Summary

Epilepsy surgery is a successful treatment option for pharmaco-resistant focal symptomatic epilepsies. However, cognitive impairments are very common in epilepsy patients and may be negatively or positively affected by surgery. In the long-standing discussion as to whether any surgical approach in temporal lobe epilepsy patients may be superior in regard to seizure control a recent meta-analysis votes for more extended resections. Larger temporal lobe resections, however, raise concerns that more unaffected and functional tissues may be involved, this causing worse cognitive outcome. This review collects published evidence collected over a long period along with changing diagnostics and surgical methods, focusing mainly on the experiences from one epilepsy center. The review highlights the effects of standard vs. selective surgery, the question of different selective surgical approaches in selective surgery, determinants other than surgery determining cognitive outcome, and the methodologically important question of outcome assessment and of how neuropsychological test selection may bias the result. Overall, from a neuropsychological point of view, there is a clear vote for individual and selective surgery which aims at seizure control while minimally affecting tissues or fiber tracts which are still functional. Cognition matters for everyday functioning and this should be kept in mind independent on which kind of surgery is preferred.

Key words: Temporal lobe epilepsy, cognition, epilepsy surgery, surgical approach

Conséquences cognitives des différentes voies d’abord chirurgicales dans l’épilepsie du lobe temporal

La chirurgie de l’épilepsie est une option thérapeutique très efficace pour les formes structurelles pharmaco-résistantes. Rappelons toutefois que les épilepsies s’accompagnent très souvent de déficits cognitifs sur lesquels une opération peut avoir des effets aussi bien positifs que négatifs. Concernant la question de la voie d’abord à choisir pour un meilleur contrôle des crises, des méta-analyses montrent que les résections

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plus étendues sont supérieures aux sélectives. Les résections étendues sont cependant associées à un plus grand risque d’ablation de tissus sains et encore fonctionnels, avec pour conséquence une aggravation proportionnelle du trouble cognitif. Ce passage en revue repose sur des publications parues sur une large période de temps avec des méthodes diagnostiques et chirurgicales changeantes, et se réfère en premier lieu aux expériences d’un seul centre de lutte contre l’épilepsie. Il compare les conséquences cognitives d’interventions standard et sélectives et tâche des différentes voies d’abord chirurgicales lors d’opérations sélectives, d’autres facteurs sans lien avec l’opération, mais déterminants pour l’évolution cognitive postopératoire, et de questions plus méthodologiques sur la façon de vérifier le succès d’une opération et sur l’influence que peut avoir le choix des instruments sur le résultat. En résumé, on préfère d’un point de vue neuropsychologique une voie d’abord chirurgicale individuelle et sélective qui vise la disparition des crises tout en préservant au maximum les tissus et voies nerveuses fonctionnels. La cognition est un élément clé de la fonctionnalité au quotidien, il faut en être bien conscient au moment du choix de la voie d’abord chirurgicale.

Mots clés : Epilepsie du lobe temporal, cognition, chirurgie de l’épilepsie, type d’opération, voie d’abord chirurgicale

The cognitive outcome of temporal lobe epilepsy surgery

Epilepsy surgery represents a very successful treatment option for patients with focal symptomatic epilepsies. Comparing surgical versus conservative medical treatment in 80 randomized patients with temporal lobe epilepsy, successful seizure control is achieved in 58% of operated versus 8% of medically treated patients in a twelve-month observation period [1]. This corresponds to what we found in our own non-randomized longitudinal 2 - 10 years follow-up study in 102 medically (12% seizure free) vs. 147 surgically (63% seizure free) treated patients with temporal lobe epilepsy (TLE) [2]. As a conclusion and without any further differentiation, about two thirds of the operated patients with TLE have the chance to become (permanently) seizure free [3].

Table 1: Cognition in TLE before and after surgery

<table>
<thead>
<tr>
<th>Domain</th>
<th>Preoperative impairments*</th>
<th>Postoperative changes (1 year)*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>L TLE (%)</td>
</tr>
<tr>
<td><strong>Verbal memory</strong></td>
<td>732</td>
<td>69</td>
</tr>
<tr>
<td><strong>Figural memory</strong></td>
<td>716</td>
<td>49</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>717</td>
<td>21</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>653</td>
<td>39</td>
</tr>
<tr>
<td><strong>Motor function</strong></td>
<td>717</td>
<td>30</td>
</tr>
<tr>
<td><strong>Visuo-construction</strong></td>
<td>602</td>
<td>19</td>
</tr>
<tr>
<td><strong>Vocabulary - IQ</strong></td>
<td>591</td>
<td>8</td>
</tr>
<tr>
<td><strong>Atypical language dominance (IAT)</strong></td>
<td>320</td>
<td>41</td>
</tr>
</tbody>
</table>

*a^2 (note that the table displays % but that statistics were calculated for patient numbers).
*bWilcoxon Signed Ranks Test.

IAT: Intracarotid Amobarbital Test; L TLE: left temporal lobe epilepsy; R TLE: right temporal lobe epilepsy.
*p<0.05; **p<0.01; ***p<0.001; downward arrow=significant loss (p<0.01); upward arrow=significant gain (p<0.01).
Seizure control is definitely the primary aim of epilepsy surgery. Successful seizure control understandingly reduces behavioural and mood problems and it improves overall quality of life. However, apart from seizure control, brain surgery can have negative effects on cognition and behaviour resulting in impairments which quantitatively and qualitatively exceed those seen before surgery [4].

