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The Neuropsychological Outcomes of Surgery for Drug-Resistant Temporal Lobe Epilepsy and Underlying Pathologies

Die neuropsychologischen Folgen von Operationen bei medikamentenrefraktärer Temporallappenepilepsie und zugrundeliegende Pathologien

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ABBREVIATIONS

AED	Anti-epileptic Drug
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATL	Anterior Temporal Lobectomy
AVM	Arteriovenous Malformation
BDI	Beck Depression Inventory
CNS	Central Nervous System
EEG	Electroencephalography
GTCS	Generalized Tonic-Clonic Seizure
HS	Hippocampal Sclerosis
IED	Interictal Epileptiform Discharge
ILAE	International League Against Epilepsy
IQ	Intelligence Quotient
IQR	Interquartile Range
M	Mean
Mdn	Median
MRI	Magnetic Resonance Imaging
mTLE	mesial Temporal Lobe Epilepsy
N	Count
RAVLT	Rey Auditory Verbal Learning Test
ROCFT	Rey-Osterrieth Complex Figure Test
RWT	Regensburger Wortflüssigkeits-Test [Regensburg Verbal Fluency Test]
SAH	Selective Amygdalohippocampectomy
SD	Standard Deviation
TIQ	Total Intelligence Quotient
TLE	Temporal Lobe Epilepsy
VLMT	Verbaler Lern- und Merkfähigkeitstest [Verbal Learning and Memory Test]
VLMT7	Verbaler Lern- und Merkfähigkeitstest - Round 7
VLMTR	Verbaler Lern- und Merkfähigkeitstest - Recognition
VOSP	Visual Object and Space Perception Battery
QOLIE	Quality of Life in Epilepsy Inventory

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1 INTRODUCTION

1.1 Epilepsy

Epilepsy is a pathological condition of the central nervous system (CNS) causing epileptic seizures due to a functional or anatomical change in the brain. A seizure occurs if a temporary nervous dysfunction generates an excessive neuronal discharge through enhanced excitability or reduced inhibitory functions (Fisher et al., 2005). This can either happen without provocation or after exposition to a momentary factor (e.g., hypoglycemia) or recurring triggers (e.g., photostimulation), in which case it is referred to as a reflex seizure (Aird, 1983). According to the International League Against Epilepsy (ILAE), the diagnosis of epilepsy is indicated if either two unprovoked or reflex seizures caused by recurring triggers occur with an intermediary time span of at least 24 hours, if a single unprovoked or reflex seizure caused by recurring triggers is combined with a recurrence risk of 60% or higher, or if an epilepsy syndrome can be diagnosed (Fisher et al., 2014). Globally, epilepsy affects roughly 50 million people, making it one of the most frequently diagnosed neurological diseases (WHO, 2019). In Germany, the total count of cases is estimated to lie somewhere between 400,000 and 800,000, with about 30,000 new cases per year (Brandt, 2016).

1.2 Temporal Lobe Epilepsy

With a prevalence of 66%, the epilepsies of the temporal cerebral lobe constitute the majority of the focal epilepsies (Semah et al., 1998), which qualifies them as the subject of recent research (Usui, 2016). Temporal lobe epilepsies (TLE) can be subclassified by the affected regions: The most common form is the mesial temporal lobe epilepsy (mTLE), constituting about 40% of all epilepsies in adults (Cendes, 2005). The mesial temporal lobe contains the structures of the hippocampus, the amygdala, the parahippocampal gyrus, and the entorhinal cortex. Its dominant (usually left) side is in charge of the verbal memory, while the non-dominant (usually right) counterpart conveys non-verbal memory content (e.g., shapes and figures). The lateral temporal subtype with seizures originating in the temporal neocortex can be found among 24% of TLE patients. Neuropsychological qualities mediated in this part of the brain are word-finding and language comprehension in the dominant- and visuoperceptual functions in the non-dominant hemisphere (Shorvon et al., 2009). The mesiolateral subtype is a hybrid of the first two subtypes with a prevalence of 33% of TLE patients (Kahane & Bartolomei, 2010; Maillard et al., 2004).

In addition, Berg and colleagues (2010) stated that apart from the localization of seizure onset, the type of lesion is to be considered to understand the cause and the prognosis of epilepsy as well. In a German study of 2812 TLE patients, 52% were diagnosed with hippocampal sclerosis (HS). Other typical diagnoses were cerebral tumor, gliosis, focal cortical dysplasia, and arteriovenous malformation (AVM) (Helmstaedter et al., 2014). While HS is a lesion of the mesial temporal lobe causing a selective neuronal cell loss associated with astrogliosis in the hippocampal formation (Blümcke et al., 2013), the other pathologies can be found throughout the entire lobe. However, it was found that they still constitute 35% of mTLE lesions (Valentín & Alarcón, 2010).

1.3 Drug-Resistant Temporal Lobe Epilepsy

After patients are diagnosed with epilepsy, which can be supported by the finding of one such lesion in the magnetic resonance imaging (MRI) or an electroencephalography (EEG) with matching interictal epileptiform discharges (IED), a pharmacotherapy with an anti-epileptic drug (AED) is initiated (Elger et al., 2017). If seizure freedom cannot be reached after the adequate use of two appropriately chosen AED schedules, epilepsy will be referred to as drug-resistant (Kwan et al., 2010), which is the case for 30% of patients (Kalilani et al., 2018) that are then considered for epilepsy surgery. The prevalence of drug-resistance is particularly severe in TLE patients, with only eight percent of them responding to medical therapy after one year (Wiebe et al., 2001). The ongoing disease constitutes a risk for cognitive decline, which increases with the number of experienced seizures (Breuer et al., 2016). At the same time, the risk of producing additional neurological or neuropsychological damage by removing the epileptogenic structures during surgery must be considered (Elger et al., 2017). Neuropsychologic testing, as applied in this study, is thus vital to determine the different competencies of both cerebral hemispheres, the availability of their compensatory mechanisms, and thereby the short- and long-term effects of resective surgery on cognition. Hence, all patients are tested for their performance in intelligence tests and assessments evaluating specific functions of the mesial temporal lobe and the temporal neocortex (Helmstaedter, 2005). Finally, the side of speech dominance is determined to allocate essential functions to either cerebral hemisphere (Baumgartner et al., 2019).

1.4 Temporal Lobe Surgery

Nowadays, there are four types of surgical approaches to treat lesional epilepsies of the temporal lobe: The anterior temporal lobectomy (ATL), developed in the 1950s, consists of the removal of the hippocampus, parahippocampus, amygdala, uncus, and adjacent structures together with the lateral neocortex (Falconer, 1953). An increasingly standard and more restrictive procedure for mTLE that came up in the 1980s is the selective amygdalohippocampectomy (SAH), which includes the resection of the hippocampal head and body, the parahippocampal- and dentate gyri, as well as the amygdaloid nucleus (Wieser & Yaşargil, 1982). Tailored resections are an option for the removal of defined lesions together with any perilesional epileptogenic tissue. Severe cases can lead to the decision for the fourth option: a complete lobectomy (Berlit, 2020).

1.5 Surgery Outcome

1.5.1 Selective Amygdalohippocampectomy & Anterior Temporal Lobectomy

A recent meta-analysis published in 2020 by Xu et al. found that 63.5% of SAH and 63.8% of ATL patients reached post-operative seizure freedom with no significant difference between the two groups. However, earlier meta-analyses reported a significantly improved seizure freedom for ATL compared to SAH (Josephson et al., 2013; Hu et al., 2013). Concerning neuropsychology, Hu et al. also showed that the total intelligence quotient (IQ) scores improved for both types of surgery, with the exception of the verbal IQ after a resection on the left side. Though in favor of ATL, the differences were not significant. The meta-analyses of Jain et al. (2018) and Kuang et al. (2014) found no significant differences between SAH and ATL with respect to seizure freedom, memory, and language. A study by Morino et al. in 2006 showed no significant differences between SAH and ATL concerning IQ and memory either. A multi-center study published in 2013 found a significantly better outcome for SAH patients concerning their visual qualities and verbal short-term memory. Additionally, they found that quality of life improved for all patients after surgery without a significant preference for either procedure (Wendling et al., 2013). Eventually, the variety of used screening procedures makes extensive meta-analyses of neuropsychological surgery outcomes difficult, and the inconsistency of study results did so far not allow a definite recommendation of either SAH or ATL. Thus, the choice of procedure stays a matter of individual decision-making and further study (Xu et al., 2020).

1.5.2 Hippocampal Sclerosis & Other Pathologies

A closer look at underlying etiologies revealed that HS patients, though worse in their pre-surgical performance, showed no decline in their tested neuropsychological abilities after surgery compared to patients with other pathologies, whose performance deteriorated (Hamberger et al., 2007). With the use of electrical stimulation mapping in 24 patients, Hamberger and colleagues detected that the presence of HS leads to intra-hemispheric reorganization of neuropsychological functions to areas not resected during conventional surgery (Hamberger et al., 2007). However, in 2019, a group of Australian researchers studied the neuropsychological differences between 19 patients with HS and 30 with other temporal pathologies and found that, contrary to their expectations, the groups did not vary significantly in their memory performances (Rayner et al., 2019). A study of 104 patients revealed that a high hippocampal cell density (indicating a healthy hippocampus) on the left side results in a significantly worse verbal memory performance post-surgically. No such parameter was found for right-sided surgery. The authors concluded that the capacities of the verbal memory can be a contributor to pre-surgical risk-benefit evaluations of the left hemisphere but that the right side still needs research (Witt et al., 2015).

1.5.3 Further Predictors of Surgery Outcome

In sum, successful surgery that results in freedom from seizures has the potential to stop the decline in memory functions and even improve neuropsychological non-memory performances (Helmstaedter et al., 2003). Strong predictors of post-surgical seizure freedom were found to be an extensive resection area as well as a history of febrile seizures, the latter associated with HS (Tonini et al., 2004). Better neuropsychological outcomes correlate with younger age, shorter duration of epilepsy, a more restrained prescription of AED's, higher intelligence, which is coherent with a higher level of education (Jokeit & Ebner, 1999), and the pre-surgical finding of IED's (Fitzgerald et al., 2021). The occurrence of generalized tonic-clonic seizures (GTCS) was found to lead to a worse memory performance (Helmstaedter et al., 2003). Sex has not been detected to affect post-surgical neuropsychological performance (Davies et al., 1998; Helmstaedter et al., 2004a). Besides a history of febrile seizures, characteristics found among patients with HS are early age at onset, a long duration of epilepsy, and a mesial-temporal location of lesions (Asadi-Pooya et al., 2015).

1.6 Aims of the Study

The first aim was to compare ATL and SAH with respect to their neuropsychological outcome in order to make a statement if either surgery can be recommended in terms of post-surgical memory performance and overall quality of life. For a more individual prediction of surgery outcomes, a range of covariates was analyzed for correlation with the neuropsychological performances.

1st Hypothesis: SAH has a better neuropsychological outcome than ATL due to its more restricted resection area and hence improves quality of life better than ATL.

2nd Hypothesis: MRI-positive lesions and IED's remaining after surgery as possible correlates of continuing seizures, the duration of epilepsy, an older age, and a high number of prescribed AED's influence test performances after both types of surgery negatively, while freedom from seizures, presence of IED's in the pre-surgical EEG, as well as a high total IQ and level of education improve post-surgical test results. Patients' sex is not expected to affect results.

The second aim of the study was to compare HS with other pathologies of the temporal lobe with respect to their neuropsychological performance pre- and post-surgically to find out which group has the greater profit from an operation and thereby add a pivotal factor to pre-surgical risk-benefit evaluations. It was also in question whether the currently used tests are suitable for the findings of significant differences in neuropsychological performance. Therefore, the tests analyzed in this study were chosen in accord with the currently most applied assessments in Europe.

3rd Hypothesis: HS patients show a smaller decline in their verbal and figural memory abilities after surgery as compared to patients with other etiologies of TLE, whereas pre-surgically, HS patients' test results are worse. Therefore, the post-surgical quality of life is better among HS patients.

4th Hypothesis: Older age, a history of GTCS, remaining MRI lesions and IED's, and more intensive use of AED's contribute to worse post-surgical test performance, while a high total IQ and education level, as well as factors associated with HS (history of febrile seizures, early age at onset, longer duration of epilepsy, mesial-temporally located lesions), the pre-surgical finding of IED's, and post-surgical freedom from seizures improve the neuropsychological outcome of surgery for either pathology. Patients' sex is not expected to affect results. Before surgery, parameters associated with HS are presumed to deteriorate performances.

2 METHODS

2.1 Patients and Study Design

The study reviewed 873 patients with drug-resistant epilepsy who received pre-surgical examination at the Epilepsy Center Hessen in Marburg between 2001 and 2018. Children, as well as adults, were regarded retrospectively. For this purpose, they were distinguished into groups according to their types of surgery and their underlying pathologies so that the results of the surgical outcomes regarding neuropsychological performance and seizure frequency could be compared. Of the 873 tested patients, 244 underwent surgery, and after applying the inclusion- and exclusion criteria, 174 of these were part of the analyses. Post-surgical follow-up examinations were scheduled for six months, one, two, and five years after surgery, with subsiding numbers of participants over time. The examination consisted of history-taking, MRI imaging, video-EEG monitoring, and neuropsychological testing.

2.2 Inclusion- and Exclusion Criteria

In order to address the two aims of the study, different numbers of patients were included in two groups. For the comparison of SAH and ATL, the pre-surgical data of 114 patients who received either surgery could be acquired from the total lot of 873 patients. One hundred and sixty patients were diagnosed with unilateral HS or a different seizure etiology based in one temporal lobe and operated upon it, which was the inclusion criterion for the second group. One hundred patients are included in both groups explaining the total of only 174 patients in the analyses. The two groups have not been put in relation at any point of the study.

Thirteen patients received brain surgery due to epileptogenic lesions prior to their pre-surgical examination. However, none of these earlier surgeries succeeded in sustainably removing seizures, which is why the patients were seen for another pre-surgical assessment and surgery and subsequently included in the study.

Patients were omitted if their epileptogenic lesions or surgeries were bihemispheric or affected more than one temporal lobe. They were also excluded if lateralization diagnostics did not yield a clear side of speech dominance. If a second epilepsy surgery took place during the five-year follow-up phase, data were excluded from the time of the second surgery.

2.3 Medical History

The available information on medical history included the assessment of the duration of epilepsy as well as the semiology of seizures and any experienced changes of semiology over time. For this purpose, the documented third-party anamneses were considered. Furthermore, information on family history, diseases other than epilepsy, risk factors (alcoholism, polytoxicomania, febrile seizures, hemorrhage or ischemia, perinatal complications, infections of the CNS, concussions, and positive family history), current and past AED's, as well as psychopathologic report and social anamnesis was ascertained.

2.4 Video-EEG Monitoring

All patients received video-EEG monitoring as part of their pre-surgical evaluation to investigate the localization of interictal epileptic discharges and seizure onset. In 127 cases, additional sphenoidal electrodes were used.

