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Cognitive outcomes of different surgical approaches in temporal lobe epilepsy

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ABSTRACT – Epilepsy surgery is a successful treatment option for pharmacoresistant focal symptomatic epilepsies. However, cognitive impairment is very common in epilepsy patients and may be negatively or positively affected by surgery. Amidst the long-standing discussion of whether a particular surgical approach for temporal lobe epilepsy patients may be superior with regards to seizure control, a recent meta-analysis indicated that this is the case for more extended resections. Larger temporal lobe resections, however, raise concerns that more unaffected and functional tissues may be involved, thus causing worse cognitive outcome. This review is based on published reports collected over a long period, with changing diagnostics and surgical methods, and focuses mainly on the experiences of one epilepsy centre. The review highlights the effects of standard *versus* selective surgery, the different surgical approaches in selective surgery, determinants other than surgery which may affect cognitive outcome, and the methodologically-important question of outcome assessment and how neuropsychological test selection may bias the result. Overall, from a neuropsychological point of view, individual and selective surgery is preferred in which the aim is to achieve seizure control with minimal effect on the functional integrity of tissues or fibre tracts. Cognition is important for the functions of everyday life and this should be kept in mind, irrespective of which kind of surgery is preferred.

Key words: temporal lobe epilepsy, selective surgery, standard surgery, outcome, cognition, memory

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The cognitive outcome of temporal lobe epilepsy surgery

Epilepsy surgery represents a very successful treatment option for patients with focal symptomatic epilepsies. By comparing surgical *versus* conservative medical treatment in 80 randomised patients with temporal lobe epilepsy (TLE), successful seizure control was achieved in 58% operated *versus* 8% medically-treated patients in a 12-month observation period (Wiebe *et al.*, 2001). This corresponds to what was found in our own non-randomised longitudinal 2-10-year follow-up study of 102 medically- (12% seizure-free) *versus* 147 surgically- (63% seizure-free) treated patients with TLE (Helmstaedter *et al*., 2003). In conclusion, and without any further characterisation, about two thirds of operated patients with TLE may become (permanently) seizure-free (Tellez-Zenteno *et al*., 2010).

Seizure control is clearly the primary aim of epilepsy surgery. Successful seizure control understandingly reduces behavioural and mood problems and improves overall quality of life. However, leaving seizure control aside, brain surgery can have negative effects on cognition and behaviour, resulting in impairments which quantitatively and qualitatively exceed those observed before surgery (Helmstaedter, 2004).

Table 1 provides a comprehensive overview of the frequency of cognitive deficits and changes in postoperative performance in a large cohort of 732 patients with TLE, who received surgery in Bonn between 1989 and 2007 (Helmstaedter *et al*., 2007). According to categorical test results (using a point system according to standard deviations, whereby 0 to 4 represents severely impaired to above average performance, and 3 represents average performance), 78% of patients with chronic pharmacoresistant TLE already had cognitive impairment (values <2) of either verbal memory, figural memory, or attention/executive functions before surgery. Regarding the localisation of the epileptogenic focus in brain regions relevant to memory processing, the most commonly affected cognitive domains in TLE are verbal and figural memory, followed by complications in language, attention, and motor and visuo-constructive functions. Consistent with the literature, lateralisation-dependent results are seen regarding verbal memory impairment and a more frequent atypical language dominance in left sided TLE, and with more frequent impairments in figural memory and attention in right-sided TLE. In addition to lateralisation, factors such as the time of epilepsy onset (during brain maturation or after), presence *versus* absence and type of underlying lesion (*e.g.* neoplastic *versus* developmental), patient variables (such as age, gender, and education), and last, but not least, medication and seizure situation differentially contribute to the cognitive capabilities observed in individual patients. One year after surgery, 65% of 732 patients were completely seizure-free, *i.e.* they did not have any seizures or aura. By applying 90% reliability of change indices (RCI), individually significant gains and losses in the assessed domains were evident for 10-40% of the patients. According to *table 1*, major gains concern extratemporal non-memory functions. Losses are prominent in memory, and here patients with left-sided temporal epilepsy are more frequently affected than those with right-sided temporal epilepsy. Patients with left-sided temporal epilepsy also worsen with regards 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 TL surgery which were published in a recent meta-study on cognitive outcomes after TL surgery (Sherman *et al*., 2011). Regarding 22 of 193 evaluated studies investigating temporal lobe surgery and taking RCI or standardised 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, compared to 20% after right-sided surgery. The gains for verbal memory were scarce; 7% (left side) *versus* 14% (right side). Losses in figural memory were not different between left-sided (15%) and right-sided (10%) surgery. The total average rate of decline in language (naming) was 34%. As in the Bonn sample, benefits were identified for executive functions after left-sided surgery (10% losses and 27% gains); for right-sided surgery, the losses and gains were 21% and 16%, respectively.

Summarising 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 reported a progressive decline, independent of seizure outcome, in a long-term follow-up study, our own long term follow-up study indicated that further decline *versus* recovery depended on seizure control (Helmstaedter *et al*., 2003; Rausch *et al*., 2003). Recent evidence from two other long term follow-up studies indicates a stable course of memory from two years after surgery (Alpherts *et al*., 2006; Andersson-Roswall *et al*., 2010).

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 brain areas affected by epilepsy which are to be resected (Chelune, 1995; Stroup *et al*., 2003). The second factor, closely connected to the question of "functionality", concerns the brain areas and functions not affected by epilepsy or surgery, referred to as the patient's "mental reserve capacity" (Helmstaedter, 1999). Mental reserve capacities can help to compensate surgical defects. Functionality of the brain also appears to predict later seizure control (Helmstaedter, 2009). 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

Table 1. Cognition in TLE before and after surgery.

	Preoperative impairments[a]			Postoperative changes (1 year)[b]				
Domain	***n***	**L TLE (%)**	**R TLE (%)**	***n***	**L TLE (%)**		**R TLE (%)**	
		impairment=x<m-1.5 SD			↓	↑	↓	↑
Verbal memory	732	69	46***	732	40	14***	27	29
Figural memory	716	49	59**	707	31	27	28	23
Attention	717	21	29*	709	11	36***	11	40***
Language	653	39	32	618	21	27	14	32***
Motor function	717	30	40	449	16	34***	16	37***
Visuo-construction	602	19	21	554	10	35***	13	31***
Vocabulary - IQ	591	8	11					
Atypical language dominance (IAT)	320	41	22***					

[a]χ^2 (note that the table displays % but that statistics were calculated for patient numbers).
[b]Wilcoxon Signed Ranks Test.
IAT: Intracarotid Amobarbital Test; L TLE: left temporal lobe epilepsy; R TLE: right temporal lobe epilepsy.
*$p<0.05$; **$p<0.01$;***$p<0.00$; downward arrow=significant loss ($p<0.1$); upward arrow=significant gain ($p<0.1$).

from surgical studies which support this assumption (Helmstaedter *et al*., 2003; Tanriverdi *et al*., 2010).

Functional integrity of the affected tissue to be resected and reserve capacity are both reflected by baseline performance. Those with a better baseline performance are at greater risk to lose cognitive functions after surgery (functionality), however, 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 is 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) with a) absolute postoperative memory (r=0.44, p=0.000) and b) loss over time calculated as the difference between pre and postsurgical performance scores (r=0.60, p=0.000).

