

# **Effects of chronic temporal lobe epilepsy on memory functions**

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## **Introduction**

Declarative memory processing, that is the acquisition of and the later access to newly acquired information, is one of the most essential human cognitive functions. Declarative memory establishes continuity in a steadily changing world and thus provides the basic of the individuals biography, its identity, and its cognitive behavioral development. In temporal lobe epilepsy, this type of memory is characteristically impaired when mesiotemporal and associated neocortical structures are affected by lesions, ongoing epileptic activity, or undesired treatment effects [e.g. operative treatment]. Hence, major issues are the etiology, onset and course of memory impairment as well as the prevention of further memory decline during the course of epilepsy. The strong connection to questions regarding the course of temporal lobe epilepsy is at hand, particularly as to whether epilepsy is a progressive and dementing disease, whether seizures damage the brain, or which impact the treatment of temporal lobe epilepsy can have on the course of the disease.

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## **Temporal lobe epilepsy and memory**

With about 70% temporal lobe epilepsy TLE is the most common type of the focal symptomatic or cryptogenic epilepsies. TLE is most of all characterized by the repeated and unprovoked occurrence of epileptic seizures which take their origin in temporal lobe structures. Yet, temporal lobe epilepsy is not a homogeneous cerebral disorder. This fact is probably best reflected by the lasting discussion as to whether TLE with hippocampal sclerosis can be considered to be a disease or a syndrome (Wieser H.G. 2004). From a neuropsychological point of view, impaired declarative memory performance is a characteristic feature of TLE. The temporal lobes and their temporo-limbic aspects are known to be involved in the formation of new memories. Accordingly 70-80% of the more than 1000 patients with pharmaco-resistant TLE, which were evaluated in Bonn since 1988,

were found to show impairment of either verbal or figural memory (performance < m -1SD). Broken down to verbal or figural memory 50-60% of the patients show a deficit in one type of memory. Going into more detail, it is episodic memory which is particularly affected in TLE, that is the acquisition of time and context dependent information. Semantic memory may also be affected but this is a much less consistent finding [Helmstaedter C. 2002].

A general framework for an understanding of how the mesial structures are involved in declarative memory has been provided by H. Eichenbaum's proposal that neocortical perceptually and conceptually processed information is extendedly held by parahippocampal structures. These are bidirectionally connected to the neocortical association areas whereas the hippocampus contains properties which ensure encoding, retrieving and the linkage of experiences to stored representations [Eichenbaum H. 2000]. The key-role of temporo-mesial and neocortical structures for memory in TLE has been demonstrated by a variety of functional and volumetric imaging studies, invasive electroencephalographic studies, correlations of human hippocampal cell counts and LTP to memory performance. Memory impairment in lateralized TLE tends to be material-specific, i.e. left TLE is associated with verbal, right TLE with visual memory impairment. Neocortical temporal and mesial hippocampal structures are differentially involved in episodic memory, i.e. the mesial structures are more nonspecifically involved in consolidation retrieval and neocortical structures are more involved in material specific processing of the contents [Helmstaedter C. 2001, Elger CE. et al. 2004]. False lateralizing memory impairment in TLE, i.e. deviations from the left vs. right, i.e. verbal versus nonverbal dissociation are frequent. False lateralization in left TLE has been attributed to factors like hemispheric dominance and gender differences, false lateralization in right TLE to a more bilateral organization of nonverbal memory networks, covert verbalization, or the type of the test and test materials (abstractness, complexity) [Helmstaedter C. 1999; Helmstaedter C. et al. 1995] (see **fig. 1**).

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## **Cognitive impairment beyond memory**

The number of TLE patients displaying memory deficits is considerable but this must not distract one from noticing that cognitive impairment in TLE extends the memory domain. Hermann, in his 1997 article about the neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy, noted that TLE is not only characterized by memory deficits but also by considerable generalized cognitive impairment in terms of poor academic achievement and IQ [Hermann BP et al 1997]. Who are those patients who show this additional intellectual impairment and why do other patients perform quite well on IQ tests? In our center about 30% of the TLE patients show an intelligence level below IQ 85, but this still appears an underestimation. According to a recent comparison of 31 patients with mesial TLE with their healthy siblings the degree of global impairment was much greater than expected from evaluating patients on the basis of test norms. Thirty six percent of the patients versus 7% of their siblings had an IQ below 85, but 55% of the patients negatively differed by more than one standard deviation ( $> 15$  IQ points) from their healthy sibling. With the exception of nonverbal memory span there was no domain left in which patients did not perform highly significantly worse (**fig. 2**).

