Original article

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Impact of side of lesion, seizure outcome and interictal epileptiform discharges on attention and memory after surgery in temporal lobe epilepsy

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ABSTRACT – *Purpose.* To determine the impact of side of surgery, seizure outcome and interictal epileptiform discharges (IEDs) on attention and memory in a cohort of patients with temporal lobe epilepsy who had undergone unilateral mesial temporal lobe resection. *Material and methods.* Ninety-four patients were investigated pre- and postoperatively by means of a standardised neuropsychological battery measuring subcomponents of attention, as well as short-term, working and long-term memory. The side of epilepsy surgery, seizure outcome and the presence of postoperative IEDs, as well as their possible relationship to the neuropsychological changes, were assessed. Statistical data were analysed using a repeated-measures MANOVA. *Results.* The absence of seizures following surgery had a positive effect on short-term memory and attentional control. The occurrence of IEDs was found in patients with impaired figural learning. In terms of attentional control and working memory, patients who continued to present IEDs had also scored lower in these domains prior to surgery. *Conclusion.* IEDs had an effect independent of seizure presence, but were found to have a "supplementary negative effect" when the two variables were combined.

Key words: epilepsy surgery, outcome, lesion, interictal epileptiform discharges, attention, memory

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Temporal lobe epilepsy (TLE) is the most common focal epilepsy syndrome amongst adults (Engel, 2001). Cognitive deficits are frequent. Material-specific memory loss is associated with unilateral mesial temporal lobe lesions and is side dependent. Verbal memory deficits are regularly observed for left-sided lesions and, less commonly, visual memory deficits for right-sided lesions (Raspall *et al.*, 2005). On the other hand, dysfunctions of the temporolateral structures appear to be involved in short-term and working memory, in addition to attentional deficits (Squire, 1992; Helmstaedter *et al.*, 1997).

Unilateral temporal lobe surgery aims at resection of the epileptic focus and consequently the control of functional disturbances. Seizure control can be achieved in about 70% of all operated patients (Gleissner *et al.*, 2002; Sanyal *et al.*, 2005), and cognitive decline caused by chronic seizures can be stopped or even reversed (Wachi *et al.*, 2001). However, prediction of cognitive outcome depends on several interacting variables, such as age at epilepsy onset, preoperative seizure frequency, overall duration of disease, age at time of surgery (White *et al.*, 2002), the side effects of anticonvulsive medication, IQ, educational status (Piazzini *et al.*, 2006), and possibly the postoperative persistence of interictal epileptiform discharges (IEDs) in patients who have stopped experiencing clinically observable seizures. IEDs are manifested by a large intracellular depolarisation followed by inhibiting hyperpolarization, and may mimic a "miniseizure" (Holmes and Lenck-Santini, 2006). Simultaneous EEG recording and cognitive testing report that IEDs particularly influence the so-called transient features of cognition, such as attention, which is associated with a decrease in alpha activity and an increase in beta activity (Aldenkamp and Arends, 2004a; Piccirilli *et al.*, 1994; Foxe *et al.*, 1998). However, IEDs have been shown to have an "additional effect" on seizures and are often insufficient to induce cognitive impairment alone (Aldenkamp and Arends, 2004b). Other research has demonstrated that long-term consolidation processes which are required for verbal and visual memory performance were affected, especially in patients with frequent abnormal interictal epileptiform EEG activity (Mameniskiene *et al.*, 2006). In this study, we explored the effect of surgery and the side of surgery (left versus right) on attention and memory functions within a large patient group. Furthermore, we hypothesized that seizure freedom would have a favourable effect upon cognitive outcome. Finally, we analyzed the impact of IEDs on attention and memory function independently of seizure outcome, thus trying to reflect the impact of the still active irritative zone.

Material and methods

Patient characteristics

The patient cohort consisted of 94 patients with left (n=50) or right (n=44) pharmaco-resistant mesial temporal lobe epilepsy. Specifically, 14 patients had a supplementary dysplasia of the temporal lobe, ten had grey-white matter blurring, two had a volume reduction of the temporal lobe, and four patients had associated tumours in the temporal cortex (removed at the same time the amygdalo-hippocampectomies were performed).

Sixty-one patients received only selective amygdalo hippocampectomies (sAHEs), nine had sAHE in addition to anterior temporal pole resections, 22 had a two-third anterior temporal lobectomy with sAHE, and two had additional lesionectomies. Demographic and clinical variables are summarized in *table 1*.