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 the time at around 30 years of age, when reserve capacities and capabilities for compensation start to decline with age (Helmstaedter, 1999). 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 (Elger *et al*., 1997; Grunwald *et al*., 1998; Helmstaedter *et al*., 1998a), structural and functional imaging techniques (Koepp and Woermann, 2005), angiography with intracarotidal application of amobarbital, methohexital (brevital) or etomidate (Buchtel *et al*., 2002), and pre- or intraoperative electrocortical stimulation (Wellmer *et al*., 2009).

Selective surgical approaches *versus* standard anterior temporal lobectomy

The logical step following from the previous section on epilepsy surgery is to remove what is necessary to control seizures and leave as much as possible functional tissue in order to preserve the patient's cognitive functions. According to a review on the quest for the optimal extent of resection in TLE by Schramm (2008), no particular surgical approach was reported to be superior with regards to seizure control. Six of 8 studies on selective surgery *versus* temporal lobe resections reported similar seizure outcomes and 2 reported better outcome with larger resection. This report has very recently been challenged by a meta-study by Josephson *et al*. (2013) who compared selective amygdalo-hippocampectomy (SAH) and anterior temporal lobectomy (ATL) across 15 studies and found overall better outcome with larger resections 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 with regards to cognitive outcome. According to the review by Schramm (2008), 11/14 studies reported that smaller, as opposed to larger, resections are associated with better cognitive outcome. In addition, taking the extent of the mesial resection into consideration, an association between better seizure control and larger resections was reported in 5/12 studies and an association between extent of resection and neuropsychological outcome was not identified in 8/9 studies. A review provided in a study by Tanriverdi *et al.* reported that 16/21 studies demonstrated better cognitive outcome after selective surgery, compared to 5/21 studies which showed no difference (Tanriverdi *et al.*, 2010).

Within the last 20 years, surgery for TLE has become increasingly selective due to major improvements in high-resolution structural and functional imaging, with increased reliability for detecting subtle lesions such as dysplasia or hippocampal sclerosis in patients with temporal lobe epilepsies. In its beginnings, selective surgery was only performed for patients with gross lesions and/or with evidence from intracranial EEG recordings. In 1982, Wieser and Yasargil published a series of 27 patients (12 with mesial tumours and epileptogenic area identified by stereo or surface EEG in 13 and 2 patients, respectively) which showed good seizure control, improved general intelligence, and minor-to-no decline in verbal memory after SAH, compared to large temporal lobe resections which caused significant functional losses (Wieser and Yasargil, 1982). In 1993, Goldstein and Polkey reported that both surgical approaches cause similar decrease in delayed recall in logical memory, but that ATL, in contrast to SAH, causes more impairment in paired associate learning and immediate recall of visuo-spatial material (Goldstein and Polkey, 1993). A year before, the same authors reported that whereas patients who had undergone either selective surgery or en-bloc resections could be distinguished based on a traditional memory test score, this was not the case for memory measures more related to everyday behaviour (Rivermead Behavioural Memory Test) (Goldstein and Polkey, 1992).

For a long time, selective surgery was performed exclusively at a few centres. However even for ATL resections it was demonstrated that lateral extent of resection (<3 cm) (Helmstaedter and Elger, 1996), consideration of cortical eloquent sites for language or memory (Ojemann and Dodrill, 1985), and the patients pathological status (presence/absence of hippocampal pathology) (Hermann *et al.*, 1992) were decisive determinants for memory decline after surgery. In a retrospective study by Wolf *et al.*, performed in 1993, no difference in memory outcome (RAVLT, WMS) was reported, taking the extent of mesial (>/<2 cm) or lateral (>/<4 cm) resection into consideration. Instead, older age at seizure onset was decisive for worse outcome (Wolf *et al.*, 1993).

The earlier studies performed in patients undergoing standard ATL already implicitly hinted that different surgical procedures within the language-dominant lateral temporal neo-cortex affect learning capability, rather than delayed recall, and that, based on memory measures (mainly RAVLT, CVLT and WMS), the patient language capabilities should be taken into consideration in order to understand the memory impairments observed in TLE (Hermann *et al.*, 1988) (see below under *Living in a different test universe*). In the Ojemann and Dodrill study from 1985, 80% of the memory outcomes assessed by WMS could be predicted based on the association between the resection and sites essential for naming, encoding, or memory storage, as identified by electrical stimulation mapping. This close relationship between verbal memory and language indicates that preoperative determination of language sites can be used to protect against losses in either function (Hamberger, 2007; Hamberger *et al.*, 2010).

Differential cognitive sequelae of surgery of temporo-mesial and temporo-lateral structures for different aspects of verbal learning and memory were demonstrated in a study which compared patients who underwent cortical lesionectomy to patients with ammonshorn sclerosis who either underwent SAH or ATL (Helmstaedter *et al.*, 1996; Helmstaedter *et al.*, 1997) (*figure 1*). This study had been performed at a time in Bonn when selective surgery had become a new treatment option for mesial TLE. Thus, a retrospective comparison was possible between two groups of M-TLE patients; one group who, according to the new treatment guidelines, underwent left-sided SAH and another who, according to the old guidelines, 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 compare between cortical lesionectomy and cortical resection of non-lesional tissue in ATL. Consistent with the presence of left TLE, patients from all groups showed impaired verbal memory before surgery, but differed considerably with regards to postoperative memory outcome. With regards to average group data, least losses (*i.e.* unchanged performance) were observed after lesionectomy, SAH mainly caused a loss in long-term memory 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 observed in the longitudinal study published in 2003 which had