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The number of patients who significantly differed from their sibling with respect to IQ was not different from that observed for memory [Roeschl-Heils A. et al. 2002]. The emerging picture is similar to that reported by Oyegbile et al. in 2004 who compared TLE patients with a larger group of controls who all run through the same test battery. The observation of impairments exceeding those which would be expected from circumscribed temporal lobe lesions directly puts us to the issue of the effects of chronic TLE on cognition and memory in particular. Is it possible, and some argue in this direction, that not only poor memory but also general intellectual impairment is the consequence of chronic TLE?

## **Chronic epilepsy and memory in TLE**

The evaluation of the effect of chronic TLE on cognition is difficult when considering the multifactorial nature of cognitive impairment in this disease. Apart from seizures and epileptic dysfunction, underpinning developmental disorders, acquired lesions, and negative treatment effects must be considered as factors potentially influencing cognition. In what follows, an approach to the question of the impact of chronic epilepsy on memory is chosen, which explicitly places the etiological factors within a developmental neuropsychological framework. This will consider differences resulting from interactions and interference of epilepsy with the maturing and the aging brain as well.

Up to now there is no longitudinal study available on patients with TLE starting from the very beginning of this disease and tracking etiologically homogeneous groups and those who will become seizure free versus those who will not. Instead we have to infer the answers to our question from reviewing a mixture of cross-sectional and longitudinal studies, most of them performed in adults and in patients with heterogeneous pathologies.

### *Initial damage versus chronic epilepsy*

About cognitive impairment in epilepsy we know that it results from the complex interaction of more static and irreversible versus more dynamic and reversible factors. On the one hand there are structural lesions, on the other hand there are epileptic activity, seizures, or drug treatment. The crucial point is, that the dynamic factors can have an irreversible negative impact on structure by causing damage or on development by causing retardation with which the patients cannot catch up later on, even when the negative factors are under control.

It is seductive to evaluate the effects of chronic TLE on cognition by focusing on the duration of epilepsy. Duration of epilepsy is then taken as representative for the accumulation of seizures and other epilepsy related noxes during the course of the disease. However, since TLE mostly starts early in life, a longer duration of epilepsy is almost synonymous with an

earlier onset of epilepsy and/or an older age, both being factors, which themselves affect the type and degree of cognitive impairment. The age at the onset of epilepsy is furthermore heavily confounded with the etiology of epilepsy, i.e. early onset TLE is mostly due to developmental malformations and later onset TLE is more likely associated with tumors, trauma etc.. Whether an early and a late onset TLE with hippocampal sclerosis form one entity or belong to the same nosological category remains to be demonstrated [Wieser HG. 2004]. From a developmental neuropsychological point of view the age at the onset alone makes a significant difference (see next paragraph).

Patients with symptomatic or cryptogenic TLE either have or must be assumed to have cerebral lesions or malformations underpinning their epilepsy. These can already be assumed to be associated with dysfunctions. In addition one must assume an epileptic process which is active already before the first seizure. Thus, for patients with chronic epilepsies the question is, which part of the actual impairment is due to the initial pathology and epileptic process before or at epilepsy onset, and how much chronically occurring seizures and accumulating other noxious events adds to this. Evaluation of patients with new onset versus chronic TLE and the study of the effects of seizures and seizure control on cognition may provide some clues to this question.

#### - Cognition in newly diagnosed epilepsy

Studies addressing the cognitive status at the onset of the epilepsy comprise idiopathic or a mixture of symptomatic and cryptogenic epilepsies. However, these studies on children or adults with newly diagnosed epilepsy provide ample evidence that cognitive impairment and behavior problems are present already at baseline before treatment [Ostrom KJ. Et al. 2003; Austin JK. et al. 2002; Pulliainen V. et al. 2000; Ogunrin O. et al. 2000]. In TLE patients, the comparison of newly diagnosed and chronically ill patients with left TLE shows that both groups suffer from verbal memory impairment [Aikia M. et al. 2001]. Pretreatment impairment appears less specific than generalized and pertains to visual motor performance,