Table 1 provides a comprehensive overview of how frequently cognitive deficits and postoperative performance changes have been seen in a large cohort of 732 patients with temporal lobe epilepsy operated in Bonn in the time between 1989 and 2007 [5]. According to categorical test results (0 - 4 points according to standard deviations: 0 = severely impaired to 4 = above average with “3” representing average performance) 78% of the patients with chronic pharmacoresistant TLE suffer from significant cognitive impairment (values < 2) in either verbal memory, figural memory, or attention/executive functions already before surgery. Corresponding to the localization of the epileptogenic focus in brain regions relevant for memory processing, the most commonly affected domains in TLE are verbal and figural memory, followed by problems in language, attention, motor and visuo-constructive functions. Consistent with the literature, lateralization-dependent results are evident in regard to more frequent verbal memory impairment and atypical language dominance in left sided TLE, and in regard to impairments in figural memory and attention in right sided TLE. In addition to lateralization, factors like the time of epilepsy onset (during brain maturation or after), presence vs. absence and the type of the underlying lesion (e.g. neoplastic vs. developmental), patient variables like age, gender, education and last but not least medication and seizure situation differentially contribute to the cognitive capabilities seen in the individual patient. One year after surgery 65% of the 732 patients were completely seizure free, i.e. they had no single seizure nor aura. Applying 90% reliability of change indices (RCI), individually significant gains and losses in the assessed domains were evident in between 10 - 40% of the patients. According to Table 1 major gains concern extratemporal non-memory functions. Losses are prominent in memory and here left temporal patients are more frequently affected than right temporal patients. Left temporal patients additionally worsen in regard to language functions which tend to improve after right sided surgery.

The findings in this large cohort of patients fit well with base rate estimates of expected gains and losses after temporal lobe surgery which have been published in a recent meta study on cognitive outcomes after TL surgery [6]. Summarizing 22 out of 193 evaluated studies which involved temporal lobe surgery and took RCI or standardized regression-based (SRB) change scores into consideration the pooled estimates of gains and losses for the assessed cognitive domains indicated a rate of 44% patients with verbal memory decline after left sided surgery as compared to 20% after right sided surgery. The gains for verbal memory were rare with 7% (left) versus 14% (right). Losses in figural memory were not different for left (15%) and right (10%) surgery. The total average rate of decline in language (naming) was 34%. As in the Bonn sample, benefits were found for executive functions after left surgery (loss 10%, gain 27%). The respective results for right sided surgery were 21% losses and 16% gains.

Summarizing the findings so far, TLE patients and those with left TLE in particular, bear an increased risk of cognitive decline in memory after temporal lobe surgery. In some patients improvement of cognitive functions is possible. The role of seizure control for the postoperative course of cognition is still a matter of debate. While Rebecca Rausch in her long term follow up study reported a progressive decline independent on seizure outcome, our own study indicated that further decline versus recovery depended on seizure control [2, 7]. Recent evidence from two other long term follow-up studies indicates a stable course of memory from two years after surgery [8, 9].

Determinants of cognitive outcome after surgery

Two major factors determine the cognitive outcome of epilepsy and its treatment. The first and probably most predictive factor is the “functionality” of the brain areas which are affected by epilepsy and which are going to be resected [10, 11]. Closely connected to the question of “functionality” is the second factor, which addresses brain areas and functions not affected by epilepsy or surgery and which is called the patient’s “mental reserve capacity” [12]. Dependent on the age of the patient, mental reserve capacities can help to compensate surgical defects. Functionality of the brain also appears to predict later seizure control [13]. Seizure control may be discussed as a third determinant of cognitive outcome. Here the principal idea is that of a release of functions due to control of epileptic dysfunction. However, up to now there is only sparse evidence from surgical studies which would support this assumption [2, 14].

Functional integrity of the affected and to-be-resected tissue and the reserve capacities are both reflected by baseline performance. Those with a better baseline performance are at greater risk to lose cognitive functions after surgery (functionality), but at the same time those with a better baseline performance will still have better performance after surgery than those with a poor baseline performance (reserve). This can be demonstrated by correlating the preoperative memory performance (total score: verbal + figural memory) of the large sample from Table 1 (left and right-sided TLE patients) a) absolute postoperative memory (r = 0.44, p = 0.000) and b) loss over time calculated as the difference between pre- and postsurgical
Both, functionality and reserve capacity depend on the patient's age at the time of surgery. The critical phases of cerebral functional plasticity are the times of language acquisition (until age 6), puberty (until age 15), and then the time around 30 years, when reserve capacities and capabilities for compensation start to decline with aging [12]. Methods to estimate functional integrity and reserve capacity in addition to neuropsychological assessment are intracranially recorded event related potentials or nonlinear EEG measures of complexity [15 - 17], structural and functional imaging techniques [18], angiography with intracarotid application of amobarbital, methohexital (brevital) or etomidate [19], and pre- or intra-operative electrocortical stimulation [20].