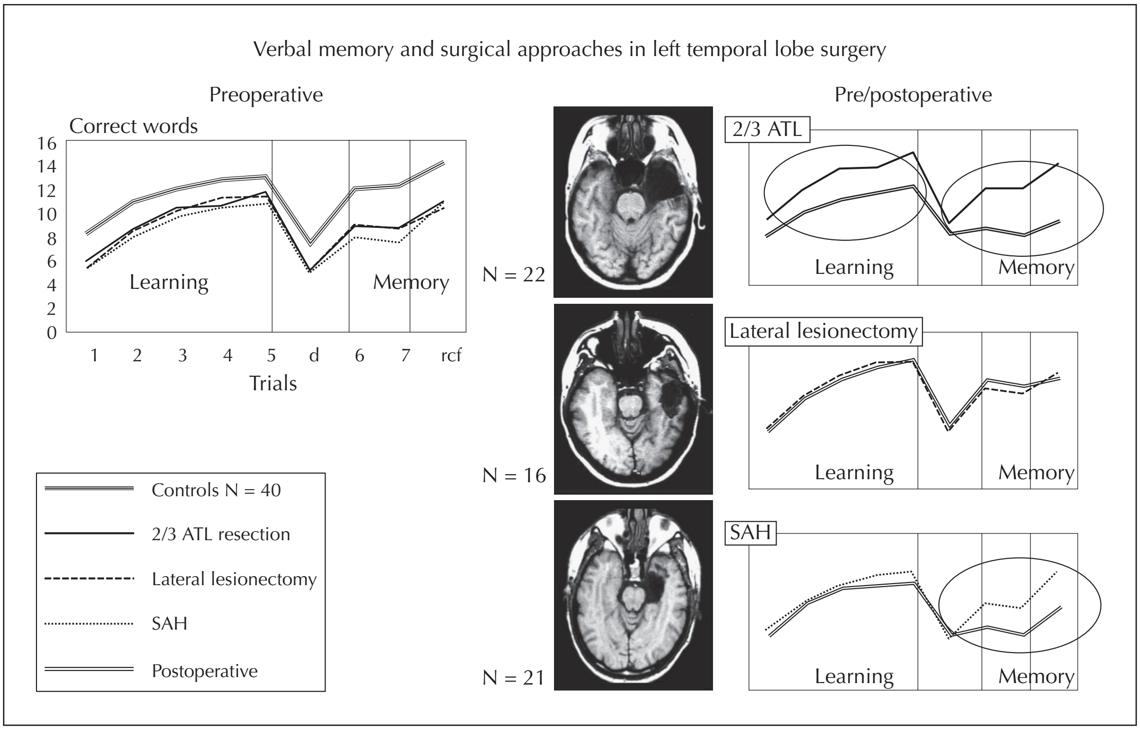

Figure 1. Pre- and postoperative verbal learning and memory (VLMT /German AVLT) in left TLE patients with hippocampal pathology who underwent ATL *versus* SAH and patients with lateral lesions who underwent cortical lesionectomy.
Before surgery, the three groups showed similar impaired memory (left panel). Excellent outcome was observed after lesionectomy, a decrease in long-term retrieval after ATL and SAH, and a decrease in learning after ATL.

follow-up intervals of 2 to 10 years, and which also comprised some of the patients included in the early investigation (Helmstaedter *et al*., 2003). Later, in 2005, LoGalbo *et al*. confirmed the negative impact of performing ATL on memory in patients with exclusive AHS (LoGalbo *et al*., 2005).

Since this time, there have been several other studies in which SAH or individually tailored temporal lobe surgery were compared with ATL. In general, selective surgery appears to be more favourable but this is not a consistent finding. Continuing with controlled studies, Renowden *et al*. reported reduced memory after SAH and ATL, although to a greater extent, after en-bloc ATL. In addition, non-memory functions increased to a greater extent after SAH (Renowden *et al*., 1995). Interestingly, this group previously reported larger-than-expected collateral damage for selective surgical approaches (trans-sylvian, trans-temporal), an issue which will be dealt with later in greater detail.

In a multicentre study from 1997 (Jones-Gotman *et al*., 1997), in which 71 seizure-free patients who had successfully received surgery were evaluated, the memory outcomes following ATL (performed in Montreal, Canada), lesional neocorticectomy sparing the amydgala and hippocampus (performed in Dublin, Ireland), and SAH sparing the neocortex (performed in Zürich, Switzerland) were compared. Unfortunately, this study considered only postoperative performance in verbal and figural list learning and, in addition, the surgical procedures appeared less distinct than previously planned. The results indicated impairments in patients, relative to controls, independent of the type of resection and lateralisation effects (more for verbal than figural materials), and no advantage of one type of surgery over another could be discerned. The 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 or change over time into consideration.

Pauli *et al*. (1999) compared left ATL, tailored temporolateral resections, and SAH and found that better memory outcome was associated with sparing the neocortex for SAH and ATL and sparing the hippocampus for tailored surgery.

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, relative to standard ATL, resulted in better outcome of attention, verbal memory, and a compound measure of cognitive performance (Clusmann *et al*., 2002).

Morino *et al*. (2006) demonstrated better preserved memory function after trans-sylvian SAH, compared to ATL, and Paglioli *et al*. (2006) reported greater post-operative improvements after left SAH, as opposed to left ATL. Alpherts *et al*. (2008) 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 with regards to verbal intelligence and verbal comprehension.

A more recent study from the Montreal group (Tanriverdi *et al*., 2010) compared large samples of patients who underwent left/right cortectomy, including a comparison between AH (ATL; *n*=123) and selective AH (*n*=133). The findings indicated that general intelligence increased after epilepsy surgery, but that verbal IQ was negatively affected by left SAH. Verbal memory declined and non-verbal memory improved after left-sided surgery, and non-verbal memory decreased after right ATL. In addition, later surgery was associated with worse 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 after left-sided surgery. This is in line with what was previously discussed; learning parameters are more significantly affected by left neocortical resections than left mesial resections, and delayed memory parameters are similarly affected following left neocortical resections using both approaches.

Resection *versus* preservation of non-affected tissue

In concluding the neuropsychological findings on selective surgery *versus* ATL, selective surgery is clearly preferred. From a neuropsychological point of view, the functional integrity of brain tissue to be resected, and thus the question of sacrificing *versus* preserving functional tissue, appears to be of major importance regarding cognitive loss observed after surgery (Chelune, 1995; Helmstaedter, 1999; Stern, 2003).

The evaluation of impact of resection of non-lesional tissue, however, is not that straightforward since for two-third standard temporal lobe surgery, and even more so for selective surgery, it is very difficult to determine the proportion of functional and lesional/epileptogenic tissues with regards to cognitive outcome. Resection of non-lesional tissue requires clinical and ethical justification. The negative effects of resection of unaffected lateral cortex in ATL performed in patients, with AHS as the sole pathology, were reported in the previous section (Helmstaedter *et al*., 1996; LoGalbo *et al*., 2005). In contrast to this, surgery, which is confined to neocortical temporal lobe lesions, appeared to be associated with very good cognitive outcome.

Very recently, Hamberger *et al*. (2010) demonstrated that resection of a structurally intact hippocampus resulted in loss of visual naming ability, despite pre-operative mapping of the cortical naming sites.

As a proof of principle that resection of presumably unaffected brain tissue worsens cognitive outcome in TLE, we recently compared memory outcome after temporal lobe surgery in 15 MRI- and histopathologically-negative patients and 15 pairwise-matched patients with MRI and histopathologically-proven lesions. Clinical (*e.g*. side and site of surgery, type of surgery, and onset and duration of epilepsy) and neuropsychological performance, other than memory (*e.g*. IQ, attention), were considered as the matching criteria. As for the question of whether resected tissues were involved in epilepsy, it is important to note that 12/15 non-lesional patients showed no postoperative response with regards to seizures. It was hypothesized that preoperative differences in memory outcome should reveal the impact of the lesion on memory, whereas postoperative differences should reveal the impact of resection of non-lesional tissues on memory. The results impressively showed that for the truly non-lesional TLE patients, memory is mostly unimpaired before surgery and drops to a postoperative level which is also observed in lesional patients after surgery (Helmstaedter *et al*., 2011a) (*figure 2*).

How selective is selective surgery?