mental flexibility, memory, reaction times, and attention. This is confirmed by own data on 29 newly diagnosed adult patients with symptomatic/cryptogenic epilepsies who, with the exception of IQ, displayed significant impairment in one or more cognitive domains in > 70% of the cases [fig. 3]. The individual domains were affected in 36-55%, which parallels the numbers seen in patients with treated chronic epilepsies. As a trend the subgroup of 7 patients with TLE showed the poorest performance in verbal memory. Interestingly the duration of epilepsy before diagnosis and treatment (range 0-11 yrs., median 2.3 yrs) did not explain the degree of pretreatment impairment. In contrast a greater impairment was associated with an older age and a later onset of epilepsy [Helmstaedter C. et al. 2005]. As observed in later onset TLE, the mean IQ of the newly diagnosed patients was within a normal range (m=102 SD=20), and the incidence of 17% patients with an IQ below 85 was not increased.

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Coming back to the already mentioned study on mesial TLE patients and their siblings, a greater distance in performance between the siblings in IQ and memory was not related to a longer duration of epilepsy but rather to an earlier age at the onset of epilepsy. This has been taken as another indicator that impairments in patients must have been present already at the time of epilepsy onset [Roeschl-Heils A. et al. 2002]. The results are furthermore in line with the fact that in early onset epilepsies earlier cerebral damage has more negative consequences for cognitive development than later damage.

- Cognition and seizures

Seizures in TLE can damage the brain, and therefore they can negatively affect memory. This is most impressively demonstrated by TLE patients who became global amnesic after a convulsive or non-convulsive status epilepticus [Dietl T. et al. 2004]. But will each seizure do so? Are all brain regions similarly susceptible to damage by temporal lobe seizures? Is there

a systematic accumulation of damage with chronicity, or is there an initial homeostatic change followed by a more stable period. The example of status epilepticus demonstrates what can be taken as common sense, that more severe seizures bear a greater risk of damage than less severe seizures. However, Dodrill, in a comprehensive review on this topic, comes to the conclusion that the literature in the field supports *definite but only mild* relationships between seizures and mental decline [Dodrill CB 2004]. Experimental models of TLE in animal research reveal inconsistent findings on this issue. Epilepsy inducing status epilepticus clearly damages the mesial structures but this is less clear for spontaneous seizures in the further course of epilepsy [Pitkanen A. et al. 2002]. In another model clear relations between the number of induced seizures, hippocampal damage and memory loss can be demonstrated [Kotloski R. et al. 2002]. In this respect also recent longitudinal quantitative MRI studies in new onset epilepsies are of major importance. These studies address the question of hippocampal damage in the first years after the onset of epilepsy . They did not find a significant relationship between seizures and hippocampal volume changes but individual pretreatment differences as well as individual patients, who newly developed hippocampal pathology [Liu RS. Et al. 2002; Salmenpera T. et al. 2005]. A recent report on 28 TLE patients with chronic epilepsies whose MRI volume changes and performance changes were longitudinally followed (4 yrs.) comes to a very similar conclusion when these changes are compared to those obtained in 21 healthy subjects [Hermann BP. et al. 2004]. Although these studies span maximally 5 years they raise evidence that there is less progress of structural damage due to chronic epilepsy than expected.

#### - Cognition and interictal activity

These latter studies so far were dealing with the question of irreversible damage by lesions and seizures. More obvious, at least in the context of a seizure, is the impact of ictal epileptic dysfunction on cognition. After a temporal lobe seizure, memory impairment may last for hours despite otherwise complete recovery. This is easily demonstrated by formal

postictal testing [Helmstaedter C. et al. 1994a]. The question as to whether interictal activity transiently or permanently affects cognition is less easily determined. The concept of TCI (transient cognitive impairment) which assumes a direct relation between interictal epileptic activity and cognitive impairment has been overstressed in symptomatic focal epilepsies, where it appears to fit to nonconvulsive seizures rather than to single intermittent epileptic discharges [Aldenkamp AP et al. 2004]. However, interictal epileptic activity is not without an effect on cognition and memory. Cognitive improvement in seizure free patients after surgery indicates that an epileptic process was active before surgery which had caused a persistent or tonic change in cognition. Epileptic activity in TLE exerts a negative effect on distant extratemporal functions and, due to the strong connectivity, on frontal lobe functions in particular. Accordingly, significant recovery of mostly frontal or contralateral functions is observed within the first year after successful epilepsy surgery. Later, after years, recovery can be observed also with respect to the primary affected temporal lobe memory functions [Helmstaedter C. et al 2003]. Comparable postoperative recovery has been reported with regard to behavioral disturbances in children who became seizure free [Lendt M. et al. 2000]. An effect of AED withdrawal on functional recovery in seizure free patients is reasonable but remains to be demonstrated.

