Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease?

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To what degree does the so-called ‘initial hit’ of the brain versus chronic epilepsy contribute towards the memory impairment observed in chronic temporal lobe epilepsy (TLE) patients? We examined cross-sectional comparisons of age-related regressions of verbal learning and memory in 1156 patients with chronic TLE (age range 6–68 years, mean epilepsy onset 14 ± 11 years) versus 1000 healthy control subjects (age range 6–80 years) and tested the hypothesis that deviations of age regressions (i.e. slowed rise, accelerated decline) will reveal critical phases during which epilepsy interferes with cognitive development. Patients were recruited over a 20-year period at the Department of Epileptology, University of Bonn. Healthy subjects were drawn from an updated normative population of the Verbal Lern- und Merkfähigkeitstest, the German pendant to the Rey Auditory Verbal Learning Test. A significant divergence of age regressions indicates that patients fail to build up adequate learning and memory performance during childhood and particularly during adolescence. The learning peak (i.e. crossover into decline) is seen earlier in patients (at about the age of 16–17 years) than for controls (at about the age of 23–24 years). Decline in performance with ageing in patients and controls runs in parallel, but due to the initial distance between the groups, patients reach very poor performance levels much earlier than controls. Patients with left and right TLEs performed worse in verbal memory than controls. In addition, patients with left TLE performed worse than those with right TLE. However, laterality differences were evident only in adolescent and adult patients, and not (or less so) in children and older patients. Independent of age, hippocampal sclerosis was associated with poorer performance than other pathologies. The results indicate developmental hindrance plus a negative interaction of cognitive impairment with mental ageing, rather than a progressively dementing decline in chronic TLE patients. During childhood, and even more so during the decade following puberty, the critical phases for establishing episodic memory deficits appear. This increases the risk of premature ‘dementia’ later on, even in the absence of an accelerated decline. Material specific verbal memory impairment in left TLE is a characteristic of the mature brain and seems to disappear at an older age. The findings suggest that increased attention is to be paid to the time of epilepsy onset and thereafter. Early control of epilepsy is demanded to counteract developmental hindrance and damage at a younger age.

Keywords: temporal lobe epilepsy; verbal memory; ageing; development; lateralization
Introduction

Temporal lobe epilepsy (TLE) is the most common form of chronic focal epilepsy. Due to the localization of neuropathology in memory-relevant brain structures, problems in episodic memory represent the major cognitive co-morbidity of TLE. Episodic memory is defined as the ability to acquire and later retrieve new space- and time-related information. It is, therefore, an essential component in establishing continuity and biographic identity. Memory impairment in TLE reflects loss of structural morphological integrity of the temporal lobe structures, as well as the dynamic and potentially reversible influence of seizures and treatment on brain function. However, we must also consider whether epilepsy and seizures interfere with brain maturation, and if chronic uncontrolled epilepsy causes a progressive mental decline with ageing.

In 2002, an international multidisciplinary meeting was held to discuss whether seizures damage the brain. The results were published in Progress in Brain Research (Sutula and Pitkänen, 2002). The collected evidence showed that seizures represent only a part of the problem and that complex molecular, cellular, synaptic and system level dysfunctions must also be considered when questioning the chronic cognitive and behavioural impairments in epilepsy. At first glance, it would appear almost certain that uncontrolled epilepsy causes a mental decline. However, the surprising conclusion of Tom Sutula and Asla Pitkanen was that seizures may damage the brain only ‘in some individuals, in some conditions, …’ (Chapter 47, p. 513).

Lifetime-spanning studies on cognition in patients with chronic epilepsy are not available. At best, longitudinal studies cover an interval of up to 10 years. Studies addressing TLE were mostly conducted on surgically treated patients (as opposed to pharmacologically treated patients), and although they indicate some decline and a slight relevance of uncontrolled seizures, the results are inconsistent and do not particularly favour the idea that epilepsy is a progressively dementing disease (Elger et al., 2004). A review of 20 longitudinal studies examined the cognitive outcomes in patients with epilepsy and concluded that there is a ‘mild but definite’ relationship between seizures and mental decline (Dodrill, 2004). However, these studies, and particularly the older reports, comprise patients with very different epilepsy conditions and they may well have included patients with mental decline due to progressive aetiology. Particularly, for those patients who today would be considered as suffering from progressive mitochondrial or auto-immunological inflammatory brain diseases, it is very difficult to separate the negative cognitive effects of pathology from those of the severe seizures that are an expression of the progressive pathology (Helmstaedter, 2007).