SAH is a procedure aimed at the specific resection of pathological mesial brain tissue whilst preserving non-affected lateral cortex which, to a varying degree, is included in standard ATL. However, the selectivity of TLE surgery is limited by the fact that it may cause collateral neocortical damage due to the surgical approach. In this regard, we demonstrated that damage of neocortical tissues adjacent to trans-sylvian surgery should be considered as a decisive determinant for postoperative decline of 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 regards 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 mesial resection, negatively assessed by measurement of the residual hippocampus after surgery, was of no relevance for outcome in verbal learning or memory (Helmstaedter *et al*., 2004). With this study, we identified one of

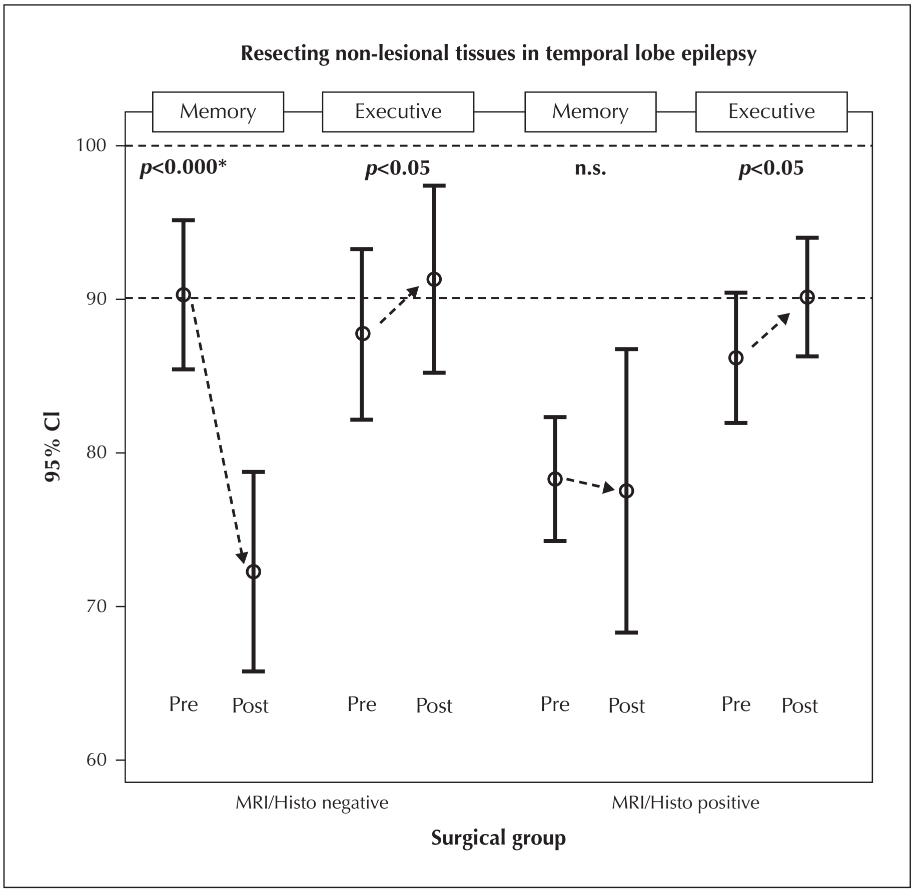

Figure 2. Differential pre- and postoperative combined memory (verbal/nonverbal: VLMT German AVLT, DCS-R) and executive score (letter cancellation/verbal fluency) for 10 left- and 5 right-sided resected patients with MRI and histopathologically-negative TLE *versus* 15 matched lesional controls.
Note 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 tended to improve in both groups, which may by part be due to a practice effect.

the possible reasons for inconsistent memory outcomes reported by studies which compared surgical approaches in the literature.

Another factor may be the dissection *versus* preservation of fibre tracts. At present, there are three major approaches to access the mesial structures in selective AH; the trans-sylvian, trans-cortical/trans-temporal, and sub-temporal approach. The trans-sylvian approach may affect the superior temporal gyrus and the adjacent frontal lobe, the trans-temporal approach may affect the middle temporal gyrus, and the sub-temporal approach may affect the inferior temporal gyrus. Another difference between 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 discussed the potential role of the temporal stem in the appearance of amnesia in a study in which lesional models of amnesia were compared between humans and animals (Horel, 1978).

By comparing trans-sylvian and trans-cortical surgery in a randomised trial of 80 patients who received surgery, we were unable to find a difference in outcome with regards to memory, however, better postoperative recovery of executive functions following the trans-temporal approach was observed (Lutz *et al.*, 2004). We were surprised to find no difference with regards to learning or memory, however, in the light of what is discussed below, it cannot be excluded that the effects were overlooked by the memory test used (German AVLT).

Very positive cognitive outcomes, *i.e.* almost no memory decline or improvements, have been reported in two studies on SAH using a sub-temporal approach (Hori *et al.*, 2003; Hori *et al.*, 2007). In a third study, Takaya *et al.* (2009) furthermore found that memory, assessed using the Wechsler Memory Scale

(WMS), 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 only 7 patients. Unfortunately, a control condition (another type of surgery) was not used in any of these studies, nor was the eventual effect of basal temporal lesions on language taken into consideration (Trebuchon-Da Fonseca *et al*., 2009). A study by Mikuni *et al*. (2006), in which the potential functional relevance of the basal language area was considered, focused only on memory. In this study, the basal language area, defined by 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 WMS was chosen for memory assessment at baseline and follow-up without explicitly controlling for practice effects. The WMS is highly confounded by non-memory functions (IQ, language, and executive functions) (Helmstaedter *et al*., 2009a). 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* trans-sylvian surgery (von Rhein *et al*., 2012). In this evaluation, both surgical approaches caused a comparable decline in verbal learning and memory performance. Differential effects became evident with regards to decline in verbal recognition memory (more affected by left trans-sylvian SAH), as well as in verbal semantic fluency and figural memory (more affected by subtemporal SAH) (for memory outcomes independent of side of surgery; see *figure 3*). The findings were discussed and thought to be probably due to the effect on the basal language area which is involved in lexical processing and the effect on the inferior temporal gyrus and ventral stream which have significant roles in visual perception, imagery, and memory (Hamame *et al*., 2012; Hitomi *et al*., 2013).

The temporal stem is not only preserved using the trans-cortical or sub-temporal approach, but also preserved after surgery towards the mesial structures following removal of the tip of the temporal pole until the mesial structures are visually accessible. By comparing memory outcomes after left/right trans-sylvian SAH with those after temporal pole resections and AH in 97 postsurgically seizure-free patients, an association between material (verbal/figural) and side of surgery (left/right) was revealed (Helmstaedter *et al*., 2008). For left-sided surgery, verbal memory outcome was better after temporal pole resection and AH, compared to trans-sylvian SAH; for right-sided surgery, figural memory outcome was better after the trans-sylvian approach, compared to the pole resection and AH. The results were discussed in terms of different importance of the temporal stem and temporal pole for verbal and figural memory processing, respectively. In concluding this section, no single surgical approach may be discerned to be the safest with regards to cognition, irrespective of seizure control. According to the surgical approach, different tissues and fibre tracts that hinder the surgical procedure or locate to adjacent areas may be affected and, either way, this has consequences for cognition.

Variation of the extent of mesial hippocampal resection

In 1995, Wyler and colleagues published the first report of a randomised study of mesial resection length in patients who underwent ATL (Wyler *et al*., 1995). In this study, a maximal mesial resection to the level of the superior colliculus led to a better outcome with regards to 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, adverse memory outcome was associated with resection of non-sclerotic left hippocampus. In contrast to the findings of Wyler *et al*., an early study by Katz *et al*. in 1989 reported greater losses in WMS performance (percent retained), related to the extent of the medial resection (Katz *et al*., 1989). 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, reported an association between verbal memory decline and only larger resection of the inferior and basal temporal gyrus in regression analysis (Joo *et al*., 2005). In the above-mentioned study of Wolf *et al*. (1993), an association between either the lateral or mesial extent of resection and memory outcome was not identified when patients were categorised 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 (Helmstaedter *et al*., 2004).