In summary, cognitive as well as behavioral changes after successful surgery indicate that the brain becomes functionally reorganized on different levels when seizures and epileptic activity are under control. The fact that epilepsy, beyond overt seizures, interferes with brain function leads to the assumption, that this negative influence, even if reversible, can have irreversible consequences on cognitive development in children when falling into particular sensitive periods. This applies also to negative side effects of AED. Recent reports on developmental problems in children born to mothers taking valproic acid may be taken as an example [Adab N. et al. JNNP 2004]. The issue of retarded brain development leads us to the next topic.

### *Mental retardation versus loss of acquired cognitive functions*

Impairments observed at a given age may reflect loss and decline of already acquired functions and/or developmental delay or retardation. We know that the same lesions acquired at different developmental stages may present themselves as different impairments depending on the age of the patient. Children, for example, can grow into impairment, when the affected brain structures mature late. Furthermore, dependent on the age of lesion onset, different functional plasticity and capacities for compensation must be suggested. A late onset left temporal lobe epilepsy for example may result in a characteristic deficit in verbal episodic memory. An early onset left TLE in contrast can induce a shift of functions to the right hemisphere leading to largely preserved verbal memory while sacrificing originally right hemisphere nonverbal functions [Helmstaedter C. et al. 1994b]. As demonstrated in **figure 1**, a figural memory deficit instead of a verbal memory is often the consequence. Finally, an early onset TLE and associated dysfunctions can be assumed to interfere negatively with the development of other cognitive domains.

According to this, developmental questions may be answered by focusing on the effect of the age at the onset of epilepsy on cognition or by comparing performance in children and adults with comparable pathology. Memory loss after surgery in young and older patients can reveal some insight into the question of the loss of already acquired functions at different ages and the capability to compensate newly acquired damage.

#### - Age at the onset of epilepsy

In 1995, the Bozeman Epilepsy Consortium, which represents 8 major epilepsy centers in the USA, examined the contribution of age, age at seizure onset, duration of epilepsy, focus laterality and other variables not only to IQ but also to memory performance in 1141 patients with pharmaco-resistant epilepsy. The main finding of this study was that for IQ and memory an earlier onset of epilepsy was the only variable which predicted of a poorer performance [Strauss E. et al. 1995]. However, the following data may serve as a good example for the difficulty to statistically disentangle the effects of onset and duration of epilepsy and age in

cross sectional research. **Figure 4** demonstrates IQ and memory data from a group of 74 adult TLE patients which was broken down into patients with an onset of epilepsy  $\leq$  and  $>$  age 14. The onset of epilepsy made a big difference with regard to the WAIS-R IQ ( $F=16.6$ ,  $p<0.000$ ) but not with regard to a measure of delayed free recall as assessed with a verbal word list learning paradigm ( $F=0.012$ ,  $p=0.914$ ). The mean age was 38 yrs. in both groups and, as it can be expected from different age at the onset of epilepsy, there was a considerable difference in the duration of epilepsy (18 yrs.;  $F=45.4$ ,  $p<0.000$ ). The results did not change when the analyses were restricted to the subgroup of 25 patients with TLE and hippocampal sclerosis.

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Matching in this example the patients with respect to the duration of epilepsy would have resulted in different age at the onset of epilepsy or different chronological age. Thus, without longitudinal data, a decision can be taken only on the basis of theoretical and practical plausibility. Does it make sense that chronic TLE, i.e. a longer lasting TLE, more seizures etc. causes diffuse and generalized brain damage but not a change in the primarily affected temporal lobe structures? The assumption that early onset epilepsy and its underlying etiology negatively interfere with brain development appears more adequate to explain this dissociation.