Epileptic seizure findings were classified according to Kellinghaus et al. (2006) until 2012, when a new classification by Lüders et al. was published in Epilepsia and then applied at the Epilepsy Center Hessen. Before 2006, the medical reports only described seizure semiologies in detail rather than classifying them. For the analysis, the recorded findings and semiology descriptions were transformed to be consistent with the current classification standards suggested by Fisher et al. in the "Instruction manual for the ILAE 2017 operational classification of seizure types".

2.5 Magnetic Resonance Imaging

MRI was used to validate suspected diagnoses that resulted from the video-EEG findings in combination with the anamneses and, in some cases, noticeable cerebrospinal fluid values acquired during lumbar punches. An epilepsy protocol including T1-, T2-, fluid-attenuated inversion recovery-, and susceptibility-weighted imaging with angulation oriented along the hippocampal longitudinal axis was conducted to find possible structural lesions. It was also employed for the evaluation of surgery practicability and planning. Post-surgical MRI scans were not performed with the regularity of the other assessments but rather near-term to check on the success of the surgery in removing the epileptogenic tissue that was intended to be extracted and at individual points in time made necessary in particular by the persistence of seizures.

2.6 Neuropsychology

Neuropsychological testing included a wide range of tests, some of which were only performed within the scope of the pre-surgical examination. This was the case for intelligence tests and lateralization diagnostics. In order to make the results more easily comparable to other studies, the “Current standards of neuropsychological assessment in epilepsy surgery centers across Europe“ (Vogt et al., 2017) were considered during the selection of tests to be analyzed. This trans-European survey ascertained the different Wechsler Intelligence Scales to be the most frequently used among adults as well as children and adolescents. The non-verbal memory was assessed with the Rey-Osterrieth Complex Figure Test (ROCFT) (adults) by most epilepsy centers and therefore analyzed in this study. Further neuropsychological tests that were included because among the tests performed at the Epilepsy Center Hessen they were the most prevalent in Europe were the Verbaler Lern- und Merkfähigkeitstest (VLMT) for the verbal memory, the Visual Object and Space Perception Battery (VOSP), as well as the Regensburger Wortflüssigkeitstest (RWT) for attention and executive functions, Beck’s Depression Inventory (BDI) to assess mood, and finally the Quality of Life in Epilepsy Inventory (QOLIE).

For the analysis, particularly representative values of VLMT, ROCFT, VOSP, RWT, BDI, and QOLIE were chosen to illustrate patients’ neuropsychological capabilities.

2.6.1 <u>Intelligence</u>

Intelligence was tested using different German versions of the Wechsler Intelligence Scale. In detail, this meant the revised version of the Hamburger-Wechsler-Intelligenztests für Erwachsene (Hamburg Wechsler Intelligence Test for Adults) from 1991 to 2006, Wechsler-Intelligenztests für Erwachsene (Wechsler Intelligence Test for Adults) from 2006 to 2013, and Wechsler Adult Intelligence Scale since 2013 for adults. Children’s intelligence was assessed using Hamburger-Wechsler-Intelligenztests für Kinder (Hamburg Wechsler Intelligence Test for Children) until 2011 when the Wechsler Intelligence Scale for Children was established. Throughout the survey period and with changing clinic-internal methods, the Standard Progressive Matrices, Mehrfach-Wortschatz-Intelligenztest (Multiple Choice Vocabulary Intelligence Test), Culture Fair Intelligence Test, and a social estimation formula were used instead of or in addition to the tests mentioned above.

The Wechsler Intelligence Tests examined four different qualities: verbal comprehension, perceptual reasoning, working memory, and processing speed. Several subtests were implemented for this purpose. This included finding similarities and a vocabulary test for verbal comprehension as well as a mosaic and a matrix test for perceptual reasoning. Digit span and arithmetic thinking were tested to make a statement concerning the working memory, and a symbol- and a digit-symbol test were used to enquire patients' processing speeds (Jacobs & Petermann, 2007).

All the results of the respective intelligence test were summed up into one total IQ (TIQ) value for each patient, which was employed in the analysis.

2.6.2 Verbal Memory and Fluency

The German equivalent to the Rey Auditory Verbal Learning Test (RAVLT) is the VLMT for children and adults starting from the age of six years. With this test, verbal material of the declarative episodic memory could be examined by giving patients a list of 15 words that they had to learn and then reproduce after 30 minutes, as well as recognize from a list including the 15 words that were to be learned, 15 words from an interference list, and 20 distractors. Learning and reproduction were done in eight steps. The examiner read out the 15 words from the learning list, followed by a free reproduction of the patient. This was repeated five times. Patients then got to hear an interference list of 15 words that they also had to repeat. For step six, they then had to repeat the original learning list once again. After a delay of 30 minutes, the 15 words had to be reproduced freely (round seven). The eighth and final round was recognizing the original 15 words from a list that also included the interference words and 20 more distractors (Helmstaedter et al., 2001). For the analysis, the values of round seven (VLMT7), representing the free delayed recall, and the number of words recognized (VLMTR) were singled out to be most representative of the verbal declarative memory functions of consolidation and retrieval grounded in the mesial temporal lobe (Helmstaedter & Elger, 1998).

The lexical verbal fluency, short-term- and working memory, vigilance, inhibitory functions, and cognitive flexibility were examined using a subtest of the RWT (English version: Controlled Oral Word Association Test). As part of the assessment, tested persons were asked to produce as many words as possible starting with the letter "S" in one minute. Admissible answers were verbs, adjectives, and nouns. Perseverations, neologisms, names, and words with a stem equal to a word that had already been mentioned were counted as breaches. The total number of valid words was used to analyze patients operated on the dominant temporal lobe, where parts of these functions are based. In detail, these were priming, a feature of the non-declarative memory, hence located in the neocortex, and the semantic memory as a representative of the mesial temporal lobe (Aschenbrenner et al., 2001).

2.6.3 Figural Memory and Visuospatial Functioning

For the examination of the non-dominant side of the mesial temporal lobe, the ROCFT was performed. In this test, patients had to copy a figure consisting of 18 geometrically arranged pieces. A delay of 30 minutes followed. Patients then had to reproduce the figure for a second time corresponding to the free delayed recall in the VLMT, this time allowing a statement concerning the figural memory (Shin et al., 2006). The result of the delayed recall of the ROCFT was included in the analysis; a score of 36 points was the maximal possible achievement, two points for every correct piece of the figure.

Visual information processing was tested using the VOSP. In the subtest analyzed in this study, patients were asked to identify 30 silhouettes of objects and animals as a function of the ventral (occipito-temporal) pathway, thereby serving as a representative value for the temporal neocortex of the non-dominant hemisphere (Warrington & James, 1992).

2.6.4 Mood

The revised 1996 version of the BDI is a questionnaire containing 21 groups of statements aiming at detecting the extent of depressive thoughts. The questions concern sadness, pessimism, feelings of failure, loss of joy, feelings of guilt and punishment, self-rejection, self-blame, suicidal thoughts, crying, anxiety, loss of interests, abulia, worthlessness, loss of energy, change in sleeping habits, irritability, change in appetite, concentration difficulties, exhaustion, and loss of libido. Respondents could choose between answers that ranged from 0 “nothing has changed negatively compared to usual” to 3 “strong experienced negative change”. The higher the score of the BDI turned out to be, the more subjected a patient was to depression. With 14 to 19 total points, patients were considered to have mild depression, while scores from 29 to 63 implied severe depression (Beck et al., 1996).

2.6.5 Quality of Life

For the assessment of the subjective health-related quality of life, patients were asked to answer the questionnaire of QOLIE consisting of 31 questions, which were ascribed to the following six subgroups: overall quality of life, emotional well-being, energy or fatigue, cognitive functioning, medication effect, and social functioning (Vickrey et al. 1993). The total value that resulted from all these questions was evaluated in the analysis, with higher scores indicating a higher perceived quality of life.

2.6.6 Lateralization Diagnostics

As part of the pre-surgical assessment, patients were asked to complete the Edinburgh Handedness Inventory, composed of ten questions inquiring about the employment of either their left or right hand for everyday tasks (Oldfield, 1971). In addition to this, a functional Transcranial Doppler Sonography was performed to also monitor cerebral activation by measuring the blood flow velocity in both mid cerebral arteries during speech production. The results of these diagnostics were used for dividing patients into “operated on the speech-dominant side” and “operated on the non-dominant side” throughout the analysis. In patients operated on the dominant side, results of the VLMT and RWT were analyzed. Results of the ROCFT and VOSP were used to assess changes after surgery in the non-dominant hemisphere. BDI and QOLIE are independent of the side of surgery; hence they were analyzed before and after surgery on either side.

2.7 Covariates

By comparison with formerly used covariates in other publications, a group of variables was identified as possible covariates for the research questions at hand. These variables included the duration of epilepsy, the age at onset and at the time of surgery, the TIQ, the sex, the education divided dichotomously into people who received nine or fewer years of education and people who were educated for more than nine years, the exact location of the temporal lesion – dividing between mesial- and neocortical temporal or both, the history of febrile seizures, the current intake of AED’s divided into patients either taking or not taking any AED’s at follow-up examinations, the occurrence of GTCS, the post-surgical MRI with respect to remaining epileptogenic lesions, the current freedom from seizures, and finally the pre- and post-surgical EEG with respect to IED’s and focal slowing (cf. Table A8).

2.8 Seizure Outcome

Seizure outcome was measured with both the Engel- and ILAE seizure-outcome scales. The ILAE scale ranges from 1 “completely seizure-free; no auras” to 6 “more than 100% increase of baseline seizure days; ± auras” with 2 and 3 indicating a small number of seizures or auras per year, and 4 and 5 comparing the individual seizure frequency before and after surgery in percent of reduction or increase. The Engel classification consists of four categories from I “free of disabling seizures” to IV “no worthwhile improvement” with subclasses from A to D, again, higher numerals and letters indicating worse seizure outcomes (Wieser et al., 2001). ILAE outcomes of 1 and Engel outcomes from IA to ID were considered as freedom from seizures.

2.9 Statistical Analysis

Patients’ information was extracted from medical and neuropsychological reports and transferred to Excel 2010. The analyses were performed with IBM SPSS (Statistical Package for the Social Sciences) 26.0. By way of illustration, additional graphs were programmed using RStudio 1.2.1335 with R 3.6.1.

Normality was examined for all variables included in the analysis using the Kolmogorov-Smirnov test. For the exploration of demographic and clinical differences among the groups comparing SAH with ATL and HS with other pathologies, a Kruskal-Wallis H test was performed if a numerical variable was not normally distributed. In the case of normal distribution, an analysis of variance (ANOVA) was done. Non-parametric variables were examined by using the Chi-square test of independence.

In order to compare the post-surgical neuropsychological results with the baseline values without generating discrepancies by means of consistently high or low test results, each baseline value was subtracted from the corresponding follow-up results, indicated by the character “Δ”. Consequently, the follow-up data did not display a raw value, but each patient’s change of performance in a test as compared to their pre-surgical performance. Hence, the baseline value would always be 0.

The adjusted data was searched for significant differences between the subgroups by applying an independent samples t-test to normally distributed variables and a Mann-Whitney U test to non-normally distributed or non-parametric data. Depending on normal distribution, possible covariates were identified by calculating correlations according to either Spearman or Pearson and subsequently ascertaining R^2 from linear regression. Finally, an analysis of covariance (ANCOVA) was conducted for each significant test variable and its correlating covariates.

The same procedure was used in the group comparing temporal pathologies for the analysis of the patients' pre-surgical test results.

3 RESULTS

3.1 Patient Characteristics

In total, 174 pre-surgically tested patients were included in the study. These patients were assigned to two groups depending on their types of surgery and seizure etiology. Of the 114 patients who received an SAH or ATL, 100 were found to have a verified diagnosis that qualified them also to be a part of the second group (*N* = 160) for the comparison of HS and other pathologies located in the temporal lobe. This left a number of 91 and 129 at the six-month, 97 and 131 at the one-year, 88 and 125 at the two-year, as well as 70 and 93 at the five-year follow-up for each the comparison of surgery types and epilepsy etiologies. Fifty-seven patients undergoing SAH or ATL showed up at all examinations, whereas in the group comparing HS and other temporal pathologies, this was the case for 74 people. The sample included 92 females and 82 males with an age median of 35 (*IQR* = 18) years. Four patients (2.3%) were younger than 18 years. Using a Kruskal-Wallis H test, it was found that the median duration of epilepsy was 13 (*IQR* = 21) years, with a significant difference ($p < .001$) among patients with HS (*Mdn* = 20.5, *IQR* = 24 years) as compared to patients with other pathologies (*Mdn* = 6.5, *IQR* = 16 years).

Of the 114 patients in the SAH/ATL-group, 95 were questioned about possible risk factors. It showed that 41.3% (*N* = 26) of the SAH patients had zero risk factors. In the ATL subgroup, there have been 37.5% of patients (*N* = 12) registered as free of risk factors. One risk factor was found among 39.7% of SAH patients (*N* = 25). This was also the case for 40.6% of ATL patients (*N* = 13). Two risk factors could be found in 15.9% of SAH patients (*N* = 10) and 21.9% of ATL patients (*N* = 7). Finally, there were 3.2% of SAH patients (*N* = 2) who had three risk factors. A χ^2-test of independence found that the number of risk factors did not significantly differ among the two subgroups ($p = .68$). In the SAH subgroup, the most frequently reported risk factors after febrile seizures were positive family history, a concussion, and an undergone infection of the CNS, each with 14.3% (*N* = 9). Positive family history was the most common risk factor in the subgroup of ATL patients with 24.2% (*N* = 8). A χ^2-test of independence showed a significant difference between the two subgroups concerning post-ischemic lesions ($p = .01$), ATL patients having suffered from ischemia more often.

In the HS/other-group, 139 of the 160 patients provided details on their risk factors. The HS-subgroup included 30.9% ($N = 21$) patients with zero risk factors, 47.1% ($N = 32$) with one, 19.1% ($N = 13$) with two, and 2.9% ($N = 2$) with three. By comparison, 60.6% ($N = 43$) of patients of the subgroup with other pathologies didn't have any risk factors, 32.4% ($N = 23$) had one, 5.6% ($N = 4$) had two, and 1.4% ($N = 1$) had three. This difference was significant ($p = .003$). The most common risk factor among patients with HS was febrile seizures followed by a positive family history ($N = 12$, 17.6%) and a past CNS infection ($N = 11$, 16.2%). Patients with other pathologies were found to have a positive family history most frequently ($N = 9$, 12.5%) followed by a concussion ($N = 7$, 9.9%).

Regarding the use of AED's, there could not be seen any significant pre-surgical differences in the group comparing surgery types ($N = 105$, $p = .37$). Most SAH patients ($N = 39$, 56.5%) took two AED's, 21.7% ($N = 15$) took one, and 21.7% ($N = 15$) took more than two AED's. In the subgroup of ATL patients 47.2% ($N = 18$) used two AED's, 33.3% ($N = 12$) used one, and 19.4% ($N = 7$) used more than two. At the five-year follow-up, the percentage of people taking more than two AED's shrank to 6.7% ($N = 3$) in the SAH and to 4.0% ($N = 1$) in the ATL sample ($p = .47$).