**Selective surgical approaches versus standard anterior temporal lobectomy**

The logical consequence from the previous section for epilepsy surgery is to remove what is necessary to control seizures, and to leave as much as possible functional tissue in order to preserve the patient's cognitive functions. According to a review on the quest of the optimal extent of resection in temporal lobe epilepsy dating back to 2008, no surgical approach seemed superior to others in regard to seizure control [21]. Six out of eight studies on selective surgery versus temporal lobe resections reported similar seizure outcomes, two reported better outcome with larger resection. This report has very recently been challenged by a meta study by Josephson et al. [22] who compared selective amygdalo-hippocampectomy and anterior temporal lobectomy across 15 studies and found an overall advantage of the larger resection in 13 studies (risk ratio 1.32, 95% confidence interval CI 1.12 - 1.57; p < 0.01). This study, however, did not address the question of whether one approach might be superior to the other in regard to cognitive outcome. According to the review by Schramm et al. 2008 [21] 11/14 studies reported that smaller as opposed to larger resections have a better cognitive outcome. Taking additionally the extent of the mesial resection into consideration 5/12 studies saw better seizure control with greater resections, 8/9 studies did not see a relation of the extent of the resection to neuropsychological outcome. A review provided in a study by Tanriverdi et al. in 2009 reported that 16/21 studies demonstrated better cognitive outcome after selective surgery as compared to 5/21 studies which showed no difference [14].

Within the recent 20 years surgery in temporal lobe epilepsy became increasingly selective since there were major improvements in high resolution structural and functional imaging with an increasing reliability of detecting subtle lesions like dysplasia or hippocampal sclerosis in mesial temporal lobe epilepsy (M-TLE). In its beginnings selective surgery depended on gross lesions and/or results from intracranial EEG recordings. In 1982, Wieser and Yasargil published a series of 27 patients (12 of them with mesial tumors, 13 with hints by stereo EEG, 2 with hints by surface EEG) which showed good seizure control, improved general intelligence and minor to no decline in verbal memory after selective amygdalo-hippocampectomy (SAH) as compared to large temporal lobe resections, which caused significant functional losses [23]. In 1993 Goldstein and Polkey reported that both surgical approaches cause similar decrease in delayed recall in logical memory but that ATL (anterior temporal lobectomy) in contrast to SAH produces more impairment in paired associate learning and immediate recall of visuo-spatial material [24]. A year before the same authors had made the observation that although traditional memory tests distinguished between selective surgery and en-bloc resections, memory measures more related to everyday behaviour (Rivermead Behavioural Memory Test) did not [25].

For a long period of time selective surgery was performed exclusively at a few centres, but even with standard 2/3 resections only, it was possible to demonstrate that restriction of the lateral extent of the resection (< 3cm) [26], consideration of cortical sites eloquent for language or memory [27], and the pathological status (presence/absence of hippocampal pathology) [28] are decisive determinants of memory decline after surgery. In an earlier retrospective study by Wolf et al. performed in 1993 no different memory outcomes (RAVLT, WMS) were found taking the extent of mesial (> < 2 cm) or lateral (> < 4cm) resection into consideration. Instead a later age at seizure onset was decisive for a worse outcome [29].

The earlier studies performed in patients undergoing standard ATL already gave implicit hints that variations of surgery within the language dominant lateral temporal neo-cortex affect learning capability rather than delayed recall and that with the memory measures in use (mainly RAVLT, CVLT and WMS) the patients language capabilities must be taken into consideration to understand the memory impairments seen in TLE [30] (see also the discussion in the paragraph “Living in different test universes”). In the Ojemann and Dodrill study from 1985 [27], 80% of the memory outcomes as assessed by WMS could be predicted from the relationship between the resection and sites essential for naming, encoding or memory storage as identified by electrical stimulation mapping. This close relation of verbal memory and language indicates that preoperative determination of language sites can be used to protect against losses in either function [31, 32].

Differential cognitive sequel of surgery in temporo-mesial and temporo-lateral structures on different aspects of verbal learning and memory have been demonstrated by a study which compared cortical lesionectomy in patients with cortical temporal lobe le-
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C. Helmstaedter

Sections with SAH or ATL in patients with AHS as the sole pathology [33, 34] (Figure 1). This study was performed at a time when in Bonn selective surgery had become a new treatment option in mesial TLE. This allowed for the retrospective comparison of a group of M-TLE patients who, according to the new treatment guideline, underwent left sided SAH to a group of M-TLE patients who, according to the old guideline, had received left sided ATL including amygdalo-hippocampectomy. The third group with neocortical temporal lobe lesions and circumscribed lesionectomy not affecting the mesial structures served as another control in order to contrast cortical lesionectomy to cortical resection of non-lesional tissue in ATL. Consistent with the presence of left temporal lobe epilepsy, patients from all groups showed impaired verbal memory before surgery but they differed considerably in regard to postoperative memory outcome. Referring to average group data, least losses, i.e. unchanged performance, were seen after lesionectomy, SAH mainly caused a loss in long term retrieval aspects of verbal learning and memory, and ATL, in which unaffected neocortical tissues had been removed, additionally caused a significant loss in the short-term and working memory aspects of verbal learning and memory. The differential effects of left SAH and ATL on verbal learning and memory which we described in 1996 and 1997 were also seen in the longitudinal study published in 2003 which had follow-up intervals of 2 to 10 years and which comprised also some of the patients included in the early investigation [2]. Later, in 2005, LoGalbo et al. confirmed the negative impact of performing ATL on memory in patients with exclusive Ammon’s horn sclerosis [35].

Since this time there have been several other studies comparing SAH or individually tailored temporal lobe surgery with ATL. In general selective surgery appears more favourable but this is not a consistent finding. Continuing with controlled studies, Renowden et al. found drops in memory after SAH and ATL but to a greater extent after en-bloc ATL. In addition non-memory functions increased to a greater extent after SAH [36]. Interestingly this group already noticed a larger than expected collateral damage in selective approach (trans-sylvian, trans-temporal), this being an issue which will be dealt with later in greater detail.