The age at the onset of TLE has a different impact on episodic and semantic memory. While no relation between performance in episodic memory and the age at the onset of epilepsy can be discerned, early acquired neocortical lesions in particular interfere with knowledge acquisition and the development of the semantic networks [Helmstaedter C. 2002, Lutz et al. 2004]. This finding nicely complements that on developmental amnesia where semantic memory acquisition is preserved despite early temporo-mesial damage [Vargha-Khadem F et al. 2001].

## - Mental retardation and functional cerebral plasticity

Children with a longer duration of an active epilepsy are reported to have lower IQs than children with a shorter seizure history [Farwell JR. et al 1985; Robinson S. et al. 2000]. However, when children responded well to drug treatment no intellectual decline is indicated [Bourgeois BF. et al. 1983; Ellenberg JH. et al 1986]. Another position claims that persistent seizures in childhood probably slow the rate of cognitive and psychological development [Hirsch E. et al. 2000; Oguni H. et al. 2000]. This latter view is also supported by longitudinal data on intellectual development in children and adults [Bjornaes H. et al. 2001].

When children with TLE are compared with adolescents with TLE there is evidence that children are more diffusely impaired than adults. Memory problems do not represent the major impairment in children and language problems for example are as common as well [Helmstaedter C & Lendt M 2001]. This result can be replicated even when children and adults with TLE are matched with regard to the underlying pathology [Gleissner U. et al. 2005]. Age dependent differences in the pattern of impairment appear to be due to the fact that children are still involved in development and that they display greater capacities for functional restitution and compensation than adults. As mentioned before early onset TLE can lead to contralateral functional compensation and this capability is largely fixed to a time window until puberty [Helmstaedter C. 1999, Helmstaedter C. et al. 2004].

Greater functional plasticity for memory functions in children is also supported by studies on memory outcome after temporal lobe surgery. Temporal lobe surgery, and surgery within the language dominant hemisphere in particular, bears an increased risk of causing additional memory impairment [Lee TM, et al. 2002]. The degree of the postoperative losses depends the degree of damage of functional tissues on the one hand and the brains reserve capacities for compensation of newly acquired damage on the other hand. As for memory, there is recent evidence that reserve capacities are different for its mesial and neocortical aspects. Reserve capacities for the more neocortical aspects of memory (learning or short term memory) is strongly related to age, i.e. the outcome tends to be better with a younger age and it is worse with increasing age. The capability to compensate unilateral damage of

mesial functions (long term consolidation) in contrast appears less age dependent [Helmstaedter C. 1999 / **fig. 5**].

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This has been explained by the more bilateral disposition of these processes and the lesser degree of specialization of the mesial structures for verbal or nonverbal information. The fact that only bilateral but not unilateral mesial temporal lobe resections in adults lead to global amnesia provides striking evidence for this assumption.

In summary early onset TLE interferes with mental development. In early onset TLE, a more generalized pattern of impairment is the consequence as compared to later onset TLE. The finding of generalized abnormalities in cerebral grey and white matter in early onset TLE could be the structural equivalent of such generalized impairment [Hermann B et al. 2002; Arfanakis K et al. 2002; Hermann B. et al. 2003]. As for memory, different outcomes on episodic and semantic memory must be suggested as dependent on whether early damage concerns mesial or neocortical memory processing structures. Childhood is a period of greater plasticity and compensational capacities, and this is reflected by the fact that memory impairment and losses due to temporal lobe surgery are less severe in childhood and adolescence than in adulthood. Dependent on unilateral or bilateral disposition different reserve capacities must be supposed for mesial and neocortical memory functions.

#### *Aging versus chronic epilepsy*

Recent cross sectional studies in TLE patients raised concerns about intellectual decline with a longer duration of epilepsy [Jokeit H. & Ebner A. 2002]. According to this refractory TLE seems to induce a very slow but ongoing cognitive deterioration. A high cognitive reserve capacity may postpone this deterioration, and the estimated time interval required for a significant change was greater than thirty years. This is quite a long time. The question of

what happens with cognitive performance in healthy subjects over such an interval is at hand as well as the question of how cognitive change with a longer duration of epilepsy can be separated from that associated with normal aging.