When comparing the use of AED's among different seizure etiologies, there could be found a significant difference between HS patients and patients with other pathologies ($p = .008$). Pre-surgically, there were 54.1% ($N = 40$) of HS patients who used two AED's at this moment, 25.7% ($N = 19$) who used more than two, and 20.3% ($N = 15$) who used one. Of the patients with other pathologies 35.4% ($N = 28$) took two AED's, 13.9% ($N = 11$) took more, and 50.7% ($N = 40$) took one AED. There remained a significant difference between the two subgroups at the six-month- ($p = .006$), one-year- ($p < .001$), and two-year follow-ups ($p < .001$) with HS patients taking a larger number of AED's on average. At the five-year follow-up, there remained 47.1% ($N = 24$) of patients in the HS and 23.8% ($N = 10$) in the subgroup of other pathologies, who took two AED's, 47.1% ($N = 14$) HS patients and 73.8% ($N = 31$) of the others, who took less than two AED's, as well as 5.9% ($N = 3$) of HS patients and 2.4% ($N = 1$) of the others, who still used more than two AED's ($p = .09$).

An ANOVA showed that there was no significant difference in the total IQ between patients who underwent an SAH ($N = 64$, $M = 86.78$) and those who underwent an ATL ($N = 34$, $M = 87.53$) ($p = .86$).

However, in the group comparing seizure etiologies, it was found that patients with HS had a significantly lower IQ (*N* = 67, *M* = 86.69) than patients with other pathologies (*N* = 72, *M* = 95.47) ($p = .008$).

Concerning the side of surgery, there were 51.9% (*N* = 40) of SAH- and 54.1% (*N* = 20) of ATL-patients operated in the speech-dominant hemisphere as well as 48.1% (*N* = 37) of SAH- and 45.9% (*N* = 17) of ATL-patients who underwent surgery on the non-dominant side ($p = .83$).

In the group of different pathologies, 53.2% (*N* = 42) of HS patients and 54.3% (*N* = 44) of the patients with other seizure etiologies had a lesion in the speech-dominant hemisphere. The non-dominant side was affected among 46.8% (*N* = 37) of patients with HS and 45.7% (*N* = 37) of patients with other types of lesions ($p = .88$).

Additional patient characteristics are provided in Tables 1 and 2.

Table 1. Socio-demographic and clinical factors of group SAH versus ATL.

SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy, GTCS generalized tonic-clonic seizure.
[a] Kruskal-Wallis H test ($\alpha = .05$).
[b] ANOVA ($\alpha = .05$).
[c] χ^2-test of independence ($\alpha = .05$).

Demographic	Subgroup		
	SAH	ATL	*p*-value
	N *Mdn* (*IQR*)	*N* *Mdn* (*IQR*)	
Age at onset[a] (years)	67 14 (21)	33 18 (14)	.19
Age on surgery[a] (years)	77 39 (19)	37 32 (20)	.03
	N *M* (*SD*)	*N* *M* (*SD*)	
Total IQ[b]	64 86.78 (17.14)	34 87.53 (25.38)	.86
	N (*%*)	*N* (*%*)	
Sex[c]			.19
Female	40 (51.9)	24 (64.9)	
Male	37 (48.1)	13 (35.1)	
Affected hemisphere[c]			.83
Speech-dominant	40 (51.9)	20 (54.1)	
Non-dominant	37 (48.1)	17 (45.9)	
Education[c]			.04
≤ 9 years	41 (55.4)	13 (35.1)	
> 9 years	33 (44.6)	24 (64.9)	
Location of lesion[c]			.01
Mesiotemporal	53 (88.3)	16 (61.5)	
Neocortical temporal	5 (8.3)	5 (19.2)	
Mesial & neocortical	2 (3.3)	5 (19.2)	
Febrile seizures[c]			.38
Yes	17 (27.0)	6 (81.2)	
No	46 (73.0)	26 (18.8)	
GTCS[c]			.12
Yes	47 (69.1)	30 (83.3)	
No	21 (30.9)	6 (16.7)	

Table 2. Socio-demographic and clinical factors of group HS versus others.

SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy, HS hippocampal sclerosis, GTCS generalized tonic-clonic seizure, SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy.
[a] Kruskal-Wallis H test ($\alpha = .05$).
[b] ANOVA ($\alpha = .05$).
[c] χ^2-test of independence ($\alpha = .05$).

Demographic	Subgroup		
	HS	Other	*p*-value
	N *Mdn* (*IQR*)	*N* *Mdn* (*IQR*)	
Age at onset[a] (years)	70 13 (19)	76 23 (23)	< .001
Age on surgery[a] (years)	79 39 (20)	81 35 (19)	.24
	N *M* (*SD*)	*N* *M* (*SD*)	
Total IQ[b]	67 86.69 (21.98)	72 95.47 (16.58)	.008
	N (%)	*N* (%)	
Sex[c]			.63
Female	36 (45.6)	40 (49.4)	
Male	43 (54.4)	41 (50.6)	
Affected hemisphere[c]			.88
Speech-dominant	42 (53.2)	44 (54.3)	
Non-dominant	37 (46.8)	37 (45.7)	
Education[c]			.04
≤ 9 years	39 (50.0)	27 (33.8)	
> 9 years	39 (50.0)	53 (66.3)	
Location of lesion[c]			< .001
Mesiotemporal	59 (100.0)	17 (27.9)	
Neocortical temporal	0 (0)	39 (63.9)	
Mesial & neocortical	0 (0)	5 (8.2)	
Febrile seizures[c]			.001
Yes	20 (29.4)	5 (7.0)	
No	48 (70.6)	66 (93.0)	
GTCS[c]			.23
Yes	52 (71.2)	49 (62.0)	
No	21 (28.8)	30 (38.0)	
Type of surgery[c]			< .001
SAH	56 (70.9)	12 (14.8)	
ATL	21 (26.6)	11 (13.6)	
Other	2 (2.5)	58 (71.5)	

3.2 Video-EEG monitoring

Pre-surgically, IED's were detected in 96.9% (*N* = 63) of SAH and 94.6% (*N* = 35) of ATL patients (p = .30). In the second sample, the χ^2-test of independence showed that 97.1% (*N* = 67) of HS patients and 88.5% (*N* = 69) of the patients with other pathologies had IED's in their pre-surgical EEG's (p = .06).

In the subgroup of HS patients, which consisted of 79 patients, the most common semiology was focal motor seizures with impaired awareness (*N* = 59, 74.7%), 91.5% of which were automatisms. This was followed by auras (*N* = 56, 70.9%) with autonomic manifestations such as epigastric auras in 71.4% of the cases. Fifty-two patients (65.8%) experienced a generalization from either focal aware or with impaired awareness to bilateral tonic-clonic.

Among the 81 patients with seizure etiologies other than HS, non-motor seizures with preserved awareness were the most prevalent semiology (*N* = 57, 70.4%), with sensory auras as the most frequent ones (40.4%). Forty (49.4%) had focal non-motor seizures with impaired awareness, which either meant behavioral arrest or aphasic seizures. Automatisms or tonic seizures with impaired awareness were found in 46.9% (*N* = 38) of patients. Focal to bilateral tonic-clonic seizures were displayed by 60.5% (*N* = 49) of patients.

Two patients of the total sample were assumed to have experienced psychogenic non-epileptic seizures in addition to their epileptic ones.

A χ^2-test of independence showed that of the patients who received an SAH 26.4% (*N* = 19) still had IED's in the post-surgical EEG, whereas this was the case for 16.7% (*N* = 6) with an ATL (p = .44). Twenty-four percent (*N* = 18) of HS patients and 23.1% (*N* = 18) of patients with other pathologies also presented IED's post-surgically (p = .99).

3.3 Magnetic Resonance Imaging

Of the 174 patients in the sample, the MRI results of 90.8% (*N* = 158) could be ascertained. An epileptogenic lesion was found in 86.2% (*N* = 150) of them. The different seizure etiologies of the two subgroups comparing SAH and ATL (p = .84) and of the subgroup of patients with other pathologies are shown in Tables 3 and 4.

The post-surgical MRI showed remaining epileptogenic lesions in 24.4% (*N* = 11) of the SAH and 26.9% (*N* = 7) of the ATL patients (p = .82). In detail, these lesions were

14 HS's, two AVM's, one tumor, and one herniation. Sixty-six percent of them ($N = 12$) were located in the dominant hemisphere.

In the subgroup of HS patients 24.5% ($N = 13$) were left with an epileptogenic lesion after surgery as compared to 23.4% ($N = 15$) in the sample with other pathologies ($p = .89$). The epileptogenic lesion was not entirely removed in 13 patients with HS, seven with AVM's, six with tumors, one with a herniation, and one with a parenchymal defect. Of those lesions, 60.7% ($N = 17$) were located on the side of speech dominance.

Table 3. Seizure etiologies among group SAH versus ATL.

SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy, HS hippocampal sclerosis, AVM arteriovenous malformation.
[a] χ^2-test of independence ($\alpha = .05$).
[b] Descriptive statistics.

Seizure etiology	Subgroup		*p*-value[a]
	SAH	ATL	.08
	N (%)[b]	*N (%)*[b]	
HS	58 (75.3)	22 (59.5)	
Neoplasia	8 (10.4)	4 (10.8)	
AVM	1 (1.3)	2 (5.4)	
Dysplasia	1 (1.3)	4 (10.8)	
Parenchymal defect	1 (1.3)	2 (5.4)	
Autoinflammation	0 (0)	0 (0)	
Cyst	0 (0)	0 (0)	
Gliosis	1 (1.3)	0 (0)	
Unknown	7 (9.1)	3 (8.1)	

Table 4. Seizure etiologies among subgroup other pathologies.

HS hippocampal sclerosis, AVM arteriovenous malformation.
[a] Descriptive statistics.

Seizure etiology	Subgroup
	Other
	N (%)[a]
Neoplasia	35 (43.2)
AVM	26 (32.1)
Dysplasia	8 (9.9)
Parenchymal defect	6 (7.4)
Autoinflammation	3 (3.7)
Cyst	2 (2.5)
Gliosis	1 (1.2)
Unknown	0 (0)

3.4 Neuropsychological Outcomes in Patients with SAH versus ATL

3.4.1 Verbal Memory and Fluency

Without exception, patients who received an SAH in the dominant hemisphere showed a change in test performance either equally well or better than patients after an ATL on the dominant side at every follow-up examination. Regarding the trend of the test results, VLMT7 results deteriorated among patients in the ATL subgroup as they never reached their pre-surgical results at any point in time. The SAH sample showed a deterioration of test results only once at the two-year follow-up. VLMTR results of ATL patients worsened likewise after one and two years but reached their starting point after five years. SAH patients, in contrast, showed performance improvements after two and five years.

However, only three significant differences existed: At the two-year follow-up, ATL patients had a significantly worse change of performance as compared to the subgroup who received an SAH: In the VLMT7, the median for ATL patients was two words less than pre-surgically, whereas the number of words remembered was unchanged among SAH patients (Mann-Whitney $U = 87.0$, $r = -.512$, $N_{\mathrm{SAH}} = 26$, $N_{\mathrm{ATL}} = 17$, $p < .001$). The same could be observed for the VLMTR at this time: The ATL sample recognized a median of two words less and the SAH subgroup a median of one word more in relation to the pre-surgical results (Mann-Whitney $U = 104.5$, $r = -.443$, $N_{\mathrm{SAH}} = 26$, $N_{\mathrm{ATL}} = 17$, $p =$

.004). At the five-year follow-up, the 21 tested SAH patients recognized one word more than in the pre-surgical VLMTR and the ATL sample recognized as many words as pre-surgically (Mann-Whitney $U = 76.0$, $r = -.373$, $N_{SAH} = 21$, $N_{ATL} = 13$, p = .03) (cf. Table A2). The test variables with a significant result in a follow-up examination are depicted in Figures 1 and 2.

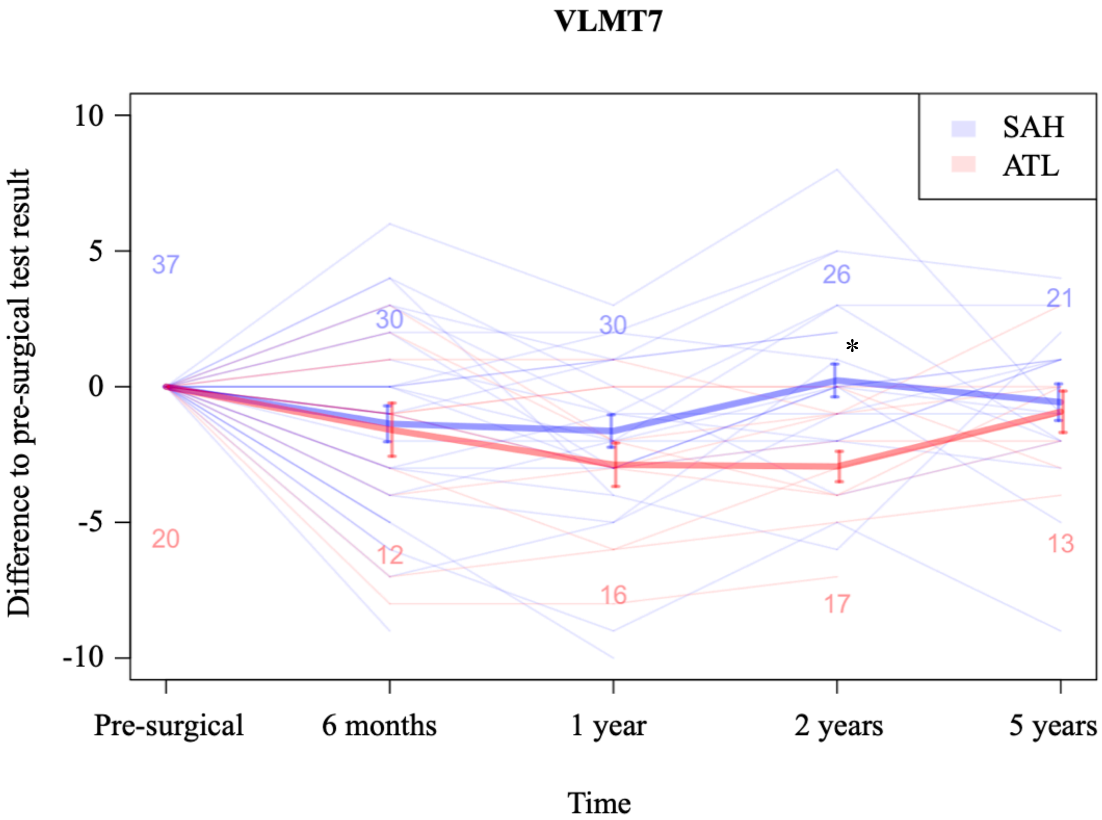

Figure 1. Spaghetti plot of the VLMT7 results by surgery
in the speech-dominant hemisphere at the pre-surgical testing and the six-month, one-year, two-year, and five-year follow-ups. The error bars show the standard errors of the means. The numbers above and below the bars represent the count of patients on each date.
VLMT7 Verbaler Lern- und Merkfähigkeitstest - Round 7, SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy.
* Significant difference ($\alpha < .05$).