Thus, based on studies that address mesial resection length, there is no consistent result regarding the question of whether sparing hippocampal tissue will cause better memory outcome or not. With this

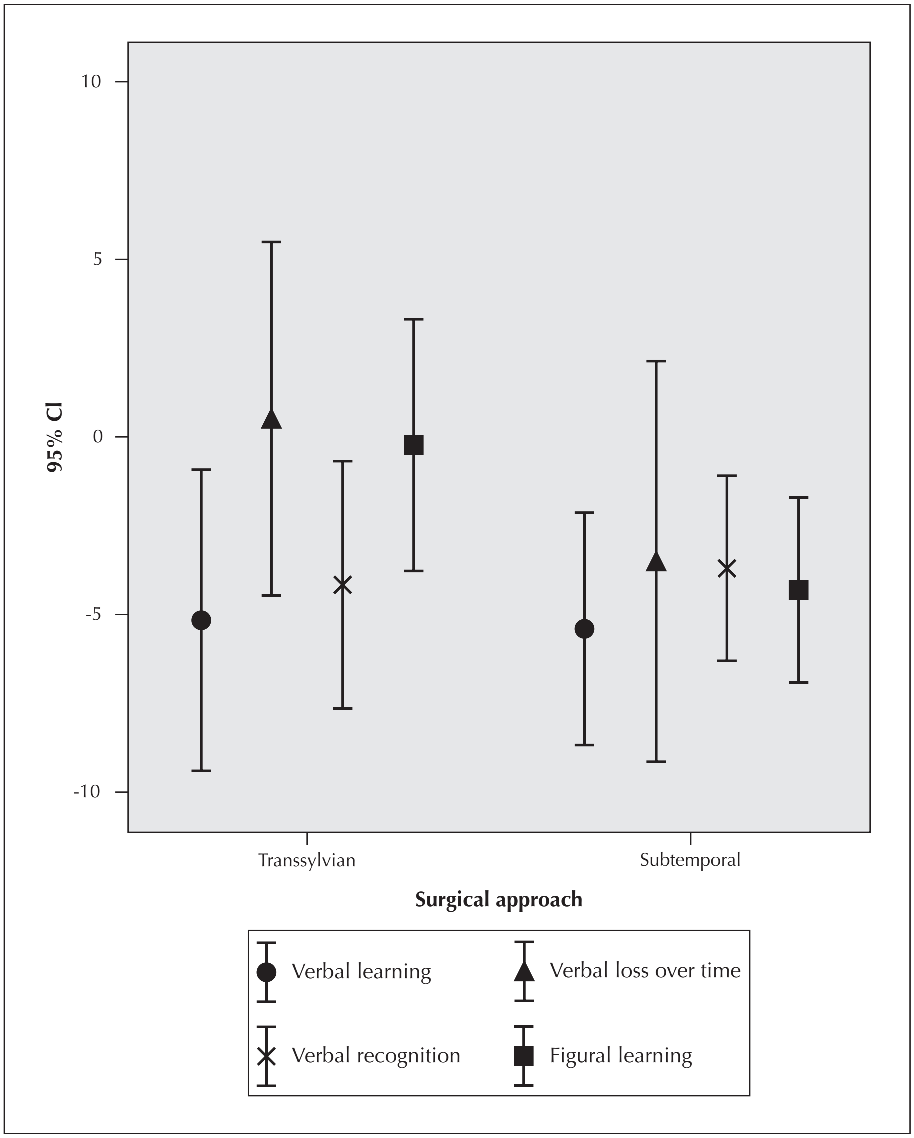

Figure 3. Verbal (VLMT: German AVLT) and figural memory (DCS-R) outcome as a function of surgical approach (trans-sylvian *versus* subtemporal).
Difference in scores (postoperative minus preoperative; standard values: one SD=10; negative values are losses and positive values gains) for verbal learning, memory (loss), and recognition and for figural learning are presented, independent of the side of surgery. The comparable negative effects of surgical approaches on verbal learning and the differential effect on figural learning, which deteriorated particularly after subtemporal surgery, is noted.

premise, we performed an analysis on a subgroup of patients recruited for a large multicentre randomised trial on mesial resection length (Schramm *et al*., 2011). This trial originally comprised all epilepsy patients from three centres in whom the hippocampus was resected, independent of pathology and type of surgery. In order to evaluate memory outcome as a function of hippocampal resection length, it was necessary to exclude possible alternative influences related to different pathologies, different lateral resections, surgical approaches, and combinations of these variables. Focussing on a homogeneous subgroup of patients, who all had mesial pathology and underwent selective surgery, the mesial resection length (2.5 *versus* 3.5 cm), which was determined under surgery using a ruler, did not correlate with seizure or memory outcome, a year after surgery. However, when considering resected hippocampal volumes (MRI volumetry), verbal memory outcome was worse after resection of larger left hippocampal volumes and figural memory outcome was worse following larger resected volumes on either side (Gross *et al*., 2008; Helmstaedter *et al*., 2011b). The respective findings for the left temporal resected group are presented in *figure 4*. Similar to