Assessments for this study were performed a few months prior to and one year after epilepsy surgery. Preoperative technical evaluation included prolonged (lasting several days) video-EEG scalp monitoring which showed IEDs in all patients. Magnetic resonance imaging (MRI) was performed using a 1.5 Tesla Magneton "Symphony Maestro Class" Siemens (Erlangen, Germany). The neuroradiological data showed hippocampal atrophy/sclerosis ipsilateral to the seizure onset zone in all patients. Further inclusion criteria consisted of native German speakers and those scoring at least 80 points on the standardized MWT-B IQ test (Lehrl, 1999). Patients who were left-handed or ambidextrous had to present language domain in the left hemisphere according to fMRI. After surgery, antiepileptic drugs (AEDs) were continued at stable doses until the one-year follow-up appointment.

Table 1. Demographic and clinical variables.

Gender (male/female)	**55/49**
Age (in years) at time of surgery	Mean 38.4 ± 10.84
Age (in years) at epilepsy onset	Mean 12.8 ± 10.22
Preoperative monthly seizure frequency	Mean 10.22 ± 16.67
IQ	Mean 108 ± 10.27
Handedness (right/left/ambidexter)	79/12/3
Education, *n* (%)	
- Abitur (high school)	15 (16)
- Realschule (middle school)	16 (17)
- Hauptschule (elementary school)	63 (67)

Seizure outcome assessment

Postoperative seizure outcome was determined at the one-year follow-up appointment, according to Engel classification.

EEG examination

Postoperative interictal epileptiform activity was evaluated by means of a 40-minute surface EEG recording (Nihon/Konden YE521AG) with the usual international 10-20 system and including three minutes of hyperventilation and photic stimulation. Patients were regrouped into two categories: those presenting normal EEG findings and those who continued to have interictal epileptiform discharges (IEDs). In every case these IEDs were recorded ipsilateral to the resected zone.

Neuropsychological testing

Neuropsychological evaluations were given to patients who had stable AED doses during seizure-free periods. The shortest interval between a seizure and neuropsychological testing was 12 hours. The pre- and postoperative test instruments were part of a standardised neuropsychological assessment battery for epilepsy surgery used at the centre. The evaluation addressed the cognitive domains of attention, numeric/spatial short-term and working memory, and verbal/figural long-term memory. The tools are presented briefly in *table 2*.

Statistics

Mean values and absolute values for the total number and percentages were calculated for parametric and non-parametric variables, respectively. The statistical analysis was run with Statistica, version 7.0. The results were obtained by repeated measurement MANOVA using side of surgery (right temporal lobe epilepsy [RTLE]/left temporal lobe epilepsy [LTLE]), seizure outcome (persistence/seizure-free) and postoperative EEG outcome (IEDs/no IEDs) as a "between factor", and time at examination (preoperative/one year postoperative) as a "within factor". Neuropsychological measures served as dependent variables. For all the aforementioned tests, except those which measure reaction time, omissions and errors (TAP 1.7), the higher the score the better the performance. TAP scores for omissions and errors were not distributed normally, and had to be transformed logarithmically (log [x+1]) prior to MANOVA analysis (according to Abdi, 1987; Lillefors, 1967). In clinical studies with large patient populations, a p-value of <0.01 is considered to be statistically significant. However, given that there was a relatively small cohort of 94 patients, a p-value of <0.05 was instead taken as statistically significant, with <0.1 taken as a trend. The impact of the secondary variables "age at time of operation", "age at epilepsy onset", "monthly frequency" and "IQ", were controlled using ANOVA which showed no significant differences between the modalities of the three independent variables: side of lesion, seizure outcome and EEG outcome.

Results

Seizure outcome and EEG findings

Of all the patients, 71.2% (n=67) who underwent surgery were seizure-free and 28.8% (n=27) continued to experience seizures. Additionally, 83% (n=78) showed an absence of IEDs postoperatively, while 17% (n=16) continued to present IEDs. Of the seizure-free patients, 14.9% (n=10) showed IEDs on the routine EEG, whereas 22.2% (n=6) of those with persistent seizures had IEDs.