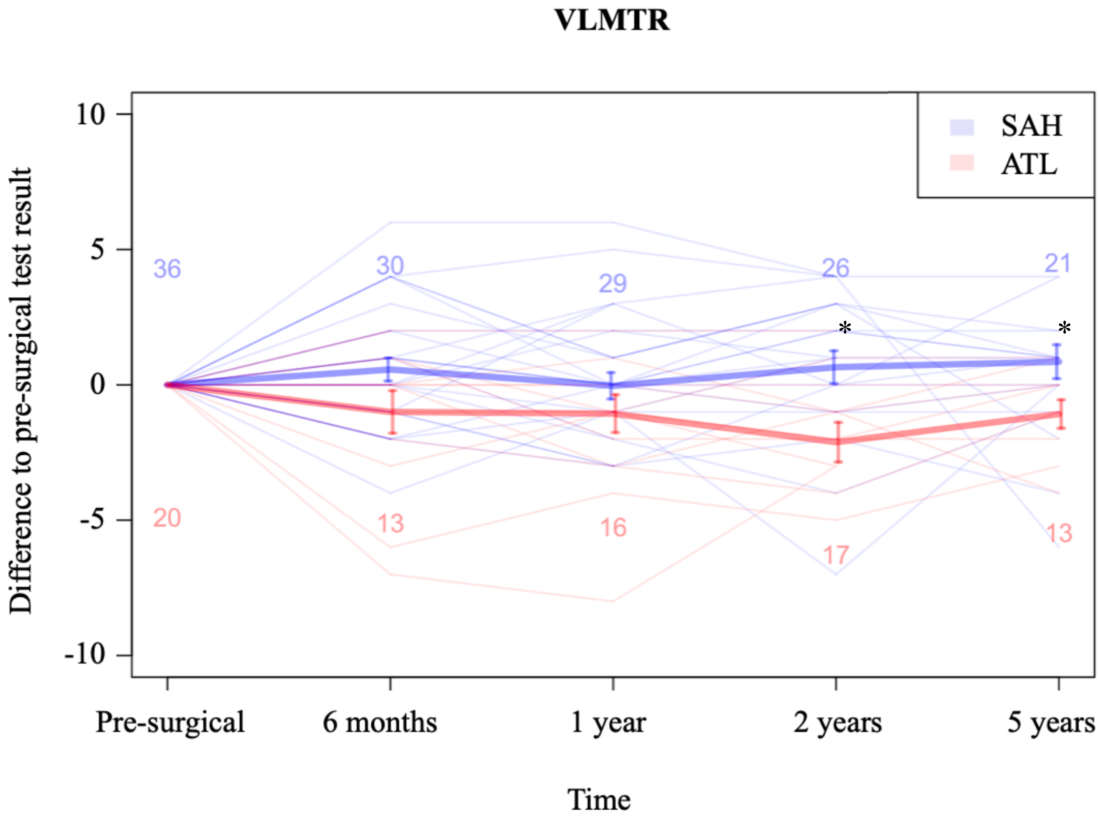

Figure 2. Spaghetti plot of the VLMTR results by surgery
in the speech-dominant hemisphere at the pre-surgical testing and the six-month, one-year, two-year, and five-year follow-ups. The error bars show the standard errors of the means. The numbers above and below the bars represent the count of patients on each date.
VLMTR Verbaler Lern- und Merkfähigkeitstest - Recognition, SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy.
* Significant difference ($\alpha < .05$).

At the two-year follow-up of the VLMT7, the post-surgical EEG was found to be a relevant covariate ($p = .04$, Spearman's $\rho = .309$, $R^2 = .125$), with the presence of focal slowing causing worse VLMT7 performances (cf. Tables A9, A10, and A15).

Subsequently, the first ANCOVA was performed with the independent variable being the type of operation, the dependent variable being the VLMT7 results of the two-year follow-up, and the post-surgery EEG as a covariate. Preliminary calculations showed no violations of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariates. After adjusting for the occurrence of IED's in the post-surgical EEG, there still was a significant difference between patients who received an SAH ($N = 26$, $M = .23$, $SD = 3.089$) and those who had an ATL ($N = 17$, $M = -2.94$, $SD = 2.304$, $p = .003$, $\eta p^2 = .206$) (cf. Table A18).

The RWT did not prove to be significantly different for the two types of surgery in the dominant hemisphere at any stage of the study. However, by means of descriptive statistics, patients always showed a better performance alteration if they received an SAH instead of an ATL. In the course of the follow-ups, patients' test results initially deteriorated but finally improved consistently compared to their pre-surgical results after one year for SAH patients and after five years for ATL patients (cf. Table A2).

3.4.2 Figural Memory and Visuospatial Functioning

Regarding the general tendencies, ROCFT results consistently improved for both types of surgery in the non-dominant hemisphere. However, the differences were not statistically significant. In the six-month, one-year, and two-year follow-ups, SAH patients showed a bigger, yet insignificant, improvement in performance than ATL patients. Five years after surgery, patients who had received an ATL did comparatively better.

The VOSP results showed an initial decline six months after SAH on the non-dominant side, which resolved after two years, while patients after ATL on this side continuously had better outcomes compared to their pre-surgical results and compared to SAH. It must yet be noted that none of these differences were of statistical significance (cf. Table A3).

3.4.3 Mood

Descriptively, BDI scores improved post-surgically among both subgroups but without significant differences. At the six-month and five-year follow-ups, ATL patients gained better outcomes in the BDI compared to SAH patients. One year and two years after surgery, SAH patients showed a comparatively higher outcome score. Medians and means varied between -1.41 and -4.37 points. Negative *Mdn*- and *M*-values indicate a better mood (cf. Table A4).

3.4.4 Quality of Life

The quality of life was not found to be significantly different at any point in time when comparing SAH and ATL. Descriptively, patients after ATL showed more considerable QOLIE improvements at the six-month, two-year, and five-year follow-ups compared to SAH patients. One year after surgery, SAH patients showed a comparatively greater outcome score. Means varied between 4.46 and 12.45 points (cf. Table A4).

3.5 Neuropsychological Outcomes of Patients with HS versus Other Pathologies

3.5.1 Verbal Memory and Fluency

The two examined VLMT values showed a *p*-value < .05 in the comparison of epilepsy etiologies at the pre-surgical testing in the speech-dominant hemisphere. HS patients reached a VLMT7 median of six words whereas patients with other pathologies remembered ten (Mann-Whitney $U = 435.0$, r = -.417, $N_{HS} = 40$, $N_{other} = 42$, $p < .001$). With HS as the pathology of the dominant hemisphere, people had a median of 12 recognized words in the VLMTR while the others had a median of 14 (Mann-Whitney $U = 566.0$, $r = -.256$, $N_{HS} = 39$, $N_{other} = 42$, $p = .02$). Figures 3 and 4 show these pre-surgical VLMT results.

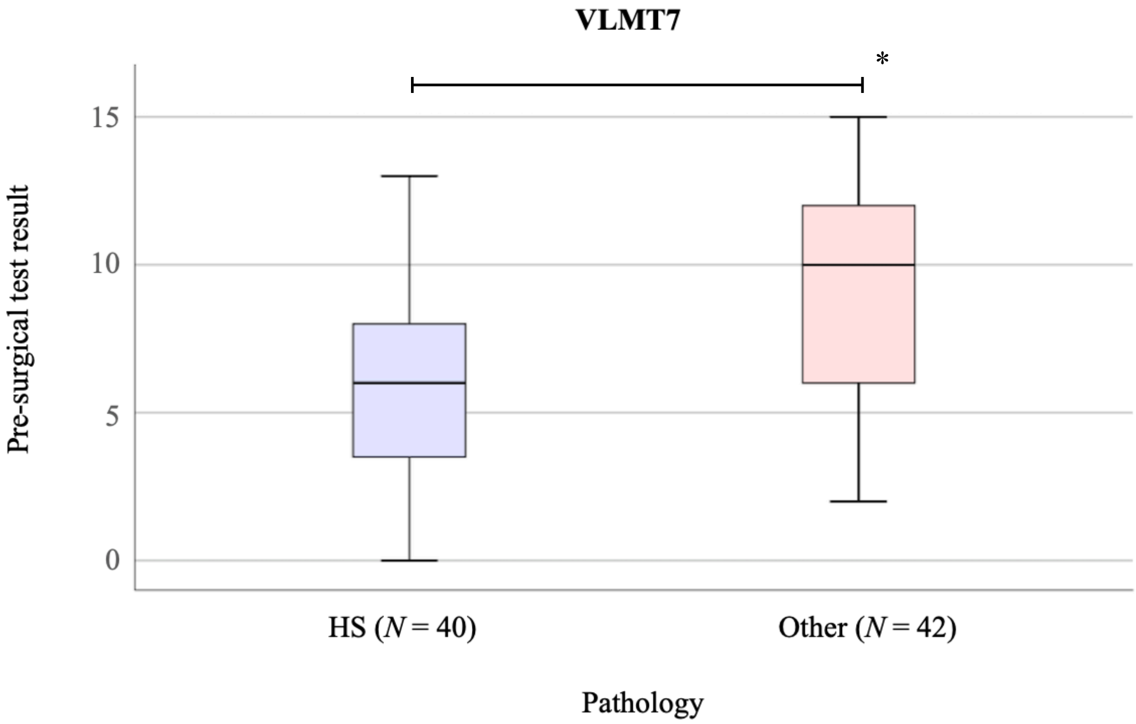

Figure 3. Box plot of the pre-surgical VLMT7 results by pathology in the speech-dominant hemisphere.
VLMT7 Verbaler Lern- und Merkfähigkeitstest - Round 7, HS hippocampal sclerosis.
* Significant difference ($\alpha < .05$).

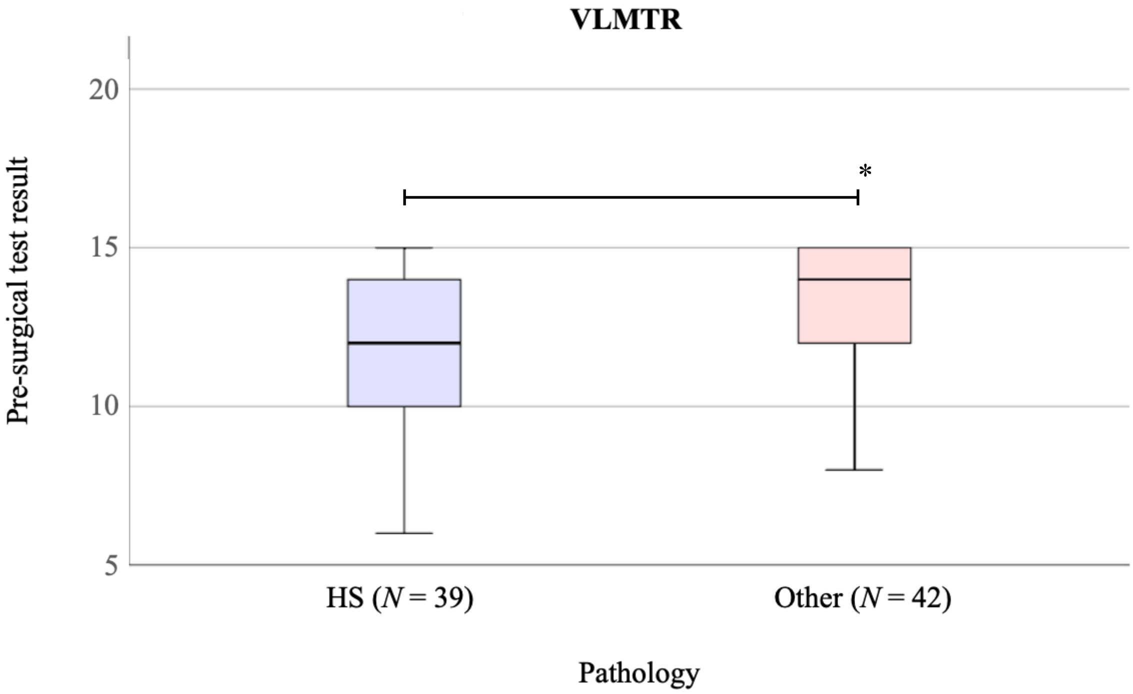

Figure 4. Box plot of the pre-surgical VLMTR results by pathology in the speech-dominant hemisphere.
VLMTR Verbaler Lern- und Merkfähigkeitstest - Recognition, HS hippocampal sclerosis.
* Significant difference ($\alpha < .05$).

However, after the operation, there could not be found any differences of significance in the comparison of the two subgroups' VLMT results. Concerning the general tendency, all VLMT7 performances deteriorated post-surgically; only the subgroup with other pathologies reached their pre-surgical baseline at the five-year follow-up. The outcomes of the post-surgical VLMTR did not differ from their starting points in either sample at any point in time (cf. Table A5).

Significantly correlating covariates of the pre-surgical VLMT7 were the age at surgery ($p = .001$, Pearson's $r = -.348$), older patients scoring fewer points, the total IQ ($p = .006$, Pearson's $r = .318$), a higher IQ leading to better results, the education level ($p = .001$, Spearman's $\rho = .376$), more than nine years of education influencing the outcome positively, and the locations of temporal lesions ($p = .02$, Spearman's $\rho = .280$), patients with mesial temporal lesions performing worse than those with neocortical temporal pathologies. This resulted in a total R^2 of .266 for all the covariates of the pre-surgical VLMT7. Correspondingly, significantly correlating covariates of the pre-surgical VLMTR are the age at surgery ($p = .03$, Pearson's $r = -.247$), the education level ($p =$

.02, Spearman's ρ = .267), and the locations of temporal lesions (p = .03, Spearman's ρ = .272) with a total R^2 of .131 (cf. Tables A11, A12, and A16).

For the first ANCOVA, the pathology represented the independent variable. Again, no assumptions were violated. With VLMT7 at the pre-surgical testing as the dependent variable and after adjusting for the age at surgery, the total IQ, the education level, and the mesial or neocortical location of lesions, there was no significant difference anymore.

In the next ANCOVA, preliminary calculations showed no violations of the assumptions of normality, linearity, homogeneity of regression slopes, and reliable measurement of the covariates. In the analysis with 34 HS patients and 32 others (total N = 66), the assumption of homogeneity of variances was violated (Levene's test for homogeneity of variances, p = .002). VLMTR was the dependent variable, and the age on surgery, the education level, and the location of temporal lesions were covariates. There was no significant result after adjusting for these covariates (cf. Table A19).

While HS and other temporal pathologies showed no significant difference in the pre-surgical RWT results – yet descriptively HS performing worse – patients operated upon an HS in the dominant hemisphere displayed significantly bigger improvements than did the subgroup of other pathologies at the one-year follow-up (Mann-Whitney U = 209.5, r = -.345, N_{HS} = 28, N_{other} = 25, Mdn_{HS} = 2, Mdn_{other} = -1, p = .01) (cf. Table A5). The trend of the RWT results showing no significant superiority of either sample except at the one-year follow-up can be seen in Figure 5.

At the one-year follow-up, age at epilepsy onset (p = .01, Pearson's r = -.343), younger patients having better results, as well as the history of febrile seizures (p = .02, Spearman's ρ = .327), febrile seizures being associated with better outcomes, were correlating covariates. The total R^2 was .151 (cf. Tables A11, A12, and A16).