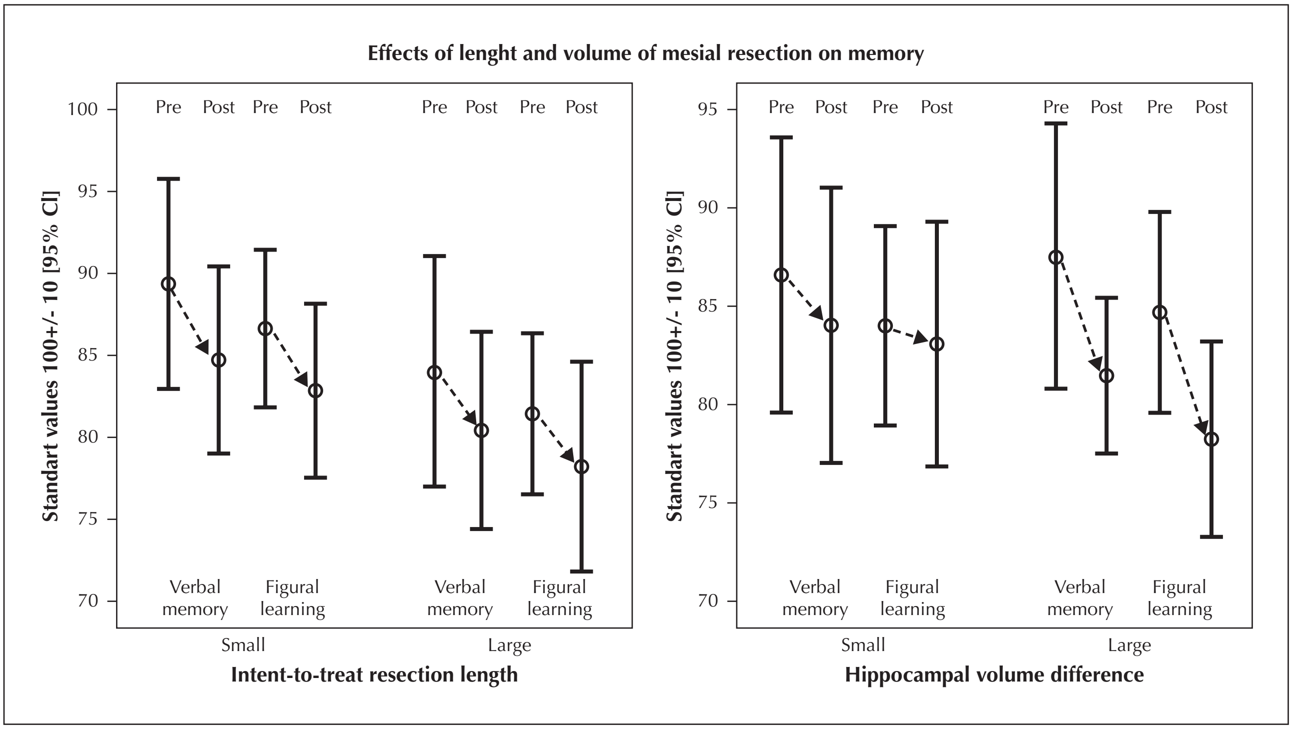

Figure 4. Verbal (VLMT: German AVLT) and figural memory (DCS-R) outcome in patients with left M-TLE after SAH as a function of the intended hippocampal resection length (2.5 *versus* 3.5 cm) and the resected hippocampal volume (median split).
Scores represent standard scores with mean=100, SD=10. The resected volume, taking preoperative pathology into account but not the intended resection length, is related to verbal and figural memory outcome.

that of Wyler's randomised study of ATL (Wyler *et al.*, 1995), the major message from this study, with regards to SAH, was that consideration of resection length is irrelevant if the pathology at baseline is not taken into consideration. Thus, a large resection of an atrophied hippocampus will have fewer consequences than a short resection of a non-atrophied hippocampus.

The importance of removal of functional hippocampal tissue is in line with Baxendaleĭs finding that shrinkage of the hippocampal remnant after surgery is relevant to memory outcome (Baxendale *et al.*, 2000) and is also in line with recent findings on the dependency of memory outcomes on functionality of the posterior hippocampus, as determined by functional MRI (Baxendale *et al.*, 2000; Bonelli *et al.*, 2010).

In conclusion, we face the same situation with regards to hippocampal resections as we have done for temporal neocortical resections, *i.e.* postoperative decline of learning and memory mostly results from resection or dissection of non-affected 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 is claimed to provide high spatial resolution with the aim of changing the intrinsic epileptic characteristics of radiated tissue. First reports on the neuropsychological outcome appear optimistic (Bartolomei *et al.*, 2008; Barbaro *et al.*, 2009). Comparably, the cognitive outcomes of deep brain stimulation will be of interest in the future. However, it should be established whether stimulation indeed preserves function or whether it interferes with the functionality of the stimulated area (Benabid *et al.*, 2002; Boon *et al.*, 2007; Velasco *et al.*, 2007). In addition, the possible effects of acute or chronic implantation of depth electrodes need to be systematically evaluated. For example, we previously described negative effects of bilateral depth electrode implantation on verbal memory, which were still evident after three months of postoperative follow-up, in patients following right-sided selective TLE surgery (Gleissner *et al.*, 2002). As an example, verbal learning and memory of a 30-year-old female patient of this series, who suffered from right TLE with hippocampal sclerosis, is presented on the left of *figure 5*. Displayed are the standardised values of learning (sum across five learning trials), free recall after a 30-minute delay, and recognition memory, at baseline, after implantation of bilateral depth electrodes (implanted posteriorly along the hippocampal axis), postoperatively. The patient became seizure-free. Following implantation, verbal memory significantly dropped with regards to long-term memory. After surgery, the patient partly recovered

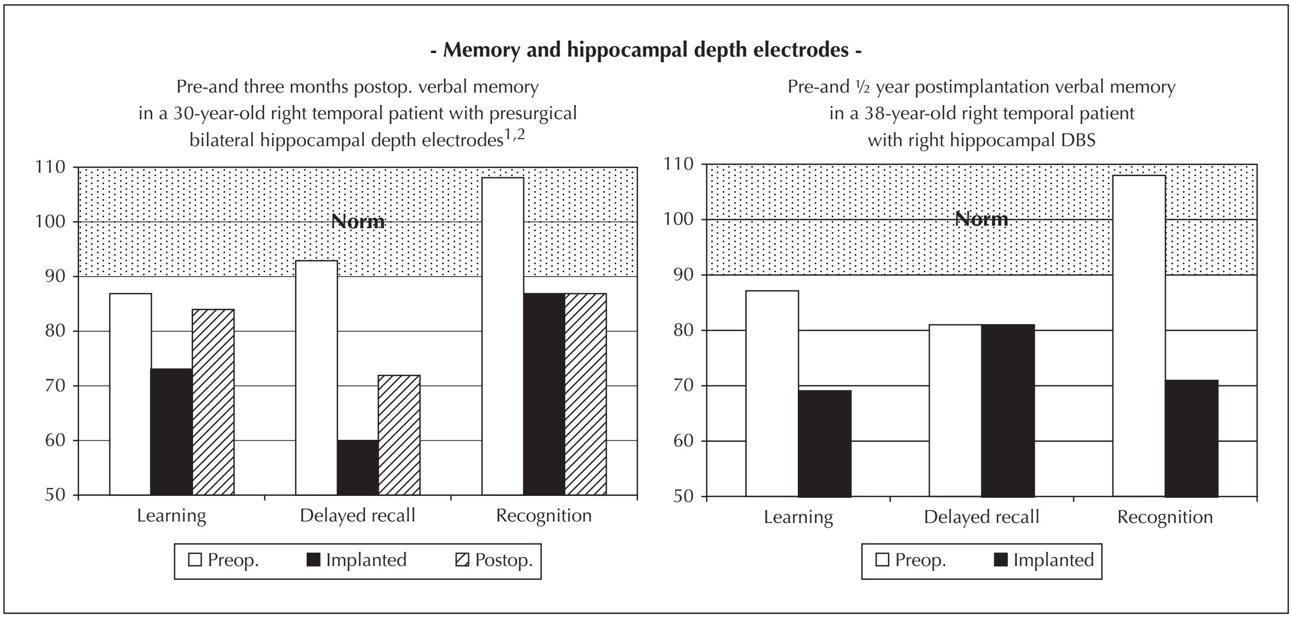

Figure 5. Left panel: impact of bilateral hippocampal depth electrodes and right SAH on verbal learning, memory, and recognition (VLMT: German AVLT: standardised values 100±10) in a patient with right M-TLE. Right panel: effect of chronic depth electrode implantation and stimulation on verbal learning, memory, and recognition (standardised values 100±10) in a patient with right M-TLE.

from this impairment, but baseline was not reached. After one year of follow-up, however, the effects of bilateral depth electrode implantation observed in the group of right temporal patients in 2002 was no longer present (Gleissner *et al.*, 2004). Verbal learning and memory performance of a patient who became seizure-free due to right hippocampal deep brain stimulation is presented on the right of *figure 5*. Displayed are the performances at baseline and six months after onset of stimulation, 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 selective injury of the hippocampi affects memory performance, but also 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 *et al.* (2010) on different effects of sparing *versus* resecting the hippocampus, a group of patients who underwent stereotactic amygdalo-hippocampectomy was compared with patients who received tailored surgery, including the entorhinal cortex but not the hippocampus. The major aim of this study was to describe dissociated impairment between recollection in hippocampectomised patients, irrespective of the side of surgery *versus* impairment of familiarity judgements after removal of the entorhinal cortex. Unfortunately, no pre- to postsurgical data were presented and healthy subjects served as a reference. If this type of surgery represents an alternative to commonly used surgical approaches, a more detailed knowledge of neuropsychological outcomes under controlled conditions would be highly appreciated.