Mental aging concerns most cognitive functions and in particular those rated as fluid intelligence (functions relying on speed, flexibility, capacity etc.). The rates of decline are similar for perceptive functions and memory [Baltes PB & Lindenberger U. 1997; Balota DA et al. 2000]. Based on this, the comparison of age regressions of cognitive performance in patients with age regressions observed in healthy subjects appeared a reasonable approach to overcome the methodological problem to disentangle aging and duration of epilepsy in early onset TLE. If epilepsy adds to the normal mental decline, the age regression of memory in TLE patients should indicate accelerated decline as compared to the age regression observed in healthy subjects. In a study, which evaluated this in adult patients with left sided left mesial TLE no accelerated decline of verbal memory performance could be discerned. Although this group of patients was considered as having high risk of memory decline with chronic epilepsy, healthy subjects and patients showed a parallel and steady decline over time [Helmstaedter C & Elger CE 1999]. The fact that patients and controls differ to about the same degree at each age clearly favors the hypothesis of an initial difference between the groups. This initial difference can also be taken from **figure 6** where the regression of preoperative verbal memory [learning over five trials] in left TLE patients was related to that in healthy subjects. The significant change of the age regression after temporal lobe surgery demonstrated in this plot, can be taken as an example of how additional acquired damage in the course of epilepsy (here damage due to surgery) can accelerate mental aging. [Helmstaedter C. et al. 2002].

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While the cross sectional approach hardly supports the idea of an increasing impairment of memory with an increasing duration of epilepsy, there is nevertheless evidence of significant

memory decline over time from longitudinal studies in TLE [Helmstaedter et al. 2003, Rausch R. et al. 2003]. In our own study with varying retest-intervals between 2 and 10 years, a significant loss in memory was indicated in medically treated patients. Losses observed due to surgery in patients one year after left temporal lobectomy were greater, but some recovery became evident when seizures were under control [fig. 7].

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Evaluating the course of memory in medically treated patients and in operated patients in the time after surgery, the correlation between memory decline and the retest interval was moderate. More decisive for the course of memory were seizure control, age, and mental reserve capacity (baseline performance and IQ). When performing analyses on an individual instead on a group level, a large proportion of operated and non-operated patients with TLE showed individual losses in either verbal and/or verbal memory over time.

The longitudinal data support a view which is currently raised also by longitudinal MRI volumetric studies, that significant changes over time are almost individual and not the rule [Liu RS. Et al. 2002; Salmenpera T. et al. 2005]. Thus no *linear* relation between time and functional decline, and thus no continuously dementing process can be discerned in chronic TLE.

## **Conclusion**

Considering that an epileptogenic process, lesions, uncontrolled seizures, and treatment are decisive determinants of the course of memory in chronic TLE, there is strong evidence that most impairment exists already at the onset of epilepsy or even in the time before. Seizures, and the more severe seizures in particular can irreversible damage the brain and cause additional impairment. Additionally, there is evidence that epileptic activity in TLE can cause generalized persistent cognitive change. This change exceeds the domain of memory and it is principally reversible when seizures are controlled. If TLE hits the maturing brain, epileptic

dysfunction and negative treatment effects, even if reversible, may cause developmental delay or retardation. Global intellectual retardation can be the consequence. If TLE hits the mature brain, partial impairment particularly in memory is observed. Early and late onset epilepsies share in common that chronic uncontrolled epilepsy can add to the initial impairment. However, additional impairment in TLE appears to be an individual condition rather than the consequence of a continuously dementing process. Progress of cognitive decline is slow and can hardly be differentiated from that observed with normal mental aging. However, because memory decline in patients starts from a significantly lower initial level than in healthy subjects, patients will end up earlier at very poor performance levels with further aging. Additionally acquired damage in the course of epilepsy can accelerate processes of mental aging, particularly in the presence of limited reserve capacities. As for memory, a principal differentiation must be taken with regard to the more cortical and more mesial aspects of memory, namely learning and short term memory versus long term consolidation. Connected to this, episodic and semantic memory must be differentiated. Presumably because its more neocortical and unilateral disposition, short term memory and learning are more coupled with intellectual development, material specificity, and aging. The more mesial function of long term consolidation appears bilaterally disposed and thus more independent from this development. This difference is of importance also for the development of semantic memory.

As for the treatment of temporal lobe epilepsy, early and complete seizure control and the prevention of any additional damage appear demanding for the prevention of developmental disablement in childhood and adolescence or accelerated cognitive decline with aging.