The final ANCOVA was conducted with the pathology as the independent and the result of the RWT as the dependent variable. The age at epilepsy onset and the history of febrile seizures were used as covariates. There was no violation of assumptions. After adjusting for the age at onset and febrile seizures, there no longer was a significant difference between HS patients and patients with other seizure etiologies (cf. Table A19).

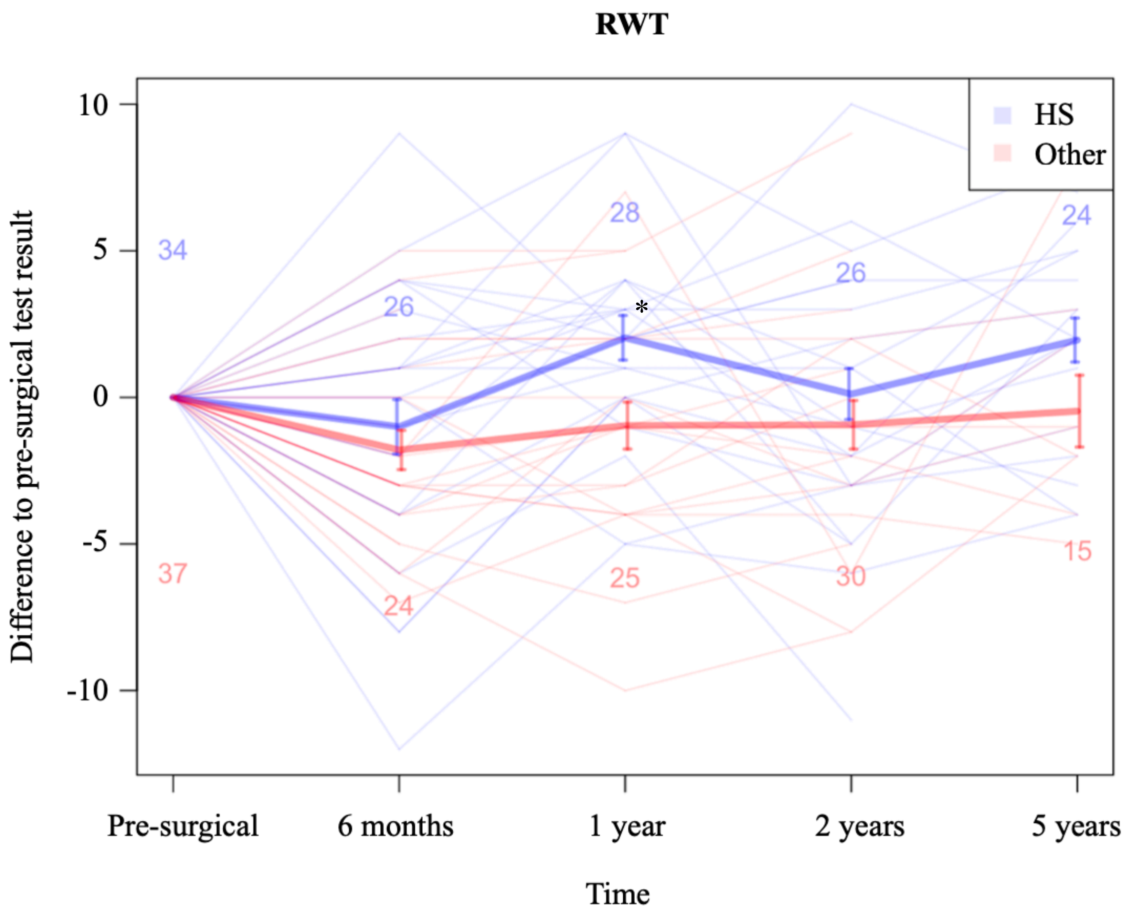

Figure 5. Spaghetti plot of the RWT results by pathology
in the speech-dominant hemisphere at the pre-surgical testing and the six-month, one-year, two-year, and five-year follow-ups. The error bars show the standard errors of the means. The numbers above and below the bars represent the count of patients on each date.
RWT Regensburger Wortflüssigkeitstest, HS hippocampal sclerosis.
* Significant difference ($\alpha < .05$).

3.5.2 Figural Memory and Visuospatial Functioning

Significant differences among the group HS versus other temporal pathologies in the non-dominant hemisphere could neither be seen in the ROCFT nor the VOSP. By means of descriptive statistics, HS patients scored lower in both the ROCFT and the VOSP than did the sample of patients with other seizure etiologies at the pre-surgical testing. Patients with HS, as well as patients with other temporal pathologies, performed non-significantly better in the post-surgical ROCFT as compared to before surgery. Correspondingly, VOSP results also improved in both subgroups throughout the follow-up period but always stayed non-significant (cf. Table A6).

3.5.3 Mood

During the pre-surgical testing, none of the subgroups were observed to be significantly more or less depressive as surveyed with the BDI. Scores consistently improved post-surgically among all patients. At the two-year follow-up, patients after HS operation had a mean result of -4.75 as compared to their pre-surgical details. Meanwhile, the sample that was operated upon other pathologies had a mean reduction of -1.12 in the independent samples t-test (Cohen's D = -.475, N_{HS} = 40, N_{other} = 51, SD_{HS} = 7.37, SD_{other} = 7.92, p = .03). More negative *Mdn*- and *M*-values indicate a better mood (cf. Table A7). Figure 6 shows the BDI results at the different follow-ups.

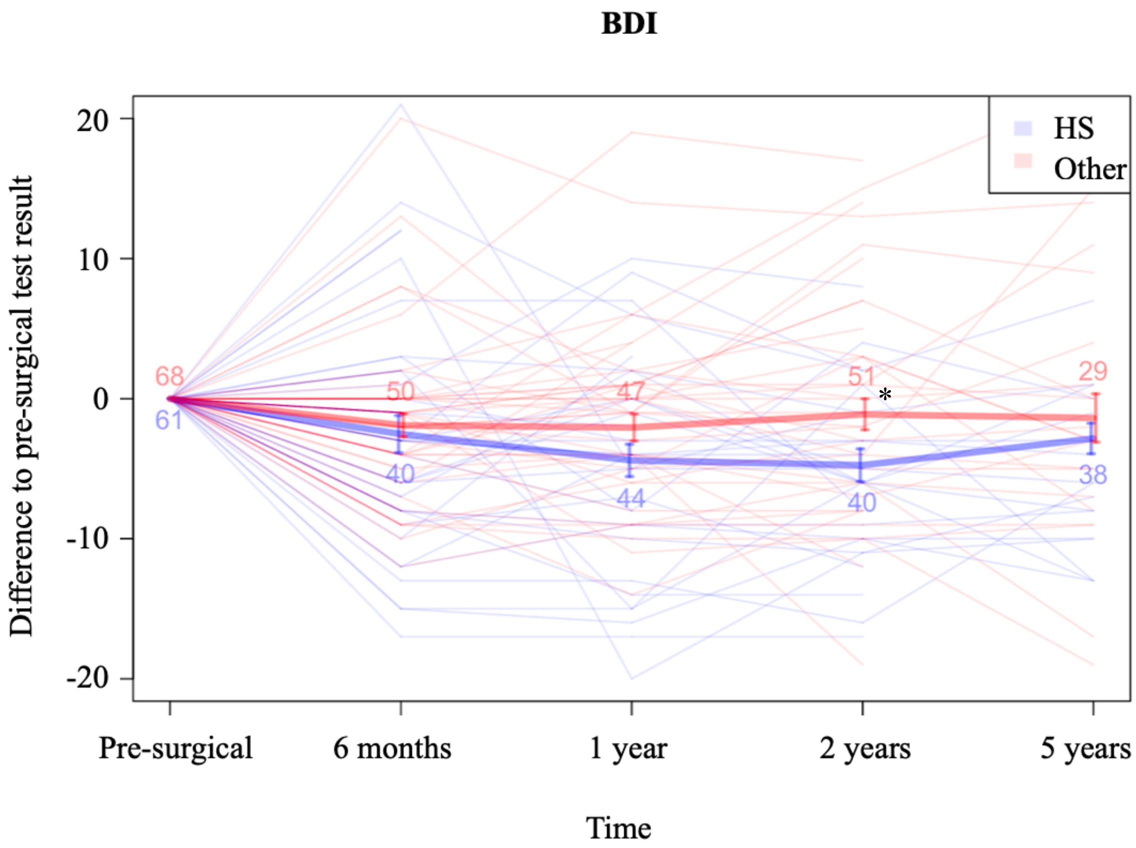

Figure 6. Spaghetti plot of the BDI results by pathology
at the pre-surgical testing and the six-month, one-year, two-year, and five-year follow-ups. The error bars show the standard errors of the means. The numbers above and below the bars represent the count of patients on each date.
BDI Beck's Depression Inventory, HS hippocampal sclerosis.
* Significant difference ($\alpha < .05$).

The Pearson's test showed that the age at onset (p = .003, Pearsons's r = .317) and the duration of epilepsy (p = .008, Pearsons's r = -.288) were significant covariates at the two-year follow-up and so was the pre-surgical occurrence of IED's in the EEG as proven by the Spearman's test (p = .03, Spearman's ρ = -.233) (total R^2 = .121). Younger age at onset, a longer duration of epilepsy, and the pre-surgical detection of IED's resulted in better post-surgical BDI outcomes (cf. Tables A13, A14, and A17).

A one-way ANCOVA was conducted with the independent variable being the epilepsy etiology and the BDI result of the two-year follow-up as the dependent variable. The covariates were the age at epilepsy onset, the duration of epilepsy, and the pre-surgical EEG. No assumptions were violated. After adjusting for the covariates, there could not be seen a significant difference between people who were operated on an HS and patients operated on other pathologies found in the temporal lobe (cf. Table A20).

3.5.4 Quality of Life

The quality of life was not found to be significantly different at any point in time when comparing HS and other pathologies located in the temporal lobe. Pre-surgically, HS and other patients had the same number of points in the QOLIE. After surgery, HS patients gained more points in the six-month, two-year, and five-year follow-ups than patients with other pathologies, who did better after one year. Means varied between 5.0 and 13.18 (cf. Table A7).

3.6 Seizure Outcome

The seizure outcomes of patients were analyzed using descriptive statistics and are shown in Tables 5 and 6. At the 6-month follow-up, 88.3% (N = 53) of patients who underwent an SAH and 70.4% (N = 19) of post-ATL patients showed a result of Engel I, meaning they were free of disabling seizures. When applied to the six grades of the ILAE outcome scale, 65% (N = 39) of SAH and 51.9% (N = 14) of ATL patients could be labeled free of seizures, including auras (ILAE 1). Of patients with an HS, 81% (N = 50) displayed a surgery result of Engel I, and 57.1% (N = 36) reached an ILAE 1 outcome. By comparison, patients with pathologies other than HS had an Engel I outcome in 85.2% of cases (N = 52) and an ILAE score of 1 in 73.8% (N = 45) of observed cases in the 6-month follow-up. A decline in the percentage of patients reaching an Engel I or ILAE 1 result could be observed for all four subgroups over the course of follow-up examinations. With the exception of ATL patients at the one- and two-year follow-ups and patients with pathologies other than HS at the two-year follow-up, less than ten percent of patients' operations resulted in an outcome suggesting no worthwhile improvement

(Engel IV). Two participant s among the 174 included patients in this study came out with an increase of ≥ 100% in seizure frequency at the five-year follow-up. This was the case for one patient with neoplasia after an ATL and one patient with an AVM after its resection.

Table 5. Seizure outcome among group SAH versus ATL.

SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy, ILAE International League Against Epilepsy.
[a] Descriptive statistics.

Outcome Scale	Subgroup Follow-up							
	SAH				ATL			
	6 months	1 year	2 years	5 years	6 months	1 year	2 years	5 years
	N (%)[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]
Engel I	53 (88.3)	53 (84.1)	43 (81.1)	33 (82.5)	19 (70.4)	21 (70)	17 (56.7)	15 (60)
Engel II	2 (3.3)	4 (6.3)	5 (9.4)	5 (12.5)	4 (14.8)	5 (16.7)	8 (26.7)	3 (12)
Engel III	3 (5)	4 (6.3)	4 (7.5)	2 (5)	2 (7.4)	1 (3.3)	2 (6.7)	4 (16)
Engel IV	2 (3.3)	2 (3.2)	1 (1.9)	0 (0)	2 (7.4)	3 (10)	3 (10)	2 (8)
ILAE 1	39 (65)	40 (62.5)	33 (63.5)	19 (47.5)	14 (51.9)	14 (46.7)	13 (43.3)	11 (44)
ILAE 2	9 (15)	10 (15.6)	7 (13.5)	9 (22.5)	5 (18.5)	5 (16.7)	4 (13.3)	4 (16)
ILAE 3	7 (11.7)	8 (12.5)	8 (15.4)	9 (22.5)	3 (11.1)	2 (6.7)	5 (16.7)	2 (8)
ILAE 4	3 (5)	4 (6.3)	4 (7.7)	3 (7.5)	3 (11.1)	5 (16.7)	5 (16.7)	5 (20)
ILAE 5	2 (3.3)	2 (3.1)	0 (0)	0 (0)	2 (7.4)	4 (13.3)	3 (10)	2 (8)
ILAE 6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)

Table 6. Seizure outcome among group HS versus other pathologies.

HS hippocampal sclerosis, ILAE International League Against Epilepsy.
[a] Descriptive statistics.

Outcome Scale	Subgroup Follow-up							
	HS				Other			
	6 months	1 year	2 years	5 years	6 months	1 year	2 years	5 years
	N (%)[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]	*N (%)*[a]
Engel I	51 (81)	52 (80)	46 (78)	38 (80.9)	55 (88.7)	52 (85.2)	47 (75.8)	32 (78)
Engel II	4 (6.3)	5 (7.6)	7 (11.9)	4 (8.5)	4 (6.5)	3 (4.9)	5 (8.1)	3 (7.3)
Engel III	5 (7.9)	4 (6.2)	5 (8.5)	4 (8.5)	2 (3.2)	3 (4.9)	2 (3.2)	2 (4.9)
Engel IV	3 (4.8)	4 (6.2)	1 (1.7)	1 (2.1)	1 (1.6)	3 (4.9)	8 (12.9)	4 (9.8)
ILAE 1	36 (57.1)	38 (58.5)	34 (59.6)	23 (48.9)	45 (72.6)	45 (73.8)	43 (68.3)	23 (56.1)
ILAE 2	11 (17.5)	9 (13.8)	9 (15.8)	11 (23.4)	5 (8.1)	7 (11.5)	2 (3.2)	6 (14.6)
ILAE 3	9 (14.3)	6 (9.2)	6 (10.5)	7 (14.9)	7 (11.3)	3 (4.9)	8 (12.7)	4 (9.8)
ILAE 4	5 (7.9)	6 (9.2)	7 (12.3)	5 (10.6)	2 (3.2)	3 (4.9)	2 (3.2)	3 (7.3)
ILAE 5	2 (3.2)	6 (9.2)	1 (1.8)	1 (2.1)	3 (4.8)	3 (4.9)	8 (12.7)	4 (9.8)
ILAE 6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)

4 DISCUSSION

This study examines two main topics: the comparison of SAH and ATL as well as HS and other temporal pathologies with respect to their neuropsychological performance, mood, and quality of life after surgery. In order to make a statement on the four respective hypotheses, the methods and results of the two research topics are hence discussed successively.

