.

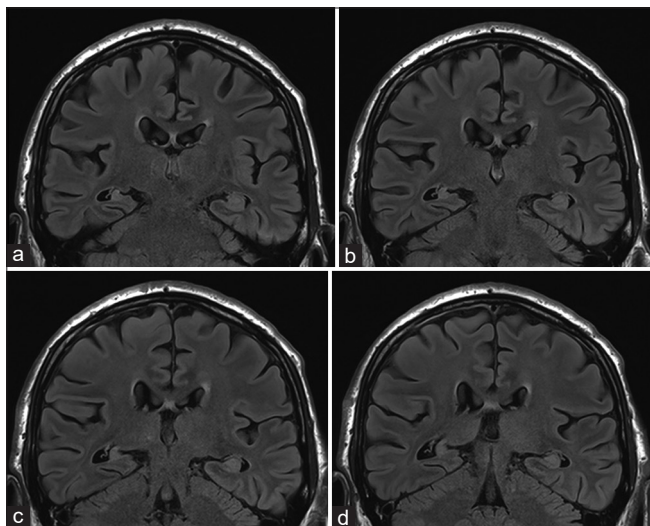
After SAHE, at the individual level, we detected deterioration in 1 (2%) patient in global MQ, 1 (2%) in visual MQ, and 1 (2%) attention. Two (5%) patients deteriorated in de-



**Figure 1:** (a-d) Gliotic changes in the temporal lobe with complete hippocampal resection in patient no. 6.

layed recall. Two patients who deteriorated in memory performance were operated on the left side with the right hand dominance (Engel Class Ia and IIIa). One patient suffered from the right upper quadrantopsia and a residuum of the hippocampus was detected in two patients.

When we compared mean postoperative change in all memory and intelligence quotients between AMTR and



**Figure 2:** (a-d) Hippocampal remnants after the right-sided anteromesial temporal resection in patient no. 2.

SAHE, we did not detect any significant differences. Thus, from the neuropsychological point of view, SAHE may not have an advantage over AMTR due to the higher risk of complications and gliosis in the access pathway and beyond. It is debatable how residual hippocampi can affect cognitive function even in patients who are seizure free after surgery. It is conceivable that this is caused by the effect of hippocampal epileptiform activity on the residual hippocampus. In patients with pre-existing extrahippocampal brain lesions or surgical complications, memory decline after operation could be expected as larger volumes of the brain are damaged. The answer to why patients with incomplete resection of the posterior hippocampus tend to suffer from postoperative amnesic deficits is less clear. In our group of patients, we suspect that persistent seizures were not likely involved as their Engel Class is mostly favorable. We hypothesize that hippocampal remnants may still be able to produce disruption of brain functions, for example, by generating interictal epileptic discharges.<sup>[1]</sup> The existence of subclinical seizure activity and/or interictal discharges which interfere with the function of unresected hippocampus seems to be the most straightforward explanation for their cognitive decline. Indeed, there are reports that support this hypothesis.<sup>[17,36]</sup> However, the causal relationship of memory decline and subclinical discharges is difficult to prove in outpatient epilepsy clinics, as some of these phenomena can only be diagnosed by intracranial monitoring. Given the reports that about 20% of hippocampal seizures start in the posterior hippocampus, it is possible that the remnants of an anteriorly resected hippocampus are no longer capable of producing overt seizures, yet, they remain dysfunctional.

In spite of the fact that AMTR involves resection of the lateral temporal cortex implicated in verbal information

processing, several studies have not confirmed greater impairment in verbal memory tasks for this type of surgery compared to SAHE.<sup>[6]</sup> SAHE is an effective treatment option for pharmacoresistant MTLE, which leads to favorable seizure outcomes<sup>[29,39,41,42]</sup> and there are reports of a trend toward better preservation of naming performance in patients undergoing SAHE versus AMTR on the dominant side.<sup>[19]</sup> According to other analyses, cognitive outcomes were not affected by variations in surgical approaches, with the exception of naming outcomes, which had better results when more conservative resections were used.<sup>[32]</sup>

The impairment of memory performance postsurgery has been in the center of attention for many years. With regard to the side of the surgery, temporal lobe resection (TLE) has a well-known effect on memory changes, especially on the verbal memory after the surgery in the functionally dominant hemisphere. Results of a meta-analysis demonstrated verbal memory decline in patients who underwent AMTR in dominant hemisphere.<sup>[2,32]</sup> In the left-sided temporal surgery patients, naming was impaired in 34% of cases, whereas scores increases were seen in only 4% of patients. As evidenced by the summary results on IQ, attention, and executive functioning, only a few patients showed declines after the surgery.<sup>[32]</sup> The study of Sauvigny *et al.*<sup>[28]</sup> demonstrates that a low verbal memory performance at follow-up relies on the functional dominance of the hemisphere, which illustrates the important role of the dominant temporomesial structures for this particular domain. Patients undergoing surgery in the left hemisphere had significantly lower verbal learning score than those after the surgery in the right hemisphere.<sup>[8]</sup>

Even though our study is observational and exploratory (we did not have predefined hypotheses about individual outcomes or random assignment to treatments), we chose to retrospectively compare the outcomes results according to the side of surgery and reported uncorrected *P*-values. We compared changes in pre- and postoperative performance according to the side of SAHE for all measures. We detected no significant differences between the left and right side of surgery.

After AMTR, we detected a significant difference between the left and right side of surgery only in verbal MQ – with worse results after the left-sided surgery. Mean decrease of verbal MQ after the left-sided surgery was –4.43 points; mean increase of verbal MQ after the right-sided surgery was 1.81 points, (*P* = 0.013).