In a multicenter study from 1997 [37] which evaluated 71 successfully operated and seizure free patients, the memory outcomes of ATL (performed in Montreal, Canada), lesional neocorticectomy sparing amygdala and hippocampus (performed in Dublin, Ireland), and SAH sparing neocortex (performed in Zürich, Switzerland) were compared. Unfortunately, this study con-

Figure 1. Pre- and postoperative verbal learning and memory (VLMT /German AVLT) in left temporal patients with hippocampal pathology who underwent ATL versus SAH, and in patients with lateral lesions who underwent cortical lesionectomy. Before surgery the three groups showed similarly impaired memory (left chart). Excellent outcome is seen after lesionectomy; long-term retrieval drops are seen after ATL and SAH; and learning drops after ATL.
considered only postoperative performance in verbal and figural list learning and in addition the surgical procedures appeared less distinctive than planned. The results indicated impairments in patients as compared to controls independent of resection types, lateralization effects (more for verbal than figural materials), and no advantage of one type of surgery over another could be discerned. Size of mesial removal did not have a differential effect on postoperative memory. The findings were rated as unexpected but one should keep in mind that the evaluation did not take baseline differences into consideration nor change over time.

Pauli et al. 1999 [38] compared left ATL, tailored temporolateral resections, and SAH and found that sparing neocortex in the comparison of SAH and ATL resulted in better memory outcome as did sparing hippocampus in tailored surgery as compared to SAH or ATL.

In a review of 321 patients operated in Bonn, Clusmann et al. concluded on the basis of gross categorical cognitive performance measures that limited resections as compared to standard ATL resulted in better outcome of attention, verbal memory, and a compound measure of cognitive performance [39].

Morino et al. [40] demonstrated better preserved memory function after transsylvian SAH as compared to ATL and Paglioli et al. [41] reported greater postoperative improvements after left SAH as opposed to left ATL. Alpherts et al. [42] showed that tailored resections caused additional problems in attention and working memory whereas ATL, dependent on the extent of the resection of the superior temporal gyrus, caused greater problems in regard to verbal intelligence and verbal comprehension.

A more recent study from the Montreal group [14] compared large samples of patients who underwent left/right cortectomy including AH (ATL, n = 123) to selective AH (n = 133). The findings indicate that general intelligence increased after epilepsy surgery, but that verbal IQ was negatively affected by left SAH. Verbal memory declined and nonverbal memory improved after left sided surgery. Nonverbal memory decreased after right ATL. In addition later surgery was associated with poorer memory, and seizure freedom was associated with better memory. Interestingly in this study immediate logical memory recall significantly decreased after left sided ATL, whereas delayed logical memory recall was similarly affected by both approaches in left sided surgery. This would be in line with what has been discussed before, that left neocortical resections affect learning parameters more than left mesial resections and that left mesial resections in both approaches similarly affect delayed memory parameters.

**Resection versus sparing nonaffected tissue**

In concluding the neuropsychological findings on selective surgery versus ATL there is a clear vote for doing more individual surgery. From a neuropsychological point of view the functional integrity of the to-be-resected brain tissue and thus the question of sacrificing versus preservation of functional tissue appears of major importance for the cognitive losses observed after surgery [10, 43, 44].

The evaluation of the impact of the resection of non-lesional tissue, however, is not that easy since in 2/3 standard temporal lobe surgery and even more in selective surgery it is very difficult to disentangle the proportion of functional and lesional/epileptogenic tissues in regard to cognitive outcome. Prospective variation of the resection of non-lesional tissue requires clinical and ethical justification which is virtually unavailable. The negative effects of resection of unaffected lateral cortex in ATL performed in patients with AHS as the sole pathology have been reported in the previous section [12, 35]. In contrast to this, surgery which is confined to neocortical temporal lobe lesions appeared to have a very good cognitive outcome.

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**Figure 2.** Pre- to postoperative changes in a combined memory (verbal/nonverbal: VLMT German AVLT, DCS-R) and executive score (letter cancellation/verbal fluency) in 10 left and 5 right resected patients with MRI and histopathologically negative temporal lobe epilepsy versus 15 matched lesional controls. Note the group difference in memory disfavouring lesional patients at baseline, the highly significant drop in memory in non-lesional patients, and the similar memory performance in both groups after surgery. Non-memory functions tend to improve in both groups, which may by part be due to a practice effect.
Very recently Hamberger demonstrated that resection of a structurally intact hippocampus results in a loss in visual naming ability despite preoperative mapping of the cortical naming sites [45].

As a proof of the principle that resection of presumably unaffected brain tissue worsens the cognitive outcome in temporal lobe epilepsy, we recently contrasted the memory outcomes after temporal lobe surgery in 15 MRI and histopathologically negative patients with those obtained in 15 pairwise matched patients with MRI and histopathologically proven lesions. Matching considered clinical (e.g. side & site and type of surgery, onset and duration of epilepsy) and neuropsychological performance other than memory (e.g. IQ, attention). As for the question of whether the resected tissues were involved in epilepsy and whether it could be suggested to be not affected it is important to note that 12/15 non-lesional patients showed no postoperative response in regard to seizures. It was hypothesized that preoperative differences in memory outcome should reveal the impact of the lesion on memory whereas the postoperative differences should reveal the impact of resection of non-lesional tissues on memory. The results impressively showed that memory in the truly non-lesional TLE patients is mostly unimpaired before surgery and that memory after surgery drops to the postoperative level seen also in lesioned patients after surgery [46] (Figure 2).