In contrast to longitudinal studies, cross-sectional studies can span a wider age range. Interestingly, such studies clearly suggest a slow cognitive decline with increased duration of epilepsy (Jokeit and Ebner, 1999, 2002). However, there is a major methodological problem with studies that examine the effect of epilepsy duration on cognition. Since most epilepsies start early in life, a longer epilepsy duration is heavily confounded by ageing, which itself is associated with cognitive decline.

A reasonable way out of this dilemma is to compare age regressions in patients with TLE against those in healthy subjects. The concept behind this comparison states that if epilepsy systematically changes age-related cognitive development, then this should become evident with significant deviations of the respective regression curves from each other. If, for example, long-lasting chronic epilepsy systematically adds to a decline, then an acceleration of such a decline should show a significantly steeper regression for the patients than for the healthy subjects. First findings in a relatively small sample indicated that, contrary to previous assumptions, the age regressions for healthy controls and patients ran in parallel (Helmstaedter and Elger, 1999). At each age, the patients performed worse than the healthy subjects and the distance between groups remained stable over time. Thus, it did not seem that progressive mental decline was caused by chronic TLE. Instead, the stable distance between patients and controls indicated that the cognitive problems in epilepsy must evolve around the time of epilepsy onset or perhaps even earlier. In keeping with this finding, there is indeed a long history documenting the negative effects of an early onset of epilepsy on cognition (Fitzhugh et al., 1965; Dikmen et al., 1975; Dikmen and Matthews, 1977; O’Leary et al., 1983; Strauss et al., 1995; Cormack et al., 2007).

Methods

We extended our previous findings with adults and focused on learning and memory performance in both children and adolescents. We evaluated memory data from a very large sample of 1156 patients with pharmaco-resistant TLE covering a wide age range. Patients were collected over a 20-year time period at the Department of Epileptology, University of Bonn. From the total neuropsychological database with approximately 6300 first presentations, we selected patients based on neuropsychological assessment of verbal learning and memory and the diagnosis of TLE defined by MRI (temporal lobe lesions) and/or ictal/interictal EEG. Of the 789 with available imaging data, the MRI indicated hippocampal sclerosis/atrophy in 62% of the patients; 19% showed developmental lesions; 9% tumours; 4% vascular lesions; and 6% had no findings. For the remaining patients, no MRI data were available. According to the MRI and/or EEG data, in 595 (52%) patients a left-sided TLE was indicated; in 538 (46%) a right-sided TLE, and uncertain bilateral findings were present in 23 (2%) patients. The mean age at the onset of epilepsy was 14 ± 11 years, with 85% of the onsets before 25 years of age (26%, age 0–5; 33%, age 6–14; 26%, age 15–24; 15%, age 25+). The mean duration of epilepsy was 18 ± 12 years.

All subjects underwent verbal memory testing using the Verbaler Lern-und Merkfähigkeitstest (VLMT) (Helmstaedter et al., 2001), a German adaptation of the well-known Rey Auditory Verbal Learning Test (RAVLT). Word-list learning is commonly used for memory assessment in epilepsy patients. When applied before and after surgery, it reliably reflects temporal lobe functioning, temporal lobe pathology and the cognitive effects of TLE (Helmstaedter et al., 1997a, b; Lee et al., 2002; Loring et al., 2008).