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## Figure legends

**Fig. 1:** Deviations from left/right verbal/nonverbal dichotomy in patients with left TLE as a function of sex and language dominance. Left dominant men only show the expected pattern of impaired verbal and unimpaired figural memory. False lateralization by unimpaired verbal memory is observed in one group (women with atypical dominance), false lateralization by impaired figural memory is observed in three groups (atypical dominant men and women, and typically dominant women).

**Fig. 2:** Cognitive performance in patients with mesial TLE, z-transformed with respect to the corresponding performance of their healthy siblings. [COWA I = phonematic fluency, COWA II = semantic fluency]

**Fig. 3:** Cognitive performance in adult patients with newly diagnosed and not yet treated symptomatic/cryptogenic epilepsies indicates considerable pretreatment impairment in partial functions. IQ in contrast appears better preserved. [data were z-transformed with regard to normative test data]

**Fig 4:** IQ and verbal memory performance in TLE as a function of the age at the onset of epilepsy within and beyond critical phases of brain development. The difference in IQ but not memory indicates developmental hindrance and retardation in the early onset group.

**Fig 5:** Postoperative loss of verbal learning and memory in left TLE patients as a function of age at the time of surgery. The data indicate a generally different plasticity for learning and memory. For learning, greater plasticity is indicated in patients with surgery before puberty.

**Fig 6:** Acceleration of the age regression of verbal memory in left temporal lobe resected patients from before to after surgery. Before surgery memory decline does not differ from that observed in healthy subjects. Different performance levels at any age indicate that patients and healthy subjects differ because of the initial damage rather than because of chronic uncontrolled epilepsy.

**Fig. 7:** Longitudinal change in a composite (verbal/nonverbal) memory score in medically treated TLE patients (2-10yrs), and early (1 yr.) versus late (2-10yrs.) changes in patients after left or right temporal lobectomy. Note the losses particularly in medically treated and left temporal resected patients, and note the decisive effect of seizure control on the course of memory.