How selective is selective surgery?

Selective amygdalo-hippocampectomy aims at the defined resection of pathological mesial brain tissue whilst preserving nonaffected lateral cortex which, to a varying degree, is included in standard ATL. However, selectivity of TLE surgery has its limits in that it can cause collateral neocortical damage due to the surgical approach. In this regard we demonstrated that damage of neocortical tissues adjacent to the transsylvian approach must be considered as a decisive determinant of postoperative decline in the more neocortical aspects of verbal learning and memory (learning, short term and working memory). This observation was made independent of side of surgery. An effect of the side of surgery became evident only with regard to a measure of verbal long term consolidation (verbal delayed recall) which was affected to a greater extent by left sided surgery. The size of the mesial resection, negatively assessed by measurement of the residual hippocampus after surgery, was of no relevance for outcome in verbal learning or memory [47]. With this study we identified one of the possible reasons for inconsistent memory outcomes reported by studies comparing surgical approaches in the literature.

Another factor may be seen in the dissection versus preservation of fibre tracts. At present, there are three major approaches to the mesial structures in selective AH. These are the trans-sylvian, trans-cortical/trans-temporal, and sub-temporal approach. The trans-sylvian approach can affect the superior temporal gyrus and the adjacent frontal lobe, the trans-temporal approach affects the middle temporal gyrus, and the sub-temporal approach the inferior temporal gyrus. Another difference of these approaches is whether the temporal stem, which connects the temporal lobe to frontal lobe structures, is transected (trans-sylvian approach) or spared (trans- and sub-temporal approaches). In 1978, Horel already discussed the potential role of the temporal stem in the appearance of amnesia when comparing lesional models of amnesia in humans and animals [48].

Comparing trans-sylvian and trans-cortical surgery in a randomized trial on 80 operated patients we did not find a different outcome in regard to memory but better postoperative recovery of executive functions in the trans-temporal approach [49]. We were surprised to find no difference for learning and memory but in the light of what is discussed later on it cannot be excluded that the memory test in use (German AVLT) missed the effects.

Very positive cognitive outcomes, i.e. almost no memory decline if not improvements, have been reported in two studies on SAH using a sub-temporal ap-
proach [50, 51]. Takaya et al. in a third study, published in Brain 2008 [52], even found that memory as assessed with the Wechsler Memory Scale improved to a larger extent than attention after dominant side resections. At the same time increased glucose metabolism in extratemporal regions was observed. However, the latter observation was made in 7 patients only. Unfortunately, none of these studies had a control condition (another type of surgery), nor was the eventual effect of basal temporal lesions on language taken into consideration [53]. A study by Mikuni et al., which cared about the potential functional relevance of the basal language area focused only on memory [54]. In this study the basal language area, as defined via strip electrodes was spared by entering the temporal horn via the collateral sulcus and verbal memory was found to be improved after surgery. However, it should be kept in mind that all these studies were uncontrolled and that the Wechsler Memory Scale (WMS) was chosen for memory assessment at baseline and follow up without explicitly control for practice effects. The WMS is highly confounded with non-memory functions (IQ, language, executive functions) [55]. Thus it cannot be excluded that postoperative improvement of frontal lobe functioning, which is commonly observed after temporal lobe surgery, had a beneficial effect on performance in the WMS. Taking this into account we very recently compared cognitive outcomes in clinically and demographically matched patients who underwent subtemporal versus transsylvian surgery [56]. In this evaluation both surgical approaches caused a comparable decline in verbal learning and memory performance. Differential effects became evident in regard to decline in verbal recognition memory (more affected by left transsylvian SAH) as well as in verbal semantic fluency and figural memory (more affected by subtemporal SAH) (for memory outcomes independent on side of surgery see Figure 3). The findings were discussed to be probably due to the affection of the basal language area which is involved in lexical processing and the affection of the inferior temporal gyrus and ventral stream which have significant roles in visual perception, imagery, and memory [57, 58].

The temporal stem is not only preserved by the transcortical or sub-temporal approach but also by a surgery which approaches the mesial structures after removal of the tip of the temporal pole until the view to the mesial structures is made accessible. Comparing memory outcomes after left/right trans-sylvian SAH with those after temporal pole resections + AH in 97 postsurgically seizure-free patients, an interaction effect of material (verbal/figural) and side of surgery (left/right) was revealed [59]. In left sided surgeries, verbal memory outcome was better after the temporal pole resection + AH as compared to trans-sylvian SAH; in right sided surgeries figural memory outcome was better after the trans-sylvian approach as compared to the pole resection + AH. The results were discussed in terms of a different importance of the temporal stem and the temporal pole for verbal and figural memory processing respectively.

In concluding this section no single surgical approach can be discerned which, irrespective of seizure control, would be the safest for cognition. Dependent on the surgical approach different tissues and fibre tracts in the way or adjacent to the approach are at risk to become affected and this has consequences for cognition in the one or the other way.