Since we standardized and published the VLMT in Germany (Helmstaedter et al., 2001), we also have the normative data for this memory test with, at present, 1000 healthy subjects tested between the ages 6 and 80 years. This allowed us to compare the age-related memory performance of patients from 6 to 70 years...
(51% males, mean age 33 ± 12 years) against the age-related memory performance of healthy subjects from 6 to 80 years (55% males, mean age 35 ± 21 years) (Table 1). The VLMT requires consecutive learning and recall of a list of 15 words (list A) over five trials; free recall of this list after each trial is requested. After the five learning trials are complete, a second word list (list B) is presented for free recall to assess the effects of interference. Finally, unannounced recall of list A is requested after a delay of half an hour, and a recognition trial is performed. Recognition requires identification of the words of list A out of an orally presented list of 50 words which comprises the words from lists A and B as well as new distractor words. Structural analysis of this test demonstrated that it reliably assesses verbal short-term or working memory as well as long-term memory (Muller et al., 1997; Helmstaedter et al., 2001). Based on the structural–functional correlation studies, out of all possible test parameters, the total number of correctly ‘recalled words in immediate recall over the five learning trials’ (learning: total trials 1–5) was selected because it is the most representative of the more neocortical aspects of short-term and working memory (Elger et al., 1997; Helmstaedter et al., 1997a, b). Of the delayed recall scores, ‘loss of words over time’ was chosen because this measure provides less redundant information to learning than absolute free delayed recall (correlation of r = 0.3 instead of r = 0.8). This measure is the representative of the more mediastem–temporal–dependent aspects of long-term consolidation and retrieval (memory: loss in delayed free recall) (Helmstaedter et al., 1997a, b; Muller et al., 1997; Helmstaedter et al., 2001, 2002).

### Results

By taking both linear and non-linear dependencies into account, we performed a combined linear and non-linear regression analysis by a modelling method called LOESS or LOWESS analysis (locally weighted scatterplot smoothing) with a smoothing parameter q = 0.3 (Cleveland and Devlin, 1988). This model more adequately described the course of memory performance over the time than standard regression methods. Instead of fitting a specification of a function to all data in the sample, this analysis fits the regression to localized subsets of data to build up a function point-by-point. The smoothing parameter ‘q’ can be flexibly chosen (typically between 0.25 and 0.5) and is the proportion of data used in each fit. The smaller the ‘q’ is, the closer the regression conforms to the data, the larger the ‘q’ is, the lesser the regression responds to fluctuations in the data.

Linear analyses for controls had indicated that the development of verbal learning memory can be best explained by a quadratic function (learning: $r^2 = 0.15, F = 87.1, P < 0.001$; memory: $r^2 = 0.03, F = 16.4, P < 0.001$); whereas in patients, learning and memory curves were best approximated by a linear and logarithmic function, respectively (learning: $r^2 = 0.031, F = 37.1, P < 0.001$; memory: $r^2 = 0.03, F = 40.1, P < 0.001$).

The cross-sectional development of verbal learning in relation to age (i.e. the comparison of the age regressions of learning in healthy subjects and TLE patients) is displayed in Fig. 1A. The performance of both groups in 5-year increments until the age of 30 years and 10-year increments until the age of 80 years is displayed in Fig. 1B. The respective courses of verbal memory are displayed in Fig. 2A and B.

Healthy controls show a course of verbal learning in relation to age as expected from developmental psychological research (Grady and Craik, 2000; Salthouse, 2009) (Fig. 1A). There clearly is a linear increase in the performance until about the age of 22–23 years, at which point a slow, but steady, linear decline is present. Comparing the course of memory in healthy subjects and patients beyond the age of 25 years shows that the decline in learning capacity in patients runs largely parallel to that in the controls, but at a much lower level. After the age of 50 years, the patients and controls come closer, but because of the decreasing number of older patients, their development is difficult to determine via the scatter plot. The results for the age groups (Fig. 1B) show that patients and controls are closer to each other between 60 and 70 years, mainly because of the large variance in patient performance.

The course of verbal memory (loss of learned words over time) shows how verbal memory performance becomes optimized in healthy subjects until young adulthood, in that retrieval efficiency steadily improves along with the increase observed for learning (Fig. 2A and B). The best retrieval performance (i.e. the best learning and least loss of what has been learned) is observed at the age of 22–23 years, where the mean loss approaches the zero line. From this age onward, a decline becomes evident until age 40, and then plateaus until the age of 70 years. After 70 years of age, some further decline is indicated. Again, the memory courses of healthy subjects and TLE patients over the age of 25 years run largely parallel and the results on ageing are in keeping with our previous findings in a selected group of patients with left mesial TLE (Helmstaedter and Elger, 1999). The results on ageing are also in line with recent longitudinal findings on quantitative MRI in patients with TLE and healthy subjects, which again fail to provide evidence that chronic TLE progressively adds damage to the brain (Helmstaedter and Elger, 1999; Liu et al., 2003, 2005).