Of the 61 patients who received only sAHEs, 41 were seizure-free (67.2%) and 20 (32.8%) had persistent seizures. Of the seizure-free patients, five had persistent IEDs (12.2 %) and 36 (87.8%) showed no sign of IEDs. For patients with persistent seizures, IEDs were present for four (20%) and absent for 16 (80%) patients. Twenty-two patients had a two-third anterior temporal lobectomy, of which four patients had persistent seizures (18.1%) and 18 were seizure-free (81.8%). Two seizure-free patients still had IEDs (11.1%) and the remaining two patients had persistent seizures (50%). Three patients had persistent seizures and no epileptiform activity, five of the six seizure-free patients showed IEDs. The two patients who received additional lesionectomies were seizure-free and had no IEDs.

Neuropsychological test scores

Attention

"d2 test". Seizure outcome showed a significant main effect (F=4.70, p=0.03). Furthermore, we found a significant two-way interaction between side of surgery and time of examination (F=5.22, p=0.025). The LTLE group improved postoperatively, but not for the RTLE group. No further effects were obtained.

"Go/No Go test". No significant effects were observed for median reaction times and omissions, although RTLE patients committed significantly more errors (F=6.43, p=0.01).

Table 2. Summary of neuropsychological tests.

Test	Author	Description
d2 Concentration Endurance Test	Brickenkamp, 2002	A "cancel test" exploring "attention to detail". The subject must cross-out the target letters "d" (with 2 bars) with distracting stimuli "d" and "p" (variable number of lines). The "GZ-F" (variable), taken for this study, measures psychomotor speed accuracy and focused attention.
Attention Test Battery (TAP 1.7)	Zimmerman and Fimm, 1992	
1. Go/No Go Test		Measures selective attention by having the subject detect five patterns, two defined as relevant, requiring a button press. This gives the median reaction time, measures of selective attention, and reactions to irrelevant stimuli. The second level of difficulty was used.
2. Incompatibility Task		Measures selective attention by assessing the affinity to interference. The subject is told to press a button each time arrows emerge from a fixed point. The parameters for incompatibility, median reaction time, and errors are assessed.
3. Flexibility Task		Measures the shifting attention from one object to another. A letter and number appear onscreen, and a button must be pressed where the target stimulus is situated. The median reaction time of shifting and false positives was taken as variables for attention flexibility.
4. Divided Attention		Measures the capacity to focus on two actions simultaneously. This requires the subject to press a button during the detection of two different stimuli: visual and auditory. Results were calculated based on the median reaction time, as well as any omissions or false positives.
Wechsler Memory Scale- Revised (WMS-R)	Härting *et al.*, 2000	
1. Digit-Span		Identifies the level of verbal memory performance requiring a repetition of an increasing number of digits in a forward or backward order. The sum of the points is taken as a parameter: short-term memory (forward), and working memory (backward).
2. Corsi-Block-Tapping		Requires the subjects to repeat a demonstrated block-tapping sequence that increases in length. The sum of the points received for each span are taken as variables for spatial short-term memory (forward) and spatial working memory (backward).
VLMT	Helmstaedter *et al.*, 2001	German equivalent of the Rey Auditory Verbal Learning Test (RAVLT). 15 nouns are read aloud by the examiner, followed by free recall (Dg1-Dg5), the variable Dg6 measures the recall after interference and the Dg7 serves as a parameter for delayed recall. Different test versions (A&D) were used pre- and postoperatively.
Diagnosticum für Cerebralschädigung (DCS)	Weidlich and Lamberti, 2001	This tests figural-memory. The subject is told to memorize the geometric images and reproduce them with five sticks after presentation is completed (DCS 6). After 30 minutes, delayed recall is performed (DCS 7). Different test versions (original and parallel) were used pre- and postoperatively.

Incompatibility

No significant effects were found for reaction time. The moment of examination turned out to be a significant within-factor for errors (F=5.30, p=0.02). One year after surgery patients committed fewer errors.

Flexibility

A main effect of examination time on median reaction times was observed (F=7.34, p=0.008). Patients acted significantly faster after surgical intervention. Patients who became seizure-free tended to perform better, regardless of the time of examination, pre- as well as postoperatively (F=3.68, p=0.06). The variable errors did not reveal any effect.

Divided attention

We observed an interaction between time of examination and seizure outcome for the median reaction times (F=4.18, p=0.04). Postoperatively, seizure-free patients were significantly faster and patients with persistent seizures were significantly slower *(figure 1)*. In addition, patients who continued to present IEDs in the one-year postoperative routine EEG tended to have a slower performance and a higher omission rate, regardless of the time of examination and their seizure outcome.