**Variation of the extent of the mesial hippocampal resection**

In 1995, Wyler and colleagues published the first paper on a randomized variation of mesial resection length in patients who underwent ATL [60]. In that study a maximal mesial resection to the level of the superior colliculus led to a better outcome concerning seizure freedom (69%) in comparison to a smaller resection to the anterior edge of the cerebral peduncle (38%). No effect of the resection length on memory outcome (assessed by the California Verbal Learning Test, CVLT) was obtained. However, when hippocampal sclerosis was additionally taken into account, an adverse memory outcome was associated with the resection of a non-sclerotic left hippocampus. In contrast to the findings of Wyler et al., an early study by Katz et al. in 1989 [61] reported greater losses in Wechsler Memory Scale performance (percent retained) to be related to the extent of the medial resection. Similarly retention (%) of visual material was correlated to the medial extent of the resection of the right temporal lobe. Both studies did not account for the covariation of lateral resections.

A study by Joo et al. in 2005 for example found a relation of verbal memory decline only to larger resection of the inferior and basal temporal gyrus in regression analysis [62]. The already mentioned study by Wolf et al. [29] did neither find a relation of the lateral nor of the mesial extent of the resection to memory outcome when patients were categorized into groups with larger versus smaller resections. In our own study on memory outcome after SAH as a function of collateral surgical damage, memory change was not correlated with hippocampal remnants as a negative indicator for the mesial extent of resection [47].

Thus from studies addressing mesial resection length there is no consistent result regarding the question of whether sparing of hippocampal tissue will cause better memory outcome or not. Taking this a premise we performed an analysis on a subgroup of patients recruited for a large multicenter randomized trial on mesial resection length [63]. This trial originally comprised all epilepsy patients from three centres in whom the hippocampus was resected independent of pathology and type of surgery. To evaluate memory outcome as a function of hippocampal resection length it was necessary to exclude possible alternative influences by different pathologies, different lateral resec-
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**Figure 4.** Verbal (VLMT: German AVLT) and figural memory (DCS-R) outcome in patients with left mesial temporal lobe epilepsy after selective amygdalo-hippocampectomy as a function of the intended hippocampal resection length (2.5 vs. 3.5 cm) and the resected hippocampal volume (median split). Scores represent standard scores with mean = 100 SD = 10. The resected volume which takes preoperative pathology into account but not the intended resection length is related to verbal and figural memory outcome.

**Figure 5.** Left part: Impact of bilateral hippocampal depth electrodes and right selective amygdalo-hippocampectomy on verbal learning, memory, and recognition (VLMT: German AVLT: standardized values 100 ± 10) in a patient with right mesial temporal lobe epilepsy. Right part: Effect of chronic depth electrode implantation and stimulation on verbal learning, memory, and recognition (standardized values 100 ± 10) in a patient with right mesial temporal lobe epilepsy.
tions, surgical approaches and combinations of these variables. Focussing thus on a homogeneous subgroup of patients, who all had a mesial pathology and who all underwent selective surgery, the intent-to-treat mesial resection length (2.5 vs. 3.5 cm) which was determined under surgery using a ruler had no effect on seizure or memory outcome one year after surgery. However, when considering resected hippocampal volumes (MRI volumetry), verbal memory outcome was poorer when the resection of larger left hippocampal volumes and figural memory outcome was poorer with larger resected volumes on either side [64, 65]. Figure 4 demonstrates the respective findings for the left temporal resected group. Similar to that of Wyler’s randomized trial in ATL [60], the major message from this study in SAH was that consideration of resection length is irrelevant if the pathology at baseline is not being taken into consideration. Thus, large resection of an atrophied hippocampus will have lesser consequences than short resection of a non-atrophied hippocampus.

The statement that removal of functional hippocampal tissue matters is in line with Baxendale’s finding that shrinkage of the hippocampal remnant in the time after surgery is relevant for memory outcome [66] and it is also in line with recent findings on the dependency of memory outcomes on functionality of the posterior hippocampus as determined by functional MRI [66, 67].

In conclusion, we face the same situation in regard to the hippocampal resections as we have for temporal neocortical resections, i.e. postoperative decline of learning and memory mostly results from resection or dissection of nonaffected functional brain tissues.

In this regard the degree of preservation of functional tissue which can be achieved with radiosurgery may be of future interest. Radiosurgery claims to have a high spatial resolution and it aims at changing the intrinsic epileptic characteristics of the radiated tissue. First reports on the neuropsychological outcome appear optimistic [68, 69]. Comparably, the cognitive outcomes of deep brain stimulation will be of interest in the future, but it still needs to be established whether stimulation indeed preserves function or whether it interferes with the functionality of the stimulated area [70 - 72]. In addition, the possible effects of acute or chronic implantation of depth electrodes need to be systematically evaluated. For example, after right sided selective TLE surgery we have described negative effects of bilateral depth electrode implantation on verbal memory in right temporal lobe resected patients which were still evident at the three-month postoperative follow-up [73]. The left part of Figure 5 displays verbal learning and memory of a 30-year-old female patient of this series who suffered from right temporal lobe epilepsy with hippocampal sclerosis. Displayed are the standardized values of learning (sum across five learning trials), free recall after a 30 minutes delay, and recognition memory, at baseline, after implantation of bilateral depth electrodes (implanted posteriorly along the hippocampal axis), and postoperatively. The patient became seizure free. Following implantation, verbal memory significantly dropped in its long term memory aspects. After surgery the patient partly recovered from this impairment but did not reach baseline. At the one year follow-up, however, the effects of bilateral depth electrode implantation observed in the group of right temporal patients in 2002 was no longer present [74]. The right side of Figure 5 displays verbal learning and memory performance of a patient who became seizure free due to right hippocampal deep brain stimulation. Displayed are the performances at baseline and 6 months after stimulation onset showing losses in verbal learning and recognition. In addition the error rate during learning and memory increased significantly (not displayed in the figure). These are examples not only of how a selective injury of the hippocampus affects memory performance but also examples of how differences in presurgical work up between centres (using depth electrode recordings or not) may affect cognitive outcome after surgery.