FIG 1

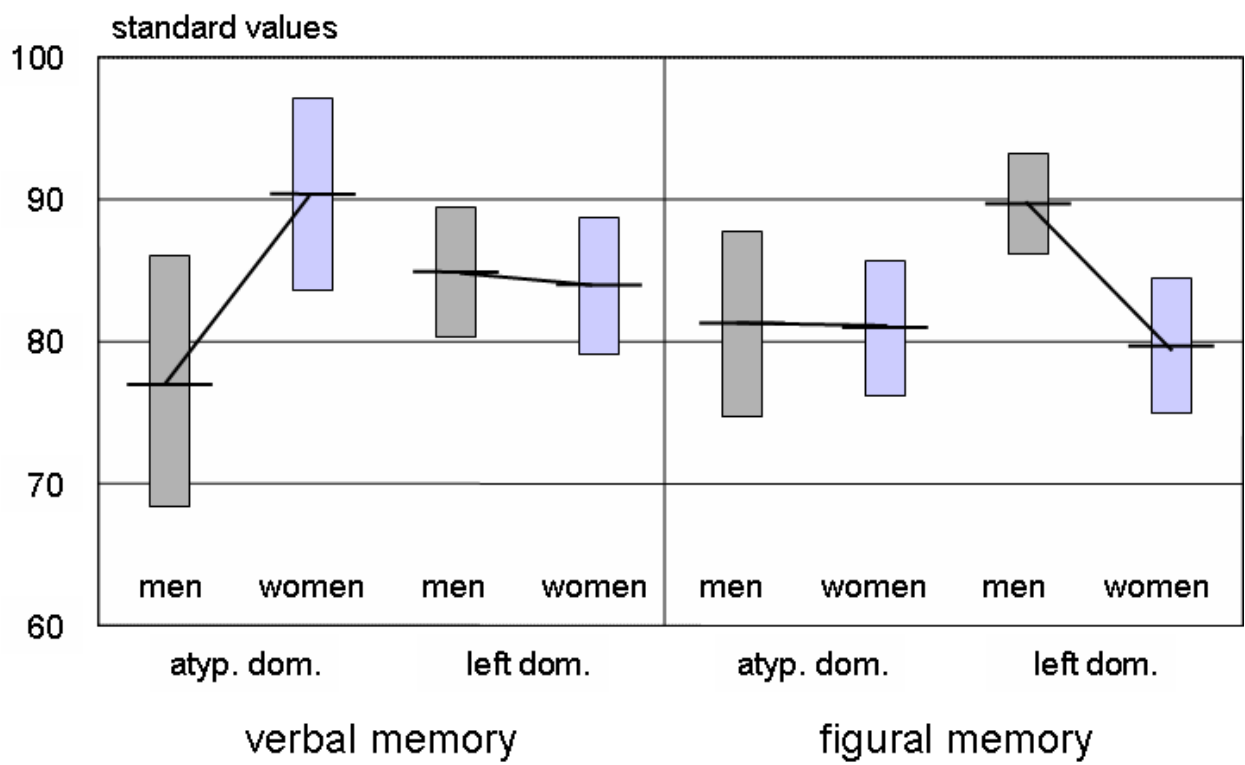
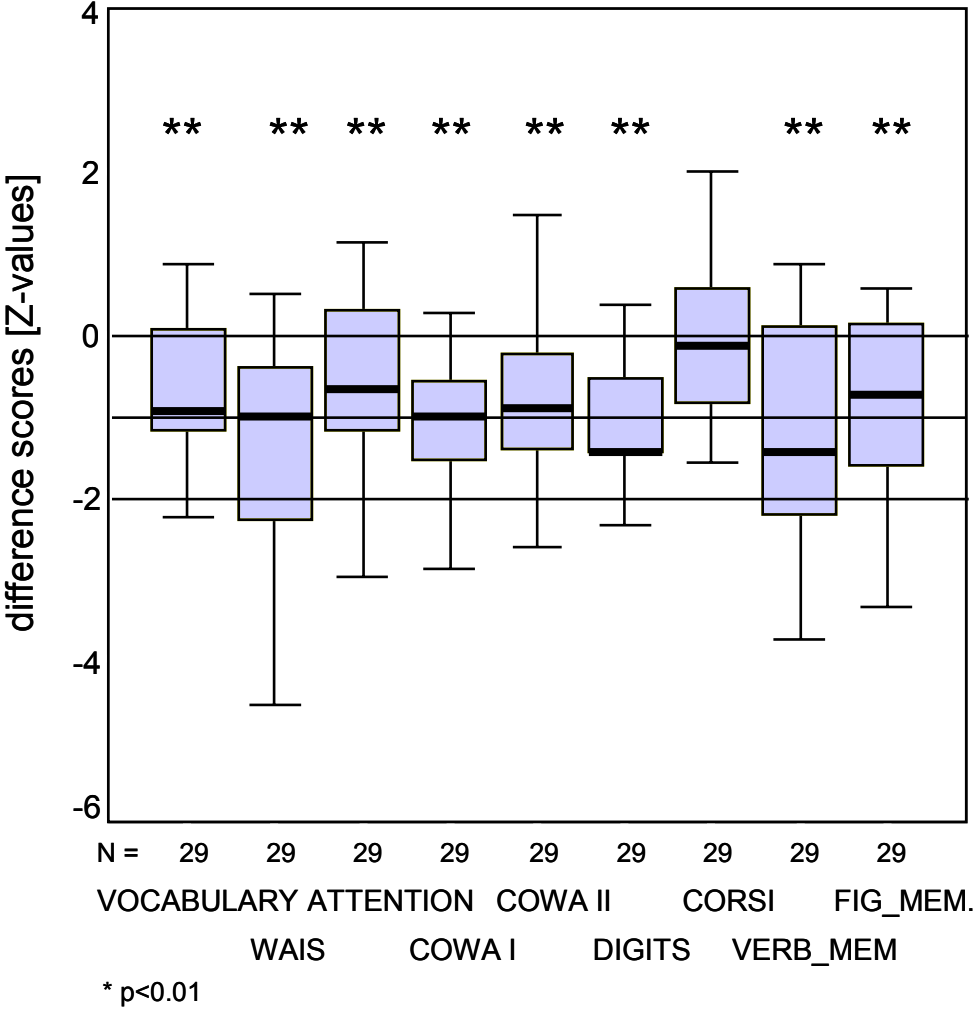


FIG 2



**FIG 3**