The major finding of this study becomes evident when the course of learning and memory development in childhood and adolescence is compared among the groups. Here, the slopes diverge significantly, in that a steep increase of the learning performance in healthy subjects contrasts with a flattened increase in

### Table 1 Distribution of patients and control subjects over age groups between 6 and 80 years

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>TLE</td>
</tr>
<tr>
<td>6–10</td>
<td>134</td>
<td>28</td>
</tr>
<tr>
<td>11–15</td>
<td>104</td>
<td>68</td>
</tr>
<tr>
<td>16–20</td>
<td>83</td>
<td>107</td>
</tr>
<tr>
<td>21–25</td>
<td>104</td>
<td>139</td>
</tr>
<tr>
<td>26–30</td>
<td>92</td>
<td>152</td>
</tr>
<tr>
<td>31–40</td>
<td>94</td>
<td>355</td>
</tr>
<tr>
<td>41–50</td>
<td>103</td>
<td>208</td>
</tr>
<tr>
<td>51–60</td>
<td>98</td>
<td>82</td>
</tr>
<tr>
<td>61–70</td>
<td>136</td>
<td>17</td>
</tr>
<tr>
<td>71–80</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>1156</td>
</tr>
</tbody>
</table>

Until the age of 30 years, 5-year increments and in the time after 30 years, 10-year increments were chosen.
patients (Fig. 1A and B). When compared with healthy subjects who increased their learning and memory performance until their early mid-twenties, the TLE patients completely failed to build-up their respective performance. They demonstrated only a very moderate increase in learning capacity which came to a halt at the age of 16–17 years. Instead of further improving their performance, the patients had already reached the point at which verbal learning turns over into a steady decline. When the groups are

Figure 1 (A) Age regressions of verbal learning (total learning over five learning trials) in patients with chronic TLE and healthy control subjects (CONTR) indicate developmental hindrance rather than progressive accelerated cognitive decline in the patient group. The figure displays a scatter plot representing all individual subjects. The two vertical lines indicate the turn over when ‘learning’ starts to decline. (B) The results on verbal learning with subjects grouped by age increments of 5 and later of 10 years. Bars represent 90% CI for the group means. Note how the gap between patients and controls increases with the age of 16–20 years and how it reaches a maximum difference with the age of 21–25 years where patients already turned into decline.
broken down into 5- and 10-year increments, the patients and control subjects are closest to each other at a young age (Fig. 1B). Thereafter, the gap opens at 16–20 years of age, and then reaches the maximum difference for the 21–25 years of age groups. At that stage, healthy subjects are still improving their performance, whereas the patients are already in significant decline. Unlike their performance in learning, the patients’ performance in memory appears to decline linearly from the very beginning until the age of 26–27 years. Memory in healthy subjects increases linearly and peaks at age 21–22 years (Fig. 2A and B). As with learning, the age group comparison shows that the gap opens at age 16–20 years and continues until 21–25 years. Accordingly, a
slow development of verbal learning and deteriorating verbal memory is implied, but there is no hard evidence suggesting an accelerated decline with a longer duration of epilepsy at an older age. Finally, it should be noted that at an older age, ‘learning’ and ‘memory’ performances show a different age dependence (i.e. ‘learning’ is more significantly modulated by ageing than ‘memory’).

With regard to the findings on ‘learning’, it might be interesting to note that separate analyses performed for memory span at the first learning trial on list A and the single learning trial on list B showed very similar results as observed with total learning. The courses of memory span performance across the ages largely mirrored those seen with learning (figures are not shown). The rationale for adding this analysis was that memory span depends on frontally mediated processes of working memory rather than on medial–temporal, long-term consolidation. However, the comparable results are not surprising since total learning and memory spans are highly correlated with each other (list A, \( r = 0.76 \); list B, \( r = 0.56 \)) (Muller et al., 1997).