4.1 Selective Amygdalohippocampectomy versus Anterior Temporal Lobectomy

Ever since the development of SAH as a new surgical technique to treat mTLE, it has been discussed whether a smaller resection area is beneficial to neuropsychological outcomes and seizure control. As of today, the results are controversial, which corroborates the need for further study.

4.1.1 Patients

The sample for the comparison of surgical procedures consisted of 77 SAH and 37 ATL patients that did not significantly differ in their prescription of AED's, the number of risk factors, age at onset, TIQ, sex, affected hemisphere, the occurrence of GTCS, underlying pathologies, and prevalence of IED's in the pre- and post-surgical EEG's. However, the duration of epilepsy was longer among SAH patients; they had a significantly lower education status and more often displayed a mesial temporal lesion. This corresponds with the MRI findings that showed relatively more HS lesions in this subgroup, which are associated with a longer duration of epilepsy that affects the mental status negatively (Marques et al., 2007). In the past, studies proceeded differently concerning the inclusion of different pathologies in their evaluation of surgical techniques. They either investigated the effects of surgery on HS exclusively (Foged et al., 2018; Morino et al., 2006) or – like this study – made a statement on surgery for TLE more generally, yet excluding dual pathologies (Nascimento et al., 2015; Clusmann et al., 2002). Some limited the temporal lesions to only mesially located ones (Sagher et al., 2012), which was not done here. However, this was considered by checking for the exact temporal location as a covariate whenever results became significant.

Another relevant difference, which is crucial for the interpretation of results, is the definition of the side of surgery. While many differentiated between left- and right-sided operations, considering the left hemisphere the language-dominant one (Boucher et al., 2015; Tanriverdi et al., 2010), this has proven to be an inexact synonym. In a study by Helmstaedter et al. in 2004(a), “34% of men and 47% of women displayed patterns of atypical language dominance”, making a distinction between left and right obsolete. By means of pre-surgical lateralization diagnostics, this bias was averted, and subsequently, results became more reliable due to a classification of sides into language-dominant and non-dominant.

Finally, there exists a large disparity in follow-up intervals in the studies conducted so far. As neuropsychological outcomes vary with the time passing after surgery (Helmstaedter et al., 2003), it is essential to compare performances only at the same moment. Most publications coincided by analyzing at least the six-month (Boucher et al., 2015) or one-year (Tanriverdi et al., 2010) follow-up. After this point in time, methods diversified, and often, rather than contrasting fixed dates, only mean follow-up durations were provided (Mansouri et al., 2014; Clusmann et al., 2002). In this study, the four follow-up dates are precisely defined, resulting in increased accuracy, yet it must be noted that only half of the patients in this group showed up at every single follow-up examination.

4.1.2 <u>Verbal Memory and Fluency</u>

The comparison of neuropsychological outcomes between different studies is complicated because of the number of available testing methods. In consequence, most meta-analyses confine themselves to seizure outcomes. For the best possible comparability, this study used the VLMT and RWT because these were the ones used at the Epilepsy Center Hessen that were most frequently referred to in Europe among the total of 168 available assessments (Vogt et al., 2017).

The significant results of the analyses comparing SAH and ATL confirm the first hypothesis that SAH patients have a better neuropsychological outcome than ATL patients after surgery on the side of speech dominance. However, this can only be said about two subtests of the VLMT at the two- and five-year follow-ups. There were no significant differences in the RWT. Nevertheless, the follow-up progress revealed a consistency of superior verbal memory and language fluency changes after SAH compared to ATL. Foged and colleagues (2018) correspond with this finding stating that SAH leads to significantly better verbal memory outcomes. Boucher et al. (2015) as well as Nascimento et al. (2015), and Mansouri et al. (2014), who used the English version of the VLMT (RAVLT), found a non-significant correlation between ATL and worse RAVLT performance. Wendling et al. (2013) were led to the same conclusion with their VLMT results, respectively. Sagher et al. (2012) found that SAH and ATL are equivalent concerning verbal memory. A 2013 meta-analysis restricted to the IQ results of four studies (Hu et al.) showed no superiority of SAH in the verbal IQ. Clusmann and colleagues (2002) stated that verbal memory, in general, deteriorated more than it improved after surgery; however, in the total neuropsychological performance, SAH led to significantly better results. In sum, research to date implies superiority of SAH concerning the neuropsychological outcome, which is in some cases significant. The results of this study fit in well with the available literature and, by means of a more consistent follow-up and precise definition of surgery sides, substantiate the validity of conclusions so far made. Many papers also analyzed the effects of surgery in the hemisphere opposite to speech dominance on verbal performance. Since the required data already exist, this can be a link for future research.

Concerning the second hypothesis about relevant covariates, only the post-surgical EEG could be found as a significant covariate in this group. Other than hypothesized, IED's did not have a significant influence, whereas focal slowing deteriorated the neuropsychological result with a large effect. This is a novel discovery for which two explanatory approaches exist. On the one hand, slowing can be generated simply by the resection of cerebral tissue. The correlation of slowing caused by resection and worse neuropsychological outcomes would hence support the advantage of more restricted surgical approaches like SAH. On the other hand, focal slowing can also be a sign of recurrent seizures (Schönherr et al., 2017), with persisting epilepsy causing worse performance in the VLMT. The fact that neither freedom from seizures nor occurrence of IED's correlated significantly with the test results makes the first explanatory model more likely.

4.1.3 Figural Memory and Visuospatial Functioning

There were no significant differences between SAH and ATL in the figural memory performance as tested with the ROCFT after surgery on the non-dominant side. On average, SAH patients showed slightly better improvements except after five years. Accordingly, visuospatial functioning assessed with the VOSP did not yield significant results either. Better performances were observed in the ATL sample. The first hypothesis can therefore not be confirmed for surgery in the hemisphere opposite to speech dominance.

These results reflect the prevalent study data. Other researchers could not detect a clear superiority of either surgical procedure in this cerebral hemisphere either (Boucher et al., 2015; Mansouri et al., 2014; Morino et al., 2006). However, studies that did not differentiate the side of surgery (Wendling et al., 2013) or tested visual performances after resections on the left side (Tanriverdi et al., 2010) found significantly better outcomes after SAH, which further supports the restriction of resection areas in the dominant hemisphere. In the future, analogous analyses can be conducted with the available data of patients in Marburg.

The validity of the second hypothesis was not investigated as there were no significant outcomes to correlate with the covariates on hand.

4.1.4 Mood and Quality of Life

Quality of life measured by the QOLIE was expected to improve with better neuropsychological performances after SAH, according to the first hypothesis. This could not be confirmed. QOLIE- and BDI scores reflected an enhanced quality of life and less depression after both types of surgery. Again, this averted the correlation of the covariates listed in the second hypothesis.

While freedom from seizures and, to a slightly lesser extent, neuropsychological outcomes are frequently investigated parameters, BDI and QOLIE are rarely considered for the recommendation of either surgery type. As far as is known, the present study is the first to include both questionnaires alongside the neuropsychological outcomes. This is of importance because patients' satisfaction with their test performances is dependent on their mood and hence the quality of life as the most comprehensive post-surgical parameter is contingent on both outcomes (Helmstaedter, 2004b). Wendling et al. (2013) coincided with the present results stating that neither type of surgery has a superior effect on the quality of life. Studies that exclusively addressed surgery outcomes in terms of patients' satisfaction found that seizure control, as well as interventions in the right hemisphere, significantly improved the psychological state (Iachinski et al., 2014; Cunha & Oliveira, 2010). Therefore, future research distinguishing between dominant and non-dominant hemispheric surgery in combination with the surgical procedure is sensible if sample sizes are large enough.

4.1.5 Seizure Outcome

This study was not designed to investigate the extent of seizure freedom after surgery for TLE. However, seizure control was considered a covariate for significant neuropsychological outcomes since persistent seizures are expected to deteriorate results (Tanriverdi et al., 2010). Consequently, the Engel and ILAE scales were applied by means of illustration. It was found that throughout the follow-up phase, SAH patients had a consistently higher percentage of seizure control than the ATL sample. This is contradictory to the existing literature, which either claims an equivalence of surgery types (Jain et al., 2018; Tanriverdi et al., 2008; Clusmann et al., 2002) or a superiority of ATL (Mohan et al., 2018; Josephson et al., 2013). An investigation of the significance of these results and their emergence is necessary.

4.2 Hippocampal Sclerosis versus Other Pathologies

Before surgery, it is important to discuss the advantages and drawbacks of temporal resections with patients. A few studies suggested a difference in neuropsychological performances for HS and temporal lesions other than that. However, as underlying pathologies are a very recent research topic (Helmstaedter & Witt, 2017), there is not a great multitude of studies, and the existing ones drew discordant conclusions. Often, HS was associated with worse pre-surgical test results and a bigger post-surgical improvement (Schoenberg et al., 2018; Witt et al., 2015). Sometimes though, researchers could not find a difference between HS and other pathologies (Rayner et al., 2019). This study was designed to investigate these differences along with further predictors of neuropsychology and quality of life to make a statement on the benefits of epilepsy surgery according to the underlying pathology.

4.2.1 Patients

First of all, it must be noted that while many of the patients examined in this section are also part of the sample contrasting the types of surgery, the two groups are not the same and hence must not be directly compared.

Seventy-nine HS patients and 81 persons with other temporal seizure etiologies were seen pre-surgically, but only 74 of them showed up for all four post-intervention follow-up examinations. Other pathologies included neoplasia, AVM, dysplasia, parenchymal defect, autoinflammation, cyst, and gliosis in decreasing order of prevalence. The samples did not significantly differ in their age on surgery, sex, affected hemisphere, or occurrence of GTCS and IED's in the pre- and post-surgical EEG. Significant disparities existed, with HS patients being younger at onset, having a worse TIQ and fewer years of education, lesions – by definition – only located in the mesial temporal lobe, SAH and ATL more commonly as the type of surgery, and a more frequent association with febrile seizures. These differences are not surprising as they have been described before (Asadi-Pooya et al., 2015). Furthermore, it was observed that patients with other pathologies were prescribed significantly fewer AED's compared to HS until the five-year follow-up.

Just like with the comparison of surgical procedures, literature varies concerning the definition of sides. Again, this study uses the accurate distinction between speech-dominant and non-dominant. As far as is known, it is the first to investigate the neuropsychological differences following surgery for different temporal pathologies that demonstrates the course of five years with defined follow-up dates.

4.2.2 Verbal Memory and Fluency

The third hypothesis stated that HS patients' pre-surgical neuropsychological performances are expected to be worse compared to patients with other pathologies. The results concerning the verbal memory confirmed this. The HS sample with lesions in the dominant hemisphere scored significantly fewer points in the VLMT7 and VLMTR. However, fluency, as tested with the RWT, did not yield a significant difference, but HS still led to worse results. These findings are in accordance with the literature to date (Witt et al., 2015). Only the most recent study by Rayner et al. (2019) contradicted this in claiming equivalence of HS and other pathologies. In the present analysis, there were found several further predictors of neuropsychological performances before surgery, which confirm the fourth hypothesis. Increasing age, decreasing TIQ, fewer years of education, and a mesial temporal location worsened verbal consolidation (VLMT7) results with a medium effect. Except for the TIQ, these parameters also had a small effect on the pre-surgical verbal recognition (VLMTR). This can be explained by the fact that HS patients had a significantly longer duration of epilepsy than the other subgroup, which leads to a deterioration of cognitive capabilities (Marques et al., 2007). While the duration of experienced seizures, again, proves to be an important factor in HS, it cannot be the only predictor of neuropsychological performance. This becomes clear when comparing the mean duration of 20 years of epilepsy in this study to a mean of 23 years in Rayner's study, where HS patients fared equally well compared to other pathologies, who had a mean of 13 years of epilepsy in both studies.

Post-surgically, the only significant difference was found in the RWT after one year, with the HS sample scoring more points than the others. Only considering the significant results of the language-dominant side, further parts of the third hypothesis can therefore be endorsed. Concerning the fourth hypothesis, the covariates that correlated significantly with a better outcome were young age at onset and a history of febrile seizures; again, these were HS-related parameters (Asadi-Pooya et al., 2015) and thus validated the hypothesis. What must still be considered are the different types of surgeries for the different lesions spread across the temporal lobe. A mesial temporal location of lesions did, however, not affect results significantly. Even if non-significant, the superiority of HS was consistent in the RWT. Non-significant yet, contradicting the expectations were the results of the VLMT. The consolidation (VLMT7) as a part of the verbal declarative memory worsened among all pathologies but less so for patients with seizure etiologies other than HS, who even regained their baseline after five years. However, this difference was insignificant. Looking at the post-surgical VLMTR scores, the resection did not have any positive or negative influence on the verbal recognition memory of either subgroup. An attempt at explaining the different outcomes concerning the RWT and VLMT could be the fact that the capabilities required for the VLMT are located in the mesial temporal lobe (Helmstaedter & Elger, 1998), while those for the RWT are more widespread (Aschenbrenner et al., 2001). The only study that also compared the RWT in its English version is Schoenberg et al. (2018). Their results are in accordance with this study. However, they also found a superiority of HS concerning RAVLT outcomes, and so did Witt et al. in 2015 with the VLMT. An essential difference is that they only considered patients with different degrees of HS and no other pathologies of the temporal lobe. Their results suggest superiority of distinct HS in verbal memory and fluency outcomes compared to low-grade HS. This study, however, found that the superiority of HS is only existent in verbal fluency once compared to other pathologies. A study designed like the present one with the consideration of different pathologies found a significant superiority of HS for properties of the dominant hemisphere, but they did not use the same testing instruments as deployed here (Shin et al., 2009). This implicates a high dependency of neuropsychological outcomes on the applied test, which reflects the findings of the present study. Finally, the post-surgical superiority of HS in verbal fluency can be explained by a reorganization of verbal capacities to areas not resected during surgery (Hamberger et al., 2007). However, this reorganization did not compensate for the deficiencies in the verbal consolidation conveyed exclusively by the mesial temporal lobe.

4.2.3 Figural Memory and Visuospatial Functioning

On the side opposite to speech dominance, the different pathologies did not have any disparities of significance concerning the neuropsychological performances. Hence, the third and fourth hypotheses were disproved in the non-dominant hemisphere. Kneebone et al. (2007) found a significant inferiority of HS patients in the pre-surgical ROCFT, but again only in comparison to HS-negative individuals. This study is in line with Witt et al. (2015), who applied a different test for the functions of the non-dominant temporal lobe, and Shin et al. (2009), who used the ROCFT. Both did not find significant post-surgical differences either. Witt and his colleagues, therefore, concluded that an alternative neuropsychological assessment has to be found in order to determine the pathological status of the non-dominant hippocampus properly. On the other hand, the fact that HS patients' post-surgical ROCFT and VOSP scores fell short of the expectations could also be explained by the very recent discovery that right-sided HS leads to more extensive atrophy of the cerebral cortex due to a higher neuronal network integration of the right hippocampus compared to the left hippocampus (Mansouri et al., 2021). Especially with long durations of HS-related epilepsy, as present here, cortical atrophy is a conceivable cause of restrained neuropsychological outcomes in this patient sample and is worth further research.