Surgery within the right non-dominant hemisphere

Up to now, this review has mainly addressed verbal learning and memory, and this focus can be discerned throughout the literature with regards to memory in TLE. There is good reason for this bias. Verbal memory, in contrast to figural memory, is relatively regularly affected when the dominant temporal lobe and its substructures are involved. Superficially, left and right hemispheric differences appear to be easily explained, however, although deficits in semantic and episodic verbal memory or language are associated with left temporal lobe epilepsies, it is in fact very difficult to determine specific deficits associated with right 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 (Saling, 2009). Unfortunately, more experimental tests on object location which appear to show specific impairment in right TLE (Abrahams *et al.*, 1997) have not been elaborated or are too complex to be used in clinical practice. Some researchers have demonstrated lateralisation-dependent impairment in visual spatial memory in patients with TLE who received surgery (Smith and Milner, 1989). The value of these results for monitoring surgery is difficult to determine since the pathological condition before surgery is not taken into consideration. Similarly, studies are difficult to rate which show differences in performances in right temporal lobe patients when compared to healthy subjects, rather than left temporal lobe patients (Saling, 2009).

Standard tests of figural and visual spatial memory only partially show the expected differences between left and right temporal lobe epilepsies (Hampstead *et al*., 2010; Helmstaedter *et al*., 1991; Piguet *et al*., 1994). More often, they fail to show differences (Barr *et al*., 2004; Barr *et al*., 1997; McConley *et al*., 2008) or require different evaluations in order to gain specificity (Helmstaedter *et al*., 1995). Moreover, even though establishing right temporal lobe dysfunction before surgery is possible, monitoring the effects of epilepsy surgery within the right temporal lobe may not necessarily be possible with such tests (*see table 1*) (Gleissner *et al*., 1998a). Two of the few studies that demonstrated dissociated surgical outcome (left/right verbal/figural) have already been cited (Katz *et al*., 1989; Helmstaedter *et al*., 2008). Right temporal lobe surgery does cause decline in verbal and also figural memory, and this is often overseen. To sum up losses in either verbal or figural memory, 45% of 365 patients with right temporal lobe resections in our series (*see table 1*) presented with memory loss and 8% presented with loss in both performances. For the 351 patients with left temporal lobe resections, 54% presented with loss of either verbal or figural memory and 16% presented with loss of both. These figures, although evaluated on the basis of gross test-wise categorisations, parallel the outcome reported on a test score level in our longitudinal study (Helmstaedter *et al*., 2003). The fact that, unlike left temporal lobe surgery, losses following right temporal lobe 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 right mesial structures, and it appears even more difficult to specifically relate impairments to right-sided surgery. We recently concluded, based on a long-term study of patients aged 6-68, that left/right temporal lobe differences in verbal memory become evident only in the mature brain and not in children or the elderly (Helmstaedter and Elger, 2009). Figural memory appears to be organised differently to verbal memory. This is indicated by observations of "crowding" or the "suppression" of figural-visual memory in the presence of atypical language dominance and the differential impact of lateralised epilepsies on material-specific memory in men and women (Helmstaedter *et al*., 1994; Helmstaedter *et al*., 1999). Similar effects on language functions have not yet been described. On discussing the "crowding" effect in 1994, we suggested that it would be better to consider two hemisphere-specific styles of information processing rather than material specificity. Material-specific tasks represent an expression and not an equivalent of the respective type of information processing (Helmstaedter *et al*., 1994). In this respect, Michael Saling in 2009 made the statement that hemispheric lateralisation is task- rather than material-specific (Saling, 2009).

Taking into account the large number of left and right temporal lobe patients who are not left-side dominant for language (*see table 1*), it comes as no surprise that lateralisation *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 verbalisation of the non-verbal material. Verbalisation almost always interferes with (or supports?) figural/visual spatial memory assessment and this should be controlled either by choosing abstract and hard-to-verbalise material or by increasing the complexity of the material in such a way that verbal memory fails to compensate for the impairment (Helmstaedter *et al*., 1995).

As a more general consideration, one may discuss whether the common concepts of testing which are relevant in the investigation of left hemisphere function (*i.e.* mental reasoning) are appropriate to further delineate right hemisphere functions. The identification and assessment of right hemisphere functions therefore 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 with a view into the nature of cognitive impairment associated with epilepsy and after epilepsy surgery. However, neuropsychological outcomes much depend on the tests used. As already demonstrated by Jones-Gotman in 1993, different epilepsy centres use different tests or test batteries (Jones-Gotman *et al*., 1993) and recent reviews suggest that this has not changed since then. At best, one can make recommendations as to which tests should be used for neuropsychological assessment in epilepsy patients. A recent evaluation of tests which are currently used in epilepsy centres in German-speaking countries showed that over 200 different

tools were in use and that there was, at best, some common sense with regards to which functional domains should be addressed (Witt and Helmstaedter, 2009a).
Hence, discussing the outcomes of epilepsy surgery and different surgical approaches also requires a discussion of the tests in use and their psychometric features. Focusing on memory tests in TLE, different tests appear to have different sensitivity and specificity with regards to differentially lateralised and localised temporal lobe lesions and epilepsies (Loring *et al.*, 2008). A comparison of the Logical Memory subtest from the WMS-R, the California Verbal Learning Test, and the Verbal Learning and Memory Test showed that although the three tests provided overlapping indicators for TLE or mesial pathology, they are barely interchangeable (Helmstaedter *et al.*, 2009b). The tests addressed different aspects of semantic processing and memory organisation, and thus were differentially sensitive to performance and impairments in non-memory domains. This is indicated by the different correlations between the three memory tests and non-memory functions which are reported in *table 2*. Accordingly, confounding memory testing by demands on language, attention, intelligence, ordering, or semantic memory can easily bias the findings. Specific temporal or temporo-mesial memory impairment may be overlooked or the memory test may pick up impairments in extratemporal executive functions, semantic memory, and language functions (comprehension, fluency). Postoperatively, for example, the often observed improvements in executive functions can support short-term and working memory which can compensate for additional problems with long-term retention. Thus, study results obtained with different tests must be compared with great caution.
Centres differ not only with regards to neuropsychological tests in use. For example, we compared baseline and outcome data obtained using the same tests at different surgical centres (Zürich, Freiburg, Berlin) and in each case, a highly significant centre effect was obtained (Helmstaedter, 2004). Different factors may contribute to centre effects and these should be controlled for when comparing or merging data from different centres. Recruited patients may differ (collection bias), presurgical diagnoses may differ (drug withdrawal, provoked seizures, subdural or dept electrodes), and only some patients are placed on a postoperative drug schedule, preoperatively. Additional scientifically-motivated neuropsychological evaluations (*e.g.* in fMRI or EEG/ERP studies) might interfere with routine neuropsychological testing. In addition, there is not yet a full consensus on interpretation of imaging and neuropathological data and neurologists/patients may be willing to take different risks with regards to referral for surgery, also surgeons may follow an individual approach. Further factors may be added, but the major message is that neuropsychologists (although not exclusively) are very likely biased by their own view and procedures, and that a greater exchange of knowledge and a common language are essential to achieve further progress in order to discern the best treatment for the individual patient with pharmacoresistant epilepsy.