The underlying pathology and the hemispheric lateralization of TLE are major determinants of the verbal memory impairment in TLE (Wieser, 2004). Since the respective subgroups were sufficiently large, we also calculated subsequent analyses by taking the presence versus absence of the hippocampal sclerosis and the lateralization of the epilepsy in the left versus right hemisphere into account.

As for the pathology, 491 (62%) of 789 patients with MRI were diagnosed with a hippocampal sclerosis/atrophy (AHS), 298 (38%) patients had another pathology. Comparison of the groups indicated that verbal learning and memory performances were worse in patients with hippocampal sclerosis than for those patients with another pathology (‘learning’ \( F = 16.1, P < 0.000 \) ‘memory’ \( F = 6.9, P < 0.01 \)). However, this difference was seen only when the total groups were taken into consideration. When the different age groups were calculated separately, the differences between patients with AHS and other pathologies were not significant.

We compared patients with left (\( N = 595 \)) and right TLE (\( N = 538 \)). Both groups were impaired in ‘verbal learning’ and ‘memory’ in relation to controls and, in addition, the patients with left TLE performed worse than those with right TLE (\( F = 140 \) and 141 with \( P < 0.000 \) for learning and memory). However, as indicated in Table 2, the left–right difference in verbal learning and memory was confined to adolescence and adulthood and the occurrence of left–right differences across the ages was different for ‘verbal learning’ and ‘memory’. In verbal learning (total: trials 1–5), significant left–right differences were observed between the age of 31–50 years. In verbal memory (loss in delayed free recall), the left–right differences were seen between the ages of 11–50 years. With an older age (>50 years), the left–right differences became less pronounced and failed to reach statistical significance.

### Discussion

Age regressions of verbal learning and memory in patients with TLE and healthy subjects were compared with the test hypothesis that significant deviations of the age regressions would reveal critical phases whereby epilepsy interferes with cognitive

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**Table 2** Differences in verbal learning (total learning) and memory (loss of learned words after delay) across the ages as dependent on the lateralization of temporal lobe epilepsy in the left versus right hemisphere

<table>
<thead>
<tr>
<th>Age categories (years)</th>
<th>N</th>
<th>mean (SD)</th>
<th>F/signif.</th>
<th>Age categories (years)</th>
<th>N</th>
<th>mean (SD)</th>
<th>F/signif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–10</td>
<td>R-TLE 12</td>
<td>40.33 (11.98)</td>
<td>0.001 NS</td>
<td>31–40</td>
<td>R-TLE 154</td>
<td>46.18 (10.06)</td>
<td>4.45*</td>
</tr>
<tr>
<td>VLMT learning (trials 1–5)</td>
<td>L-TLE 16</td>
<td>40.19 (11.16)</td>
<td></td>
<td></td>
<td>L-TLE 196</td>
<td>44.04 (8.93)</td>
<td></td>
</tr>
<tr>
<td>11–15</td>
<td>R-TLE 36</td>
<td>48.33 (9.36)</td>
<td>0.06 NS</td>
<td>41–50</td>
<td>R-TLE 101</td>
<td>45.22 (9.37)</td>
<td>13.01***</td>
</tr>
<tr>
<td>VLMT learning (trials 1–5)</td>
<td>L-TLE 31</td>
<td>46.58 (12.19)</td>
<td></td>
<td></td>
<td>L-TLE 100</td>
<td>40.13 (10.59)</td>
<td></td>
</tr>
<tr>
<td>16–20</td>
<td>R-TLE 47</td>
<td>49.06 (8.42)</td>
<td>0.039 51–60</td>
<td>R-TLE 41</td>
<td>42.85 (9.18)</td>
<td>1.84 NS</td>
<td></td>
</tr>
<tr>
<td>VLMT learning (trials 1–5)</td>
<td>L-TLE 58</td>
<td>49.41 (9.47)</td>
<td></td>
<td></td>
<td>L-TLE 38</td>
<td>40.11 (8.73)</td>
<td></td>
</tr>
<tr>
<td>21–25</td>
<td>R-TLE 71</td>
<td>48.18 (9.22)</td>
<td>4.50*</td>
<td>61–70</td>
<td>R-TLE 12</td>
<td>42.75 (9.59)</td>
<td>0.21 NS</td>
</tr>
<tr>
<td>VLMT learning (trials 1–5)</td>
<td>L-TLE 67</td>
<td>46.06 (9.27)</td>
<td></td>
<td></td>
<td>L-TLE 3</td>
<td>40.00 (6.55)</td>
<td></td>
</tr>
<tr>
<td>26–30</td>
<td>R-TLE 64</td>
<td>46.30 (10.1)</td>
<td>0.273 NS</td>
<td></td>
<td>L-TLE 3</td>
<td>6.00 (3.60)</td>
<td></td>
</tr>
<tr>
<td>VLMT Memory [loss over time]</td>
<td>L-TLE 86</td>
<td>45.48 (9.016)</td>
<td></td>
<td></td>
<td>L-TLE 12</td>
<td>40.33 (11.980)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R-TLE 64</td>
<td>2.09 (2.39)</td>
<td>13.74***</td>
<td></td>
<td>L-TLE 12</td>
<td>40.33 (11.980)</td>
<td></td>
</tr>
</tbody>
</table>