4.2.4 Mood and Quality of Life

At the pre-surgical testing, BDI and QOLIE scores did not significantly differ. Surgery improved the mood and quality of life in both samples. Concerning the third hypothesis, patients with HS only had a significantly better mood at the two-year follow-up. As stated in the fourth hypothesis, this was associated with the pre-surgical finding of ED's and the HS-related parameters of young age at onset and a long duration of epilepsy. Interestingly, it did not correlate significantly with the freedom from seizures as was found by others (Helmstaedter et al., 2003). Otherwise, the results of this study coincide with Schoenberg et al. (2018), who also reported a post-surgical improvement of BDI scores; however, a significant superiority of HS as found here is new. Quality of life, which was not significantly influenced by the underlying pathology in this study, was associated with the freedom from seizures and the employment status by others (Alonso et al., 2009).

4.2.5 Seizure Outcome

Disparities in the different types of temporal epilepsy etiologies concerning the seizure outcome were not independently investigated in this study. However, they were considered as a covariate, and it was found that until the two-year follow-up, the sample with pathologies other than HS had a higher rate of seizure freedom, whose significance was, however, not tested. From then on and by means of descriptive statistics, the freedom from disabling seizures was higher in the HS sample, yet, the freedom from all types of seizures, including auras, stayed superior in the other subgroup. Moreover, while the seizure outcome highly depends on the timing of the follow-up, this long-term inferiority of HS was already described by Berkovic et al. in 1995.

4.3 Limitations

Even though the initial sizes of the groups were comparatively large, numbers subsided with time, and hence results became less conclusive with each follow-up. Furthermore, a wide range of underlying pathologies was considered for the comparison of surgery types. This was done to make a general statement on the superiority of either surgery independent of the type of lesion. However, it was found that the two procedures were performed on distinct types of underlying pathologies. The results reflect the clinical practice of using SAH preferably for HS, but this is why the outcomes of different surgical procedures cannot be seen entirely independent of the pathologies they are more commonly performed on. By analogy, the same must be noted for the comparison of seizure etiologies. Apart from the typical locations of different pathologies, whose relevance was analyzed by applying a covariate, there existed an inevitable disparity in conducted resection types. Likewise, this caused the outcomes to depend not only on the epileptogenic pathologies themselves but also on their respective types of surgery. Finally, there was no exclusion of patients with exceptionally low IQ's. While this enabled the study to make statements for a broader range of patients, it also possibly caused a certain floor effect. Therefore, a bias due to particularly low-scoring individuals with no option to further impair an already bad performance or with fewer resources for improvement must be considered.

4.4 Conclusion

The findings of this study are an addition to the ongoing discussion of the superiority of either SAH or ATL that has so far not yielded a clear statement. It was found that for surgery on the side of speech dominance, SAH is advantageous in terms of neuropsychological outcomes. However, this cannot be said about the opposite hemisphere, in which both surgical procedures are equal in their neuropsychological results. Concerning mood and subjective quality of life, neither type of surgery stands out. In sum, this study recommends an SAH for patients with lesions in the speech-dominant hemisphere, especially because a more restricted resection was not found to affect seizure control negatively.

By means of finding more individual pre-surgical risk-benefit evaluations, the comparison of different temporal pathologies with HS rendered a greater profit from surgery for HS patients on the side of speech dominance concerning the neuropsychological outcome. It was also discovered that the older HS patients were on their date of surgery, the worse their neuropsychological baseline performance was. This speaks in favor of earlier resections once an HS has been diagnosed. Concerning neuropsychological outcomes, patients with pathologies other than HS do not profit from surgery on the side of speech dominance. In the opposite hemisphere, however, all types of lesions were found to profit from resection. Furthermore, surgery improves mood and quality of life among all patients.

4.5 Outlook

The wide range of available neuropsychological tests makes direct comparisons between studies very difficult. This circumstance is aggravated by inconsistent wording, such as referring to “the language-dominant hemisphere” as “the left side”. For the future, it is therefore desirable to standardize the pre- and post-surgical test battery as well as the applied language so that multi-center studies and meta-analyses become more feasible. As done here, neuropsychological assessments for the temporal lobe should include at least one parameter for each the mesial and the neocortical lobe in both hemispheres, and following this, the effects on patients' quality of life should be reported more frequently. Once enhanced comparability allows for greater validity, randomized controlled trials will be justified.

5 SUMMARY

Objective: With the ongoing debate on the superiority of either anterior temporal lobectomy or selective amygdalohippocampectomy, this study aims at making recommendations in terms of neuropsychological- and quality of life outcomes. Furthermore, it intends to add to pre-surgical risk-benefit evaluations by analyzing the underlying epileptogenic pathologies.

Methods: One hundred and seventy-four patients from the Epilepsy Center Hessen, who were seen between 2001 and 2018, were retrospectively included in this study. One hundred and fourteen of them were part of the cohort comparing the types of surgery; 160 were diagnosed with hippocampal sclerosis or other temporal pathologies. Neuropsychological testing was performed pre-surgically as well as six months, one year, two years, and five years after surgery. The parameters considered were verbal memory and fluency for surgery in the dominant hemisphere and figural memory and visuospatial functioning for resection on the non-dominant side. Mood and quality of life were analyzed without differentiation of sides.

Results: Patients showed better performance changes after selective amygdalohippocampectomy than after anterior temporal lobectomy on the dominant side. The differences were, however, often just observed in descriptive statistics and not always significant. Neither surgery was superior concerning the properties of the non-dominant temporal lobe or in terms of mood and quality of life. Patients with hippocampal sclerosis showed a greater profit from dominant-sided resections than individuals with other pathologies. Pre-surgically, hippocampal sclerosis led to a significantly worse verbal memory, in particular, if patients were older. In the non-dominant hemisphere, neither pathology benefited significantly from surgery. Mood improved more among patients with hippocampal sclerosis than those with other pathologies.

Conclusion: While the extent and location of lesions, as well as seizure outcome, must also always be considered, in respect of neuropsychological outcomes, selective amygdalohippocampectomy should be the surgery of choice for patients with mesial temporal lobe epilepsy in the speech-dominant hemisphere. Patients with hippocampal sclerosis in this hemisphere can expect a greater profit from surgery than those with other pathologies. On the side opposite to speech dominance, neither type of surgery or seizure etiology is superior regarding neuropsychological outcomes.

6 ZUSAMMENFASSUNG

Zielsetzung: Angesichts der aktuellen Diskussion über die Bevorzugung der anterioren Temporallappenresektion oder der selektiven Amygdalohippokampektomie zielt diese Studie darauf ab, Empfehlungen in Bezug auf die neuropsychologischen Effekte und die Lebensqualität zu machen. Darüber hinaus soll durch die Analyse der zugrundeliegenden Pathologien die Nutzen-Risiko-Abwägung erleichtert werden.

Methoden: In die Studie wurden 174 Patientinnen und Patienten aus dem Epilepsiezentrum Hessen, die zwischen 2001 und 2018 untersucht wurden, eingeschlossen. Bezüglich der Operationsarten wurden 114 von ihnen verglichen. Bei 160 wurde eine Hippokampussklerose oder eine andere temporale Pathologie diagnostiziert. Neuropsychologische Tests wurden präoperativ sowie sechs Monate, ein Jahr, zwei Jahre und fünf Jahre nach der Operation durchgeführt. Es wurde das verbale Gedächtnis und die Wortflüssigkeit auf der dominanten Seite sowie das figurale Gedächtnis und die visuell-räumlichen Fähigkeiten auf der nicht-dominanten Seite analysiert. Stimmung und Lebensqualität wurden ohne Unterscheidung der Seiten ausgewertet.

Ergebnisse: Nach selektiver Amygdalohippokampektomie auf der dominanten Seite zeigten sich größere Leistungsverbesserungen als nach anteriorer Temporallappenresektion. In Bezug auf die Funktionen der nicht-dominanten Hemisphere, die Stimmung und die Lebensqualität war keines der beiden Verfahren überlegen. Personen mit Hippokampussklerose profitierten stärker von dominant-seitigen Resektionen als solche mit anderen Pathologien. Präoperativ war Hippokampussklerose mit einem schlechteren verbalen Gedächtnis assoziiert. Die Funktionen der nicht-dominanten Hemisphäre waren nicht signifikant unterschiedlich hinsichtlich der Läsionen. Hippokampussklerose war mit einer besseren Stimmung verbunden.

Schlussfolgerung: Im Hinblick auf die neuropsychologischen Auswirkungen ist die selektive Amygdalohippokampektomie die Operation der Wahl für Patientinnen und Patienten mit mesialer Temporallappenepilepsie in der sprachdominanten Hemisphäre. Personen mit einer Hippokampussklerose in dieser Hemisphäre können einen größeren Nutzen von der Operation erwarten als solche mit anderen Pathologien. Hinsichtlich der neuropsychlogischen Leistungen auf der nicht-dominanten Seite ist weder die Art der Operation noch die zugrundeliegende Pathologie ausschlaggebend. Nichtsdestotrotz muss vor Operationen immer auch Lokalisation und Ausdehnung von Läsionen sowie die erwartete Anfallsfreiheit miteinbezogen werden.

7 REFERENCES

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APPENDIX

Table A1. Kolmogorov-Smirnov test for normality of included metric variables.

TIQ total intelligence quotient, VLMT57 verbaler Lern- und Merkfähigkeitstest difference between rounds 5 and 7, VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest - Recognition, RWT Regensburger Wortflüssigkeitstest, ROCFT Rey-Osterrieth Complex Figure Test, VOSP Visual Object and Space Perception Battery, BDI Beck Depression Inventory, QOLIE Quality of Life in Epilepsy Inventory.
$p > .05$ indicates normal distribution (bold).

Variable	Pre-surgical		Δ 6 months		Δ 1 year		Δ 2 years		Δ 5 years	
	N	*p*	*N*	*p*	*N*	*p*	*N*	*p*	*N*	*p*
Age on surgery	174	.03								
Age at onset	158	.003								
Duration of epilepsy	158	< .001								
TIQ	152	**.20**								
VLMT7	167	.001	132	.001	135	< .001	132	< .001	92	.001
VLMTR	165	< .001	131	< .001	133	< .001	131	< .001	91	< .001
RWT	142	.01	107	**.20**	113	.05	108	.05	77	**.20**
ROCFT	163	.02	127	**.20**	130	**.20**	127	.02	90	**.20**
VOSP	156	.03	115	.004	119	< .001	113	.04	84	**.08**
BDI	141	< .001	99	< .001	101	**.06**	100	**.20**	71	**.07**
QOLIE	141	.02	103	**.09**	104	**.20**	99	**.20**	72	**.20**

Table A2. Outcomes after surgery on side of speech dominance.

VLMT57 verbaler Lern- und Merkfähigkeitstest difference between rounds 5 and 7, VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest - Recognition, RWT Regensburger Wortflüssigkeitstest, SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy.
[a] Mann-Whitney U test.
[b] Independent samples t-test.
Significance level α = .05, bold values indicate statistical significance.

Variable	Time	*p*	Subgroup	*N*	*Mdn*	*M*
VLMT7[a]	Δ 6 months	.91	SAH	30	-1	
			ATL	12	-1	
VLMT7[a]	Δ 1 year	.20	SAH	30	-1.5	
			ATL	16	-2.5	
VLMT7[a]	Δ 2 years	**.001**	SAH	26	0	
			ATL	17	-2	
VLMT7[a]	Δ 5 years	.43	SAH	21	-1	
			ATL	13	-1	
VLMTR[a]	Δ 6 months	.22	SAH	30	0	
			ATL	13	0	
VLMTR[a]	Δ 1 year	.30	SAH	29	0	
			ATL	16	-1	
VLMTR[a]	Δ 2 years	**.004**	SAH	26	1	
			ATL	17	-2	
VLMTR[a]	Δ 5 years	**.03**	SAH	21	1	
			ATL	13	0	
RWT[b]	Δ 6 months	.27	SAH	25		-.68
			ATL	10		-2.40
RWT[a]	Δ 1 year	.93	SAH	25	2	
			ATL	14	1.5	
RWT[a]	Δ 2 years	.50	SAH	22	1	
			ATL	15	-2	
RWT[b]	Δ 5 years	.28	SAH	17		2.29
			ATL	12		.58

Table A3. Outcomes after surgery on side opposite to speech dominance.

ROCFT Rey-Osterrieth Complex Figure Test, VOSP Visual Object and Space Perception Battery, SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy.
[a] Mann-Whitney U test.
[b] Independent samples t-test.
Significance level α = .05.

Variable	Time	*p*	Subgroup	*N*	*Mdn*	*M*
ROCFT[b]	Δ 6 months	.57	SAH	29		1.931
			ATL	13		1.000
ROCFT[b]	Δ 1 year	.60	SAH	32		3.281
			ATL	13		2.462
ROCFT[a]	Δ 2 years	.62	SAH	27	4	
			ATL	13	3.5	
ROCFT[b]	Δ 5 years	.54	SAH	21		2.405
			ATL	10		3.650
VOSP[a]	Δ 6 months	.11	SAH	24	-1	
			ATL	11	1	
VOSP[a]	Δ 1 year	.15	SAH	28	0	
			ATL	10	1.5	
VOSP[a]	Δ 2 years	.16	SAH	24	.5	
			ATL	9	2	
VOSP[b]	Δ 5 years	.84	SAH	19		1.53
			ATL	9		1.78

Table A4. Outcomes after surgery independent of side.

BDI Beck Depression Inventory, QOLIE Quality of Life in Epilepsy Inventory, SAH selective amygdalohippocampectomy, ATL anterior temporal lobectomy.
[a] Mann-Whitney U test.
[b] Independent samples t-test.
Significance level α = .05.

Variable	Time	*p*	Subgroup	*N*	*Mdn*	*M*
BDI[a]	Δ 6 months	.46	SAH	43	-2	
			ATL	18	-3.5	
BDI[b]	Δ 1 year	.29	SAH	45		-4.18
			ATL	19		-2.05
BDI[b]	Δ 2 years	.40	SAH	43		-4.05
			ATL	19		-2.37
BDI[b]	Δ 5 years	.16	SAH	34		-1.41
			ATL	19		-4.37
QOLIE[b]	Δ 6 months	.21	SAH	41		4.46
			ATL	21		9.52
QOLIE[b]	Δ 1 year	.78	SAH	45		8.42
			ATL	22		7.36
QOLIE[b]	Δ 2 years	.68	SAH	37		9.51
			ATL	21		11.19
QOLIE[b]	Δ 5 years	.64	SAH	31		10.42
			ATL	22		12.45

Table A5. Outcomes by pathology on side of speech dominance.