Does memory impairment matter?

As discussed in the previous sections, patients undergoing epilepsy surgery have an increased risk of further memory impairment after surgery. The explicit aim of this article was to discuss whether there is a greater preservation of patients' cognitive capabilities following different individual and selective surgical approaches, relative to extended standard resections. The answer to this is yes, however, for neuropsychologists, this is a legitimate question since it may not be clear whether subtle differences in memory outcome, which are assessed using sophisticated tests in a laboratory, have any relevance for the patient who wants foremost to become seizure-free.
In this regard, it has been demonstrated that patients are, in part, willing to risk some cognitive decline in order to become seizure-free (Langfitt *et al.*, 2007; Helmstaedter, 2008). In our long term follow-up study, we discussed so called "double losers", referring to patients who, in the long run, do not become seizure-free and, in addition, experience significant memory decline (Helmstaedter *et al.*, 2003). Of the group of 732 TLE patients presented in *table 1*, about 15% belong to this group (verbal memory decline >2 SD). Including patients who are not seizure-free with milder losses (decline >1 SD), the group increases to 37%. In the long-term, follow-up study of Langfitt *et al.* (2007), a group of double losers (only 8%) were identified to be at a particular risk of losing quality of life over time.
Dependent on aetiology, 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 (Helmstaedter *et al.*, 2002).
One should bear in mind that patients with long-lasting epilepsies, particularly with early onset, have already adapted to their impairments in a way that cognitive losses due to surgery will probably not affect domains which are of major importance for their every day life. However, patients postoperative performance is still often considerably below that of healthy subjects, and patients often are still aware of, and suffer

Table 2. Correlations between verbal memory tests and tests on IQ, executive, and language functions (only statistically significant results are displayed).

		Vocabulary	WAIS-R IQ	Digits	Speed	Flexibility	Similarities	Compre-hension	Fluency	Naming
VLMT total learning	r	NA	0.444^{**}	0.417^{**}	0.268^{*}	NA	0.316^{*}	0.419^{**}	0.493^{**}	NA
	sig.		0.002	0.001	0.040		0.041	0.002	0.000	
VLMT delayed free recall	r	NA	0.348^{*}	NA	NA	NA	NA	0.402^{**}	NA	0.299^{*}
	sig.		0.015					0.003		0.035
VLMT loss over time	r	NA	NA	NA	NA	NA	NA	NA	NA	NA
	sig.									
VLMT recognition	r	NA	0.534^{**}	NA	NA	NA	0.347^{*}	0.534^{**}	0.306^{*}	0.352^{*}
	sig.		0.000				0.024	0.000	0.018	0.012
CVLT total learning	r	0.295^{*}	0.424^{**}	0.391^{**}	0.342^{**}	0.388^{**}	0.431^{**}	0.407^{**}	0.516^{**}	0.410^{**}
	sig.	0.044	0.003	0.002	0.008	0.003	0.004	0.003	0	0.003
CVLT delay free recall	r	0.317^{*}	0.474^{**}	0.324^{*}	0.470^{**}	0.423^{**}	0.393^{**}	0.562^{**}	0.554^{**}	0.463^{**}
	sig.	0.030	0.001	0.011	0.000	0.001	0.010	0.000	0.000	0.001
CVLT loss over time	r	NA	NA	NA	0.372^{**}	NA	NA	0.400^{**}	0.340^{**}	0.292^{*}
	sig.				0.004			0.004	0.009	0.04
CVLT recognition	r	NA	NA	NA	NA	0.296^{*}	NA	NA	NA	NA
	sig.					0.026				
Logical Memory I	P	0.329^{*}	0.331^{*}	NA	NA	0.376^{**}	0.404^{**}	NA	0.268^{*}	0.369^{**}
	sig.	0.024	0.022			0.004	0.008		0.040	0.008
Logical Memory II	P	0.298^{*}	0.356^{*}	0.371^{**}	NA	0.307^{*}	0.387^{*}	0.299^{*}	0.258^{*}	0.503^{**}
	sig.	0.042	0.013	0.003		0.020	0.011	0.033	0.049	0.000

VLMT: German AVLT; CVLT: California Verbal Learning Test; WMS: Wechsler Memory Scale; WAIS: Wechsler Adult Intelligence Scale revised; NA: not applicable; r: correlation coefficient; sig: significance level.
**Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed).

from, their impairments. Contrary to what one may expect, a study addressing the relationship between performance and complaint showed that lower cognitive demands were associated with stronger, rather than weaker, subjective complaints (Gleissner *et al.*, 1998b). Other studies indicate that there is no reliable correlation between subjective complaints and memory performance, and that complaints about memory problems after surgery are better considered as a marker of depression (Sawrie *et al.*, 1999; Baxendale and Thompson, 2005). Different findings and positions on the ecological validity issue demonstrate that more research, as well as presumably more reliable ways for the assessment of the consequences of memory impairment and loss on everyday functioning in TLE, are needed. In any case, quality of life questionnaires do not appear to be sufficient.

With regards to the memory tests in use, we have previously demonstrated that they not only provide clinical but also ecological validity (Helmstaedter *et al.*, 1998b). In addition, we were repeatedly able to demonstrate a correlation between surgical memory outcome and psychosocial socioeconomic outcome (Lendt *et al.*, 1997; Helmstaedter *et al.*, 2003). Thus, memory impairment and change in memory are important.

Summary

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

As already mentioned, this article focuses on the experiences, development, and observations primarily from one centre in Bonn/Germany over a period of more than 20 years, and is referenced accordingly. The different views and opinions of others are acknowledged and the ongoing discourse and initiation of further studies is highly appreciated.

Of major concern is how neuropsychology may contribute to improvements in surgical outcome. Quality and outcome control, however, require instruments which reliably reflect patients' functionality at baseline as well as changes in intervention-related performance. A consensus regarding assessments is required in order to enable better comparison and communication across centres (Witt *et al.*, 2009; Witt and Helmstaedter, 2009b; Helmstaedter and Witt, 2012). In addition, measures that are more valid than quality of life questionnaires or depression inventories are needed to assess the everyday functioning of patients (Helmstaedter *et al.*, 2011c). Finally, the long-term consequences of (additional) cognitive impairments in the developing and aging brain remain to be determined in more detail as well as the role of uncontrolled seizures, interictal epileptic activity, and antiepileptic treatment for cognitive outcomes (Helmstaedter *et al.*, 2011d). □

Disclosures.

C. Helmstaedter declares that there are no conflicts of interest with regard to the contents of this article.

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