Note that left-right differences mainly appear as a characteristic of the mature and adult brain.

*\( P < 0.05 \); **\( P < 0.01 \); ***\( P < 0.001 \); NS = not significant.
development. Since most epilepsies start early in life, with increasing age of patients at the time of evaluation, the impact of the onset of epilepsy will have a decreasing contribution to the resulting performance, whereas the contribution of the duration of epilepsy will increase. Therefore, if deviations exist at a young age, then one should be able to confirm either developmental hindrance or retardation. If there are deviations at an older age, this should be indicative of an accelerated mental decline.

If we use this as our basis, the present results provide strong evidence of a neurodevelopmental hindrance in chronic TLE patients, which becomes most evident in the decade after puberty. While the gap between patients and controls increasingly widens at a younger age, the course of learning and memory at an older age runs largely in parallel. However, patients at every age score are at a much lower level than healthy subjects. Thus, no progressive degenerative decline can be confirmed from these findings. So far, this is in keeping with the results that we published in 1999 involving a selected group of patients with pure left mesial TLE (Helmstaedter and Elger, 1999).

The age at which development comes to a halt indicates that the problems with ‘learning’ arise in later brain maturation, which is no longer intrinsically and ontogenetically determined, but rather mainly extrinsically driven by experience (Segalowitz and Hiscock, 2002). Learning (i.e. the short-term and working memory aspects of memory) highly depends on attention, executive functions and language. Healthy subjects are able to improve their learning capacity by increasing these more extra-temporally and mostly frontally-associated functions. ‘Learning’, as well as ‘memory’ in terms of the access to learned materials, improves with better behavioural organization and the extension of semantic networks and knowledge systems. One may hypothesize that patients fail in this particular respect.

It is remarkable that the age at which patients become increasingly impaired marks the approximate endpoint of functional cerebral plasticity, which helps to preserve language and language-related memory aspects in early onset epilepsy (Helmstaedter et al., 1999a, b, Helmstaedter, 1999). As pointed out elsewhere in more detail (Helmstaedter and Elger, 1998; Helmstaedter, 1999), the neocortical and mesio-limbic aspects of verbal learning and memory seem to have different functional plasticity. Mesial encoding functions are more bilaterally disposed, and unilateral damage can, in part, be compensated by homologous contralateral structures quite independent of age. Unilateral selective amygdalo-hippocampectomy demonstrates that surgical damage often causes additional memory impairment, but will not lead to global amnesia as long as no contralateral damage exists. Plasticity for material-specific neocortical functions is, in contrast, time-limited, in that neocortical functions become increasingly dependent on a single hemisphere. The critical period for contralateral restitution and compensation in the presence of unilateral damage extends to puberty (Vargha-Khadem et al., 1997; Grunwald et al., 1998; Helmstaedter and Elger, 1998; Helmstaedter, 1999; Liegeois et al., 2008). Accordingly, the time course of the more medial-temporal-dependent memory aspect among the age groups is comparably stable at an older age, whereas learning experiences a significant modulation with neocortical development. In the cross-sectional perspective, brain maturation and development also seem to be important for what is referred to as lateralization-dependent material-specific memory impairment in TLE (Saling, 2009). First, verbal learning and memory impairment are not confined to left TLE, i.e. patients with right TLE perform poorly as well, although to a lesser degree than left TLE patients. Of major interest, with regard to the lateralization of TLE is the finding that the left-right differences in verbal learning and memory are observed in adolescent and adult patients, but not (or less so) in children and older patients. Thus, the impairment of verbal memory and its material-specific affection in left TLE emerge in the mature brain when hemispheric specialization becomes complete. At an older age, the material specificity of the memory impairment in lateralized TLE interestingly seems to disappear. Whether this reflects a converging memory impairment pattern independent on lateralization because of generally decreasing memory resources and mental reserve capacities at an older age is an interesting hypothesis which deserves further attention.