Short-term and working memory

A group interaction effect which was close to significance was found between seizure outcome and time of examination (F=3.81, p=0.054), for the Digit-Span forward scores. Seizure freedom was significantly related to a longer span, while patients with persistent seizures had a shorter span score postoperatively *(figure 2)*. The Digit-Span backward measure showed a tendency towards a lower score for patients with IEDs (F=2.79, p=0.09), regardless of the time of examination or the seizure outcome. Group differences for the spatial forward and backward span were not found.

Verbal memory

No group differences were calculated for the list learning performance and the 30-minute delayed recall [VLMT (Dg1-Dg5) and (Dg7)]. However, LTLE patients had significantly lower scores on immediate recall (Dg6) than RTLE patients (F=6.44, p=0.012). No further group differences were identified.

Figural memory

For the DCS D6 learning score, a significant interaction effect was found between time of examination and EEG pattern (F=5.516, p=0.02) *(figure 3)*. Patients with persistent epileptiform activity had a poorer postoperative score than patients with a normal EEG. This difference applied to patients regardless of their seizure outcome and onset side. No effects were observed for the delayed figure recall (DCS 7).

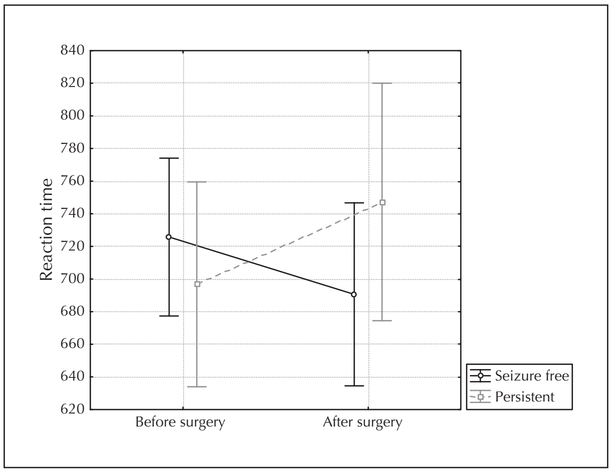

Figure 1. Seizure outcome x time at examination for reaction time on divided attention.

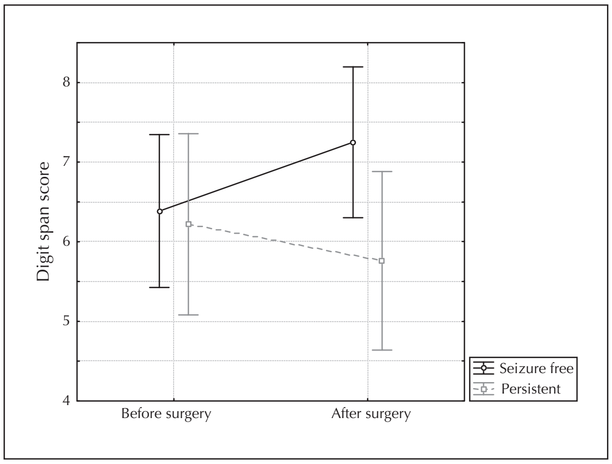

Figure 2. Seizure outcome x time at examination for digit span forward.

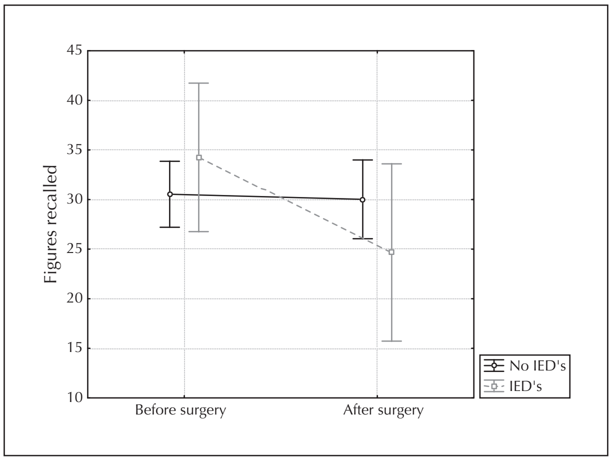

Figure 3. EEG x T for DCS 6 (see *table 2*).

Discussion

This study assessed the effects of mesial TLE surgery on memory and attentional subcomponents in a large sample of patients. More specifically, the goal was to analyse the impact of the side of lesion, postoperative seizure and EEG outcome. Special interest was directed at the investigation of cognitive deficits which may not only be attributed to unfavourable seizure outcome, but be a consequence of persisting IED activity.