More SAHE patients (59%) were operated on the left side and AMTR resections were performed in 46% of patients on the left side. Selective approach was preferred in patients almost all operated in the left, dominant hemisphere, who were right handed and who had functionally dominant side of surgery.

Other intervening factors, such as preoperative cognitive function and age, also have a well-known influence on neuropsychological testing results after the TLE surgery. Greater postoperative memory impairment has been associated with older age at seizure onset and older age at the time of surgery.<sup>[6]</sup> When we monitored the relationship between age and memory performance postsurgery (for both AMTR and SAHE), we found a trend toward negative correlation in almost all measures, although this failed to reach the level of statistical significance. The older the patient, the lower the memory performance was before and after the surgery.

Lower general cognitive skills before surgery have also been described as a predictor of better verbal learning in patients after the right temporal lobe resection.<sup>[6]</sup> However, much less attention is devoted to patients who show improved memory functioning after AMTR.<sup>[2]</sup> In our group of patients, memory performance (MQ) in AMTR and SAHE group was 1 SD and 0.5 SD below average, respectively. In accordance with other studies, more selective approaches were preferred in patients with relatively normal preoperative performance, because of the higher risk of cognitive decline after surgery.

The range of postoperative memory decline is also significantly affected by the presence of mesial temporal lobe pathology and the functional integrity of the resected mesial temporal lobe structures, as proven by preoperative memory assessment.<sup>[19]</sup> Patients with hippocampal sclerosis (HS) typically already show low memory performance at baseline, who are thus less likely to deteriorate significantly after the surgery. On the contrary, patients with minimal or no HS perform within normal range in memory tests preoperatively. Subsequent removal of a normal, functioning hippocampus leads to memory decrease.<sup>[42]</sup> We have not included the presence of HS in the analysis of postoperative memory changes but we plan on making this consideration in a future study.

Postoperative seizure freedom is associated with functional improvement in unresected areas contralaterally and ipsilaterally. The existence of an epileptogenic focus in the unilateral temporal lobe may be supported by severe hypometabolism restricted to the unilateral temporal lobe, with ipsilateral dominant hypometabolism.<sup>[34]</sup> This, in turn, supports a favorable seizure outcome after MTLE resection.

Besides seizures, TLE patients suffer from cognitive deficits that negatively influence everyday functioning and quality of life. Cognitive neuroscience traditionally researched TLE as an important model allowing for understanding human language and memory deficit as a result of hippocampal damage.<sup>[26]</sup> The assumption that verbal and nonverbal modalities of memory are separate entities localized to the left and right hippocampi is probably the most influential one in the epileptology and neuropsychology of TLE. This

concept formed the basis of presurgical decision-making, as well as the prediction of postoperative outcomes. An alternative approach to these postulates begins by critical reflection of this material-specific model. According to Saling (2009), functions of nonverbal and verbal memory are not completely lateralized; verbal memory is systematically segregated by the left MTLE foci; and particular aspects of memory are localized within the left temporal lobe.<sup>[27]</sup>

Recently, our insight into the structural and functional pathology and cognitive profile in TLE has been enhanced by the advent of high-resolution and multimodal neuroimaging and by the increased use of comprehensive neurocognitive phenotyping batteries.<sup>[26]</sup> In neuropsychology, TLE is now recognized to affect a variety of domains which are not restricted to language and memory processing.<sup>[26]</sup> The study of Foged *et al.*<sup>[8]</sup> also supports the necessity to administer various subtypes of memory tests that are sensitive to different aspect of memory processing and difficulty of the task.

#### Our study has several limitations

1. It is a single-center study
2. There are a limited number of patients in each group
3. We included different types of surgery procedures without random assignment to treatment
4. We did not analyze patients without significant postoperative neurocognitive change in detail
5. Not all patients completed the entire testing battery (sensory, movement, or verbal deficits before or postsurgery, insufficient effort, and cooperation during neuropsychological assessment)
6. Lack of administration of new comprehensive neurocognitive phenotyping batteries.

#### CONCLUSION

Improvement in seizure and neuropsychological outcomes constitutes the essential aim of successful surgical treatment of pharmacoresistant MTLE.<sup>[42]</sup> In our patient cohort, we found surprisingly satisfactory epilepsy and memory outcomes (with a minimum of deteriorated patients), despite the fact that about half of the patients were operated on the dominant hemisphere. Outcomes results were comparable for both AMTR and SAHE procedures. Our findings are similar to results of other studies evaluating effectivity and safety of temporal lobe resections.

Based on our analysis, the majority of memory declined patients experienced clinically manifested surgical complications, large postoperative gliosis, or significant residues of resected left hippocampus. We are convinced that surgical complications are important intervening factors that significantly influence postsurgical memory performance and



should be involved in the future neuropsychological outcome studies.

Our work should be the impetus for a multicenter study that would examine:

1. Not only the total volume of resected tissue but also quantification of gliotic tissue
2. Cognitive results after resections of hippocampal residues.

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### Authors' contributions

LK and ZV prepared the design of the study, participated in the acquisition, and analysis of data; LK wrote the original draft of the manuscript and critically revised the manuscript; and JS, TC, and ZV participated in the acquisition and analysis of data, critically revised and edited the manuscript. All the authors meet the standard criteria of authorship based on recommendations of the international committee of medical journal editors.

### Ethical committee agreement

All data collection, storage, and processing were done in compliance with the Helsinki Declaration. All patients provided signed, informed consent and the studies IG 171501 and IG 193001 were approved by the ethics committee of Na Homolce Hospital in Prague.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

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