Hippocampal sclerosis, which was the most frequent pathology in the evaluated group of TLE patients, had a differential impact on verbal learning and memory. The patients with hippocampal sclerosis performed worse than those with another pathology independent of age. Due to the cross-sectional study design, we cannot provide answers regarding the aetiology of the observed developmental hindrance. Do the data show additive damage, particularly in childhood and adolescence? Do they indicate early damage which subsequently grows into the impairment when the affected areas should have their developmental spurs? Does spreading epileptic activity have a distant effect on the development of brain areas not directly involved in epilepsy? Learning and memory are closely associated with temporal lobe structures and are thus most critical for the study of the effects of chronic TLE on cognition. Indeed, it is likely that the time-related changes in learning and memory are linked to fluctuations in IQ as a function of age. As already mentioned in the introduction, there is ample evidence from the literature to suggest that an earlier onset of epilepsy is associated with a poorer intellectual and educational outcome (Strauss et al., 1995; Dikmen et al., 1977; Helmstaedter, 2005; Cormack et al., 2007). Evidence for the neurodevelopmental hypothesis originates from studies using quantitative brain volumetric measures. These studies show that an early onset TLE, in contrast to a late onset TLE, has substantial negative effects on extratemporal cortical development (Hermann et al., 2002, 2003; Weber et al., 2007; Kaaden et al., 2008).

As for the concerns about ‘dementia’ in TLE, it is important to note that although the data indicate a neurodevelopmental origin of memory problems, patients are nevertheless at an increased risk of having ‘dementia’—that is, if we use the term ‘dementia’ in its broadest sense. Even without an accelerated decline, the negative interaction of the initially established damage with normal ageing significantly reduces the patients’ reserve capacities at an older age when processes of normal or even pathological ageing take place. In this regard, the present data parallel those from the extraordinary longitudinal Scottish Mental Survey, which indicated that childhood IQ is a significant predictor for later dementia and mortality (Whalley et al., 2000; Starr et al., 2008). How later acquired
brain damage can change the patients’ cognitive perspective with ageing has been demonstrated with the effects of epilepsy surgery on the age regression of verbal learning and memory performance (Helmstaedter et al., 2002).

At this stage of the evaluation, the data cannot provide final answers to the questions concerning the basic mechanisms behind the developmental hindrance and the detailed impact of different aetiologies, pathologies, seizure activity or medication on memory in the lifetime cycle. The main message of this study was to provide a macro view of verbal learning and memory in TLE patients of various ages, and to reveal that our perspective towards patients with chronic epilepsy should change; it must shift away from viewing epilepsy as a progressively dementing disease and back towards showing how epilepsy, at its origin, interferes with brain maturation and cognitive development. In the long run, this increases the risk of premature ‘dementia’. Additional efforts are thus needed to identify patients who are at risk and to counteract negative cognitive development in TLE at the very beginning.

References


Helmstaedter C, Kurthen M, Linke DB, Elger CE. Patterns of language dominance in focal left and right hemisphere epilepsies: Relation to MRI findings, EEG, sex, and age at onset of epilepsy. Brain Cogn 1997b; 33: 135–50.