Certainly, one can argue that the sample size was not completely homogenous since a considerable proportion of patients showed additional extramesial lesions prior to surgery. However, acceptable statistics would not have been possible if we had excluded these patients, due to the limited number involved. Furthermore, we feel that the almost identical results for outcome and moreover, the distribution of patients with and without postoperative IEDs in both seizure-free and seizure patient groups (even when controlling for only those with sAHE), justifies the assumption that our findings are likely to be statistically comparable to a larger patient sample and applicable if one considers purely mesial temporal lesions and sAHE.

TLE surgery candidates belong to the surgical group with the best seizure outcome (Engel, 2001). Indeed, the majority (71.2%) of our patients became seizure-free postoperatively. These findings are comparable to prior studies, such as Gleissner *et al.* (2002) and Sanyal *et al.* (2005), both of whom reported similar rates. In our sample, IEDs persisted postoperatively in 16 patients (17%), ten of whom did not experience postoperative seizures. Inversely, not all patients with persisting seizures presented IEDs during their EEG examination. Although the variable relationship between IEDs and seizures has been known in the literature since the report of Gibbs *et al.* (1936), more recent research has concluded that the relationship between seizures and IEDs is inter-dependent. Janszky *et al.* (2003) demonstrated in pharmaco-resistant pre-surgical TLE patients that IEDs are chronic time and location indicators of preceding seizures. The persistence of IEDs with an absence of seizures can be explained by the impact of the still active irritative zone (Rosenow and Lüders, 2001).

In addition, variables measuring basal selective attention components were analysed. The computerized Go/No Go test showed more errors among RTLE patients and the d2 paper/pencil task showed better postoperative scores, but only for the LTLE group. These findings most likely reflect the importance of the functional integrity of the non-dominant temporal lobe and its interaction with the large, right-sided frontoparietal network which underlies basal sustained and selective attention, as reported previously by Pardo *et al.* (1991). One year after surgery. patients performed better in the incompatibility and flexibility task. This can be explained by the fact that postoperative recuperation of attentional functions in TLE is common, irrespective of seizure outcome and has already been demonstrated through the use of various tools (Lutz *et al.*, 2004; Helmstaedter *et al.*, 2008a, Fleck *et al.*, 2002).

In tasks addressing divided attention and flexibility, seizure-free patients reacted significantly faster postoperatively than patients with ongoing seizures. Previous studies have already focused on the potential effects of seizures on attention control subcomponents. For example, McDonald *et al.* (2005) used the Colour-Word Interference Test (CWIT) to assess inhibition and attentional switching in TLE patients. Their findings revealed that seizure frequency was related to errors in the inhibition/switching task, although the side of surgery had no impact. Furthermore, right and left hemisphere regions appear to be equally distributed for inhibition tasks and more specifically, the left prefrontal cortex seems to play a role in executive control of the flexible switching (Harrison *et al.*, 2005). Previously, Billingsley *et al.* (2000) described deficits in a lexical and spatial-cue task, after LTLE surgery. RTLE patients showed deficits for the spatial-cue task only, suggesting a material-specificity effect. McDonald *et al.* (2005) referred to language demands on their inhibition/switching task (Colour Word Interference Test, CWIT) and argued that a distributed network throughout the left hemisphere could have been employed. The Flexibility test by Zimmerman and Fimm (1992) is a visual assessment tool with limited verbal demands, and thus, the absence of effects for left-sided lesions could be explained by smaller involvement of a language dimension in the flexibility task as compared to the inhibition/switching task used by McDonald *et al.* (2005).

Divided attention was poorer in patients who continued to present IEDs one year postoperatively, regardless of the time of assessment. Currently, divided attention is not frequently documented in adult epilepsy patients, although deficits have been witnessed in children with centro-temporal spikes (Baglietto *et al.*, 2001). Aldenkamp and Arends (2004a) discovered, in a simultaneous EEG/cognitive recording paradigm, that attention is extremely vulnerable to epileptic EEG discharges. In fact, attention requires specific neuronal functioning which is associated with a decrease in alpha activity and an increase in beta activity. Therefore, IEDs characterized by sharp waves followed by slow waves could possibly inhibit the recruitment of electrophysiologically recordable brain activity (Holmes *et al.*, 2006).