VLMT57 verbaler Lern- und Merkfähigkeitstest difference between rounds 5 and 7, VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest - Recognition, RWT Regensburger Wortflüssigkeitstest, HS hippocampal sclerosis.
[a] Mann-Whitney U test.
[b] Independent samples t-test.
Significance level α = .05, bold values indicate statistical significance.

Variable	Time	*p*	Subgroup	*N*	*Mdn*	*M*
VLMT7[a]	Pre-surgical	**< .001**	HS	40	6	
			Other	42	10	
VLMT7[a]	Δ 6 months	.40	HS	32	-1	
			Other	30	-1	
VLMT7[a]	Δ 1 year	.30	HS	33	-2	
			Other	29	-1	
VLMT7[a]	Δ 2 years	.34	HS	32	-1	
			Other	34	-1	
VLMT7[a]	Δ 5 years	.99	HS	28	-1	
			Other	17	0	
VLMTR[a]	Pre-surgical	**.02**	HS	39	12	
			Other	42	14	
VLMTR[a]	Δ 6 months	.93	HS	32	0	
			Other	30	0	
VLMTR[a]	Δ 1 year	.75	HS	32	0	
			Other	29	0	
VLMTR[a]	Δ 2 years	.50	HS	32	0	
			Other	34	0	
VLMTR[a]	Δ 5 years	.93	HS	28	0	
			Other	17	0	
RWT[a]	Pre-surgical	.10	HS	34	8.5	
			Other	37	11	
RWT[b]	Δ 6 months	.50	HS	26		-1.00
			Other	24		-1.79
RWT[a]	Δ 1 year	**.01**	HS	28	2	
			Other	25	-1	
RWT[a]	Δ 2 years	.32	HS	26	1	
			Other	30	-1.5	
RWT[b]	Δ 5 years	.08	HS	24		1.96
			Other	15		-.47

Table A6. Outcomes by pathology on side opposite to speech dominance.

ROCFT Rey-Osterrieth Complex Figure Test, VOSP Visual Object and Space Perception Battery, HS hippocampal sclerosis.
[a] Mann-Whitney U test.
[b] Independent samples t-test.
Significance level α = .05.

Variable	Time	*p*	Subgroup	*N*	*Mdn*	*M*
ROCFT[a]	Pre-surgical	.23	HS	35	13	
			Other	37	14	
ROCFT[b]	Δ 6 months	.40	HS	28		2.679
			Other	33		1.561
ROCFT[b]	Δ 1 year	.47	HS	32		2.828
			Other	27		1.963
ROCFT[a]	Δ 2 years	.62	HS	25	4	
			Other	30	3.75	
ROCFT[b]	Δ 5 years	.90	HS	20		2.675
			Other	23		3.000
VOSP[a]	Pre-surgical	.63	HS	30	20	
			Other	37	21	
VOSP[a]	Δ 6 months	.18	HS	21	0	
			Other	33	1	
VOSP[a]	Δ 1 year	.33	HS	25	0	
			Other	29	1	
VOSP[a]	Δ 2 years	.20	HS	19	1	
			Other	29	2	
VOSP[b]	Δ 5 years	.93	HS	16		2.06
			Other	24		1.96

Table A7. Outcomes by pathology independent of side.

BDI Beck Depression Inventory, QOLIE Quality of Life in Epilepsy Inventory, HS hippocampal sclerosis.
[a] Mann-Whitney U test.
[b] Independent samples t-test.
Significance level α = .05, bold values indicate statistical significance.

Variable	Time	*p*	Subgroup	*N*	*Mdn*	*M*
BDI[a]	Pre-surgical	.35	HS	61	9	
			Other	68	8.5	
BDI[a]	Δ 6 months	.50	HS	40	-3	
			Other	50	-1.5	
BDI[b]	Δ 1 year	.12	HS	44		-4.41
			Other	47		-2.06
BDI[b]	Δ 2 years	**.03**	HS	40		-4.75
			Other	51		-1.12
BDI[b]	Δ 5 years	.46	HS	38		-2.84
			Other	29		-1.38
QOLIE[b]	Pre-surgical	.68	HS	60		54
			Other	70		54
QOLIE[b]	Δ 6 months	.48	HS	41		6.98
			Other	53		5.00
QOLIE[b]	Δ 1 year	.85	HS	46		8.39
			Other	48		8.92
QOLIE[b]	Δ 2 years	.32	HS	38		11.87
			Other	53		9.00
QOLIE[b]	Δ 5 years	.32	HS	38		13.18
			Other	31		9.39

Table A8. Definition of covariates.

TIQ total intelligence quotient, GTCS generalized tonic-clonic seizure, AED anti-epileptic drug, IED interictal epileptiform discharge.
*At time of respective assessment.

Covariate	Definition
Age at onset	Continuous
Duration of epilepsy	Continuous
TIQ	Continuous
Sex	1 = male, 2 = female
Education	1 = ≤ 9 years, 2 = > 9 years
Location of lesion	1 = mesial & neocortical, 2 = mesiotemporal, 3 = neocortical temporal
Febrile seizures	0 = no, 1 = yes
GTCS	0 = no, 1 = yes
AED's*	0 = no use of AED's, 1 = use of AED's
Remaining MRI lesion	0 = none, 1 = remaining epileptogenic lesion
Freedom from seizures*	0 = persistent seizures, 1 = freedom from seizures
Pre-surgical EEG	0 = no pathological findings, 1 = focal slowing, 2 = IED's
Post-surgical EEG	0 = no pathological findings, 1 = focal slowing, 2 = IED's

Table A9. Covariates of surgery on side of speech dominance.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest - Recognition, TIQ total intelligence quotient, GTCS generalized tonic-clonic seizure, AED anti-epileptic drug.
a Pearson's correlation (*r*).
b Spearman's rank correlation (*ρ*)
*At time of respective assessment.
Significance level α = .05, bold values indicate statistical significance.

Covariate	Variable and time								
	VLMT7 Δ 2 years			VLMTR Δ 2 years			VLMTR Δ 5 years		
	p	*N*	*r*	*p*	*N*	*r*	*p*	*N*	*r*
Age at onset[a]	.85	39	-.030	.85	39	.031	.48	29	-.137
Age on surgery[a]	.16	43	.220	.62	43	-.078	.60	34	.093
Duration of epilepsy[a]	.27	39	.180	.78	39	-.046	.28	29	.206
TIQ[a]	.54	40	.100	.31	40	.164	.92	32	-.019
	p	*N*	*ρ*	*p*	*N*	*ρ*	*p*	*N*	*ρ*
Sex[b]	.29	43	.119	.56	43	-.092	.68	34	-.073
Education[b]	.36	43	-.142	.71	43	.059	.73	34	.061
Location of lesion[b]	.82	35	-.040	.67	35	.074	.76	28	.062
Febrile seizures[b]	.29	39	.173	.29	39	.175	.83	30	.042
GTCS[b]	.13	42	-.236	.38	42	-.140	.56	33	.105
AED[b]*	.13	43	.232	.94	43	-.012	.91	34	.019
Remaining MRI lesion[b]	.22	34	-.217	.91	34	-.019	.75	26	-.065
Freedom from seizures[b]*	.22	41	.197	.18	41	.212	.10	30	.309
Pre-surgical EEG[b]	.49	40	-.112	.73	40	.059	.44	31	.145
Post-surgical EEG[b]	**.04**	43	.309	.64	43	.074	.96	33	-.008

Table A10. Medians of Table A9.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, IED interical epileptiform discharge.

Variable and time	Covariate	*Mdn* (*N*)		
VLMT7 Δ 2 years	Post-surgical EEG	No pathological findings (0)	Focal slowing -1 (33)	IED's 0 (10)

Table A11. Covariates of pathology on side of speech dominance.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest delayed recall, RWT Regensburger Wortflüssigkeitstest, TIQ total intelligence quotient, GTCS generalized tonic-clonic seizure, AED anti-epileptic drug.
a Pearson's correlation (*r*).
b Spearman's rank correlation (*ρ*).
*At time of respective assessment.
Significance level α = .05, bold values indicate statistical significance.

Covariate	Variable and time								
	VLMT7 pre-surgical			VLMTR pre-surgical			RWT Δ 1 year		
	p	*N*	*r*	*p*	*N*	*r*	*p*	*N*	*r*
Age at onset[a]	.71	76	-.043	.23	75	-.141	**.01**	52	-.343
Age on surgery[a]	**.001**	82	-.348	**.03**	81	-.247	.12	53	-.223
Duration of epilepsy[a]	.15	76	-.279	.28	75	-.126	.28	52	.153
TIQ[a]	**.01**	72	.318	.13	72	.181	.54	48	-.092
	p	*N*	*ρ*	*p*	*N*	*ρ*	*p*	*N*	*ρ*
Sex[b]	.81	82	.027	.44	81	-.087	.83	53	.030
Education[b]	**.001**	82	.376	**.02**	81	.267	.57	53	-.079
Location of lesion[b]	**.02**	66	.280	**.03**	66	.272	.72	44	-.055
Febrile seizures[b]	.61	72	-.061	.82	72	-.028	**.02**	48	.327
GTCS[b]	.84	80	-.023	.39	80	.098	.31	53	.142
AED[b]*							.27	53	.156
Remaining MRI lesion[b]							.63	43	.076
Freedom from seizures[b]*							.98	52	.003
Pre-surgical EEG[b]	.49	77	-.080	.91	77	-.013	.08	52	.242
Post-surgical EEG[b]							.41	53	-.117

Table A12. Medians of Table A11.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest delayed recall, RWT Regensburger Wortflüssigkeitstest.

Variable and time	Covariate	*Mdn* (*N*)		
VLMT7 pre-surgical	Education	≤ 9 years	> 9 years	
		6 (41)	10 (41)	
	Location of lesion	Mesiotemporal	Neocortical temporal	Mesial & neocortical
		7 (37)	10 (21)	7.5 (8)
VLMTR pre-surgical	Education	≤ 9 years	> 9 years	
		12 (40)	14 (41)	
	Location of lesion	Mesiotemporal	Neocortical temporal	Mesial & neocortical
		13 (37)	14 (21)	12 (8)
RWT Δ 1 year	Febrile seizures	no	yes	
		0 (37)	3 (11)	

Table A13. Covariates of pathology independent of side.

BDI Beck Depression Inventory, TIQ total intelligence quotient, GTCS generalized tonic-clonic seizure, AED anti-epileptic drug.
a Pearson's correlation (*r*).
b Spearman's rank correlation (*ρ*).
*At time of respective assessment.
Significance level α = .05, bold values indicate statistical significance.

Covariate	Variable and time		
	BDI Δ 2 years		
	p	*N*	*r*
Age at onset[a]	**.003**	84	.317
Age on surgery[a]	.76	91	.033
Duration of epilepsy[a]	**.008**	84	-.288
TIQ[a]	.46	85	-.082
	p	*N*	*ρ*
Sex[b]	.80	91	.026
Education[b]	.59	91	-.058
Location of lesion[b]	.26	73	.134
Febrile seizures[b]	.88	82	.017
GTCS[b]	.15	88	-.155
AED[b]*	.33	91	.104
Remaining MRI lesion[b]	.42	78	.092
Freedom from seizures[b]*	.60	88	-.056
Pre-surgical EEG[b]	**.03**	85	-.233
Post-surgical EEG[b]	.78	91	-.029

Table A14. Medians of Table A13.

BDI Beck Depression Inventory, IED interictal epileptiform discharge.

Variable and time	Covariate	*Mdn* (*N*)		
BDI Δ 2 years	Pre-surgical EEG	No pathological findings	Focal slowing	IED's
		0 (3)	4 (4)	-3 (78)

Table A15. Linear regression of surgery on side of speech dominance.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7.
Significance level α = .05.

Variable and time	Covariate	*df*	*F*	*p*	R^2
VLMT7 Δ 2 years	Post-surgical EEG	1, 41	5.853	.02	.125

Table A16. Linear regression of pathology on side of speech dominance.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest - Recognition, RWT Regensburger Wortflüssigkeitstest, TIQ total intelligence quotient.
Significance level α = .05.

Variable and time	Covariates	*df*	*F*	*p*	R^2
VLMT7 pre-surgical	Age on surgery TIQ Education Location of lesion	4, 55	4.983	.002	.266
VLMTR pre-surgical	Age on surgery Education Location of lesion	3, 62	3.111	.03	.131
RWT Δ 1 year	Age at onset Febrile seizures	2, 45	4.011	.03	.151

Table A17. Linear regression of pathology on both sides.

BDI Beck Depression Inventory.
Significance level α = .05.

Variable and time	Covariates	*df*	*F*	*p*	R^2
BDI Δ 2 years	Age at onset Duration of epilepsy Pre-surgical EEG	3, 80	3.672	.02	.121

Table A18. One-way ANCOVA of surgery on side of speech dominance.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7.
Significance level α = .05, bold values indicate statistical significance.

Variable and time	Covariate	*N* (SAH, ATL)	*df*	*F*	*p*	η_p^2
VLMT7 Δ 2 years	Post-surgical EEG	26, 17	1, 40	10.393	**.003**	.206

Table A19. One-way ANCOVA of pathology on side of speech dominance.

VLMT7 verbaler Lern- und Merkfähigkeitstest round 7, VLMTR verbaler Lern- und Merkfähigkeitstest - Recognition, RWT Regensburger Wortflüssigkeitstest, TIQ total intelligence quotient.
* Levene's test with *p* = .002 indicating violation of homogeneity of variance.
Significance level α = .05, bold values indicate statistical significance.

Variable and time	Covariates	*N* (HS, Other)	*df*	*F*	*p*	η_p^2
VLMT7 pre-surgical	Age on surgery TIQ Education Location of lesion	32, 27	1, 53	4.080	**.048**	.071
VLMTR pre-surgical*	Age on surgery Education Location of lesion	34, 32	1, 61	.112	.74	.002
RWT Δ 1 year	Age at onset Febrile seizures	26, 21	1, 43	1.365	.25	.031

Table A20. One-way ANCOVA of pathology on both sides.

BDI Beck Depression Inventory.
Significance level α = .05.

Variable and time	Covariates	*N* (HS, Other)	*df*	*F*	*p*	η_p^2
BDI Δ 2 years	Age at onset Duration of epilepsy Pre-surgical EEG	33, 48	1, 76	1.608	.21	.021

Verzeichnis der akademischen Lehrenden

Meine akademischen Lehrenden waren die folgenden Damen und Herren Professorinnen und Professoren:

in Marburg: Bartsch, Becker, A., Becker, K., Becker, S., Bette, Bien, Boening, Cetin, Czubayko, Decher, Denkert, Dettmeyer, Eggers, Geraedts, Gress, Hofmann, Hertl, Hey, Hildebrandt, Hoyer, Kann, Kinscherf, Kircher, Kirschbaum, Knake, Köhler, König, Korte, Kruse, Lohoff, Mahnken, Maier, Moll, Nenadic, Neubauer, Nimsky, Oberwinkler, Oliver, Pagenstecher, Plant, Rastan, Reese, Renz, Richter, Roelcke, Ruchholz, Schäfer, Schieffer, Schneider, Schütz, Sekundo, Sommer, Stuck, Thieme, Timmermann, Timmesfeld, Vogelmeier, Wagner, Weihe, Wilhelm, Wulff.

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