In a recent publication by Bowles [75] on different effects of sparing versus resecting the hippocampus a group of patients who underwent stereotactic amygdalo-hippocampectomy was contrasted to patients who received tailored surgery including the entorhinal cortex but not the hippocampus. The major aim of this study was to describe a double dissociation of impairment of recollection in hippocampectomized patients irrespective of the side of surgery versus impairment of familiarity judgements after removal of the entorhinal cortex. Unfortunately, no pre- to post data are presented and healthy subjects served as a reference. If this type of surgery represents an alternative to commonly used surgical approaches more detailed knowledge of neuropsychological outcomes under controlled conditions would highly be appreciated.

**Surgery within the right non-dominant hemisphere**

Up to now this review mainly addressed verbal learning and memory, and this focus can be discerned throughout the literature addressing memory in temporal lobe epilepsy. There is a good reason for this bias. Verbal memory in contrast to figural memory is quite regularly affected when the dominant temporal lobe and its substructures are concerned. Superficially, left-right hemispheric differences appear to be common sense, but in fact it is very difficult to determine specific right temporal pendants to what semantic and episodic verbal memory or language are for left temporal lobe epilepsies. The literature attributes deficits in figural, visual-spatial memory, object processing, allocentric object location, face memory, rhythm, and learning musical associations to right temporal lobe dysfunction.
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C. Helmstaedter

Specific styles of information processing rather than of language functions have not yet been described. When memory in men and women [12, 88]. Similar effects on the “suppression” of figural-visual memory in the presence of atypical language dominance and the differential impact of lateralized epilepsies on material specific memory as well. Summing up losses in either verbal or figural memory, 45% of 365 right resected patients in our series (see Table 1), showed a memory loss, 8% showed a loss in both performances. In the 351 left temporal resected patients 54% showed a loss either in verbal or figural memory and 16% lost in both. These numbers, although evaluated on the basis of gross test-wise categorizations, parallel the outcome reported on a test score level in our longitudinal study [2]. The fact that, different from left sided surgery, losses after right sided surgery are often balanced or outweighed by gains (see Table 1), easily leads to the erroneous conclusion that losses in this group can be neglected.

Taken together it is difficult to reliably relate figural/spatial memory performance to the right temporal lobe or the right mesial structures, and it seems even more difficult to demonstrate specific impairments due to right sided surgery. For left/right temporal differences in verbal memory we recently concluded from the life time perspective that these become evident only in the mature and not yet aged brain [87]. Figural memory appears differentially organized than verbal memory. This is indicated by observations made with “crowding” or the “suppression” of figural-visual memory in the presence of atypical language dominance and the differential impact of lateralized epilepsies on material specific memory in men and women [12, 88]. Similar effects on language functions have not yet been described. When discussing the “crowding” effect in 1994 we suggested that it would be better to speak of two hemisphere-specific styles of information processing rather than of material specificity. Material specific tasks represent an expression and not an equivalent of the respective type of information processing [88]. In this respect, Michael Saling in 2009 made the statement that hemispheric lateralization is task rather than material specific [76].

Taking into account the large number of left and right temporal patients who are not left dominant for language (see Table 1) it comes as no surprise that lateralization via material-specific memory testing often fails. This is particularly true for atypical language dominance in left temporal lobe epilepsies which, due to “plasticity”, often show unimpaired verbal and “unexpected” figural memory impairment. One reason why right temporal patients often do not show the expected impairment is verbalization of the non-verbal material. Verbalization almost always interferes with (or supports?) figural/visual spatial memory assessment and this needs to be controlled either by choosing abstract and hard-to-be-verbalized material or by increasing the complexity of the material in such a way that verbal memory must fail to compensate for the impairment [85].

As a more general consideration one may discuss whether the concept of a defined test and testing itself rather refers to left hemisphere function, i.e. reasoning, to allow a grip on right hemisphere functions. Thus identifying and assessing right hemisphere functions remains a challenge.

Living in a different test universe

The discussion in the previous section demonstrates that neuropsychological assessment like other diagnostic tools opens a window and allows a view on the nature of cognitive impairments in epilepsy and after epilepsy surgery. However, neuropsychological evaluation much depends on the tests in use. As demonstrated already by Jones-Gotman in 1993 different epilepsy centres use different tests or test batteries [89] and recent reviews suggest that things have not changed since then. At best one can make recommendations as to which tests should be used for the neuropsychological assessment in epilepsy patients. A recent evaluation of which tests are currently used in epilepsy centres in German speaking countries showed that over 200 different tools were in use and that there is at best some common sense on which functional domains need to be addressed [90].

Hence, discussing the outcomes of epilepsy surgery and of different surgical approaches also requires a discussion of the tests in use and their psychometric features. Focusing on memory tests in temporal lobe epilepsy, different tests appear to have different sensitivity and specificity in regard to differentially lateralized and localized temporal lobe lesions and epilepsies [91]. A comparison of the Logical Memory subtest from the WMS-R, the California Verbal Learning Test and the Ver-
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**Table 2:** Correlations between verbal memory tests and tests on IQ, executive, and language functions (only statistically significant results are displayed).