Surgery did not have a general effect on verbal and spatial short-term and working memory. Previous findings for postoperative outcome are diverse; certain authors found an overall improvement (Lutz *et al.*, 2004), while others reported postoperative impairment. Bjørnæs *et al.* (2005) reported that LTLE patients, in particular, showed a decline in verbal working memory. Feigenbaum *et al.* (1995) described patients with RTLE as having lost visual-spatial working memory. In our study, seizure-free patients improved their short-term memory score, whereas patients with persistent seizures deteriorated. It is tempting to speculate that in the latter group there was a disturbing effect on underlying neurophysiological functioning. IEDs appeared to have an impact on working memory and verbal working memory tended to be lower in patients with a postoperative presence of IEDs.

Long-term memory performance was not influenced by a reduction in seizures, as previously described (Wachi *et al.*, 2001; Dietl *et al.*, 2004; Mameniskiene *et al.*, 2006). Patients with LTLE had a significantly poorer verbal memory outcome than RTLE patients. These findings are well documented (White *et al.*, 2002; Lutz *et al.*, 2004; Bjørnæs *et al.*, 2005; Helmstaedter *et al.*, 2008a, b). In our research, verbal memory performance did not change significantly after surgery. The absence of a decline has already been reported by other authors; Seidenberg *et al.* (1998) considered cognitive decline following left temporal lobe surgery to be modest and Wachi *et al.* (2001) found no decline at all with even improvement. Since most LTLE epilepsy patients have preoperative evidence of low anterograde learning and recall capacities due to the mesiotemporal dysfunction (Helmstaedter and Kurthen, 2001), we assume that they did not differ pre- and postoperatively, either because of low baseline performances or possible functional reorganisation in the surrounding tissues (Stroup *et al.*, 2003).

In addition, memory for figural contents did not change with regards to the time of examination. These findings are not surprising, since no clear consensus exists in the available literature regarding a decrease in non-verbal memory. Bjørnæs *et al.* (2005) identified no changes between the times of examination for the short delay of the Jones-Gotman Test, while White *et al.* (2002) demonstrated a significant improvement in the Rey-Osterrieth Figure scores after surgery. Moreover, poor visual memory learning and delayed recall could not clearly be attributed to lesion on one side, either left or right, whereas poor verbal memory could be attributed specifically to the left hemisphere. These findings may seem unexpected since visual memory is traditionally considered to be a right-hemispheric function, however, the data has gradually become more and more controversial. Raspall *et al.* (2005) reconsidered the theory of material specificity in TLE patients; the epileptogenic focus was clearly identified in either the left or right hemisphere and significant differences between RTLE and LTLE patients for visual memory in encoding and memory retrieval were not identified. Consequently, it was hypothesised that figural memory involves mesial temporal lobe structures more bilaterally than has been previously suggested. It is equally important to note that during the DCS examination, figures are often associated with existing objects allowing patients to use "covered" verbalisation as a strategy (Helmstaedter *et al.*, 2003).

In our study, we attempted to confirm the impact of IEDs on memory in general. A previous paper by other authors had already described poor long-term memory skills in verbal memory performance (*i.e.* Rey Auditory Verbal Learning Test) as well as in non-verbal recall (*i.e.* Rey-Osterrieth Complex Figure Test) due to IEDs being independent of seizure frequency in non-surgical patients (Mameniskiene *et al.*, 2006). Our results failed to show any effects of the modality presence or absence of IEDs upon verbal memory. For figural learning, patients with IEDs performed more poorly postoperatively than preoperatively. These findings show that IEDs would have an effect on learning, regardless of seizure outcome. Since the percentage of seizure-free patients was high, these results would not support the hypothesis that IEDs have only an additional, mild effect on cognition, and are therefore insufficient to cause impairment independently of seizures (Aldenkamp and Arends, 2004b).

This study evaluated attention and memory outcome pre- and postoperatively in a large group of patients with intractable epilepsy who underwent mesial temporal lobe surgery. Visual selective attention tasks showed more pronounced impairment among RTLE patients. In verbal memory tasks, LTLE patients scored worse and the visual memory measure showed no effect for laterality. Persistent seizures were found to be related to impaired cognition for attention control and short-term memory. In line with our assumptions, IEDs were found to have an effect independently of seizures, but only for figural learning. For attention control and working memory, patients who continued to present IEDs had already scored worse prior to surgery. Did this patient group present a higher preoperative quantity of IEDs, thus promoting a "supplementary effect" in combination with seizures? Further studies focussing upon the comparison between preoperative and postoperative EEG analyses are needed to explore this topic further. □

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