<table>
<thead>
<tr>
<th>Time and Tests</th>
<th>Verbal Memory 1</th>
<th>Verbal Memory 2</th>
<th>Verbal Memory 3</th>
<th>Verbal Memory 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMS-Verbal Learning Test</td>
<td>0.31</td>
<td>0.24</td>
<td>0.26</td>
<td>0.30</td>
</tr>
<tr>
<td>WAIS-R言语</td>
<td>0.28</td>
<td>0.19</td>
<td>0.21</td>
<td>0.25</td>
</tr>
<tr>
<td>TMT-B</td>
<td>-0.03</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>TMT-A</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-0.0</td>
<td>-0.01</td>
</tr>
<tr>
<td>Story Recall</td>
<td>0.36</td>
<td>0.28</td>
<td>0.30</td>
<td>0.25</td>
</tr>
<tr>
<td>Story Recall Delayed</td>
<td>0.33</td>
<td>0.25</td>
<td>0.27</td>
<td>0.24</td>
</tr>
<tr>
<td>Story Recall Recognition</td>
<td>0.30</td>
<td>0.23</td>
<td>0.24</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Note: Correlation is significant at the 0.05 level (2-tailed). Correlation is significant at the 0.01 level (2-tailed).
Does memory impairment matter?

In the sections before it has been shown that patients undergoing epilepsy surgery have an increased risk of additional memory impairment after surgery and it was the explicit task of this manuscript to discuss whether different individual and selective surgical approaches can preserve the patients cognitive capabilities better than extended standard resections. The answer is yes, but it is a legitimate question to neuropsychologists, whether such, in part fine graded differences in memory outcome which were assessed with sophisticated tests in a laboratory, have any relevance for the patient who in the first line wants to become seizure free.

In this regard it has been demonstrated that patients are in part willing to risk some cognitive decline in the prospect of becoming seizure free [93, 94]. In our longitudinal study we spoke from the so called double losers when patients in the long run do not get seizure free and in addition experience significant memory decline [2]. Out of the group of 732 TLE patients displayed in Table 1 about 15% belong to this group (verbal memory decline > 2 SD). Including also non seizure-free patients with milder losses (decline > 1 SD) the group increases to 37%. Langfitt et al. in his long-term follow up study published in 2007 identified the group of double losers (8% only) as being at a particular risk to loose in quality of life over time [94].

Dependent on its etiology, chronic epilepsy does not necessarily cause mental decline. Temporal lobe surgery in contrast often does, and there is the legitimate fear that every additional loss poses an increased risk of later acceleration of mental/memory decline with normal or even pathological aging [95].

One may take into consideration that patients with long lasting epilepsies, particularly when starting early, have adapted to the impairment and will most likely not be dominantly involved in domains in which they will fail because of their impairments. This is positive and may in addition inoculate to additional damage in the already affected domains. This does not, however, mean that the patients’ performance nevertheless ranges considerably below that of healthy subjects, and it furthermore does not mean that the patients are unaware of their impairments and that they do not suffer from these. Contrary to what one may expect, a study addressing the performance and complaint relationship showed that lower demands were not associated with less but with stronger subjective complaints [96]. Other studies indicate that there is no reliable relation between subjective complaints and memory performance and that complaints about memory problems after surgery should better be considered as a marker for depression [97, 98]. Different findings and positions on the ecological validity issue show that more research and presumably also more reliable ways for the assessment of the consequences of memory impairment and loss on everyday functioning in TLE are needed. Anyway, quality of life questionnaires do not appear to be sufficient.

For the memory tests we use, we have demonstrated that they not only have clinical but also ecological validity [99]. In addition, we were repeatedly able to demonstrate relations between surgical memory out-
cognitive and psychosocial socioeconomic outcome [2, 100]. Thus, memory impairment and change in memory do matter.

**Summary**

Surgery is a very successful treatment option for pharmacoresistant temporal lobe epilepsy but 30% to 50% of the surgery patients face the risk of additional postoperative memory impairment. The patients’ mental reserve capacities at baseline, seizure outcome, and most importantly, the functional integrity of the to-be-resected brain tissues are major determinants of the surgical cognitive outcome. There is now converging evidence that individually tailored and standard selective surgical approaches have a superior functional outcome as compared to extended standard anterior temporal lobectomy (including mesial structures). However, even with selective approaches collateral grey and white matter damage must be considered. Whether cognitive losses can be further reduced by superselective treatments like radiosurgery or deep brain stimulation has to be determined in the future.

As already mentioned before this review has a focus on experiences, developments, and observations mainly made in one center in Bonn/Germany over a period of more than 20 years and it is referenced accordingly. It is well understood that different views are possible and an ongoing discourse and initiation of additional studies is highly appreciated.

A major concern was to demonstrate what neuropsychology can do to contribute to improvements of surgical outcomes. Quality and outcome control, however, require instruments which reliably reflect the patient’s functionality at baseline and the intervention related performance change as well. A consensus regarding assessments is required to enable better comparison and communication across centers [101, 102, 90]. In addition, more valid measures than quality of life questionnaires or depression inventories are needed for assessing the patients every day functioning [103]. Finally, the long-term consequences of (additional) cognitive losses can be further reduced by superselective treatments like radiosurgery or deep brain stimulation has to be determined in the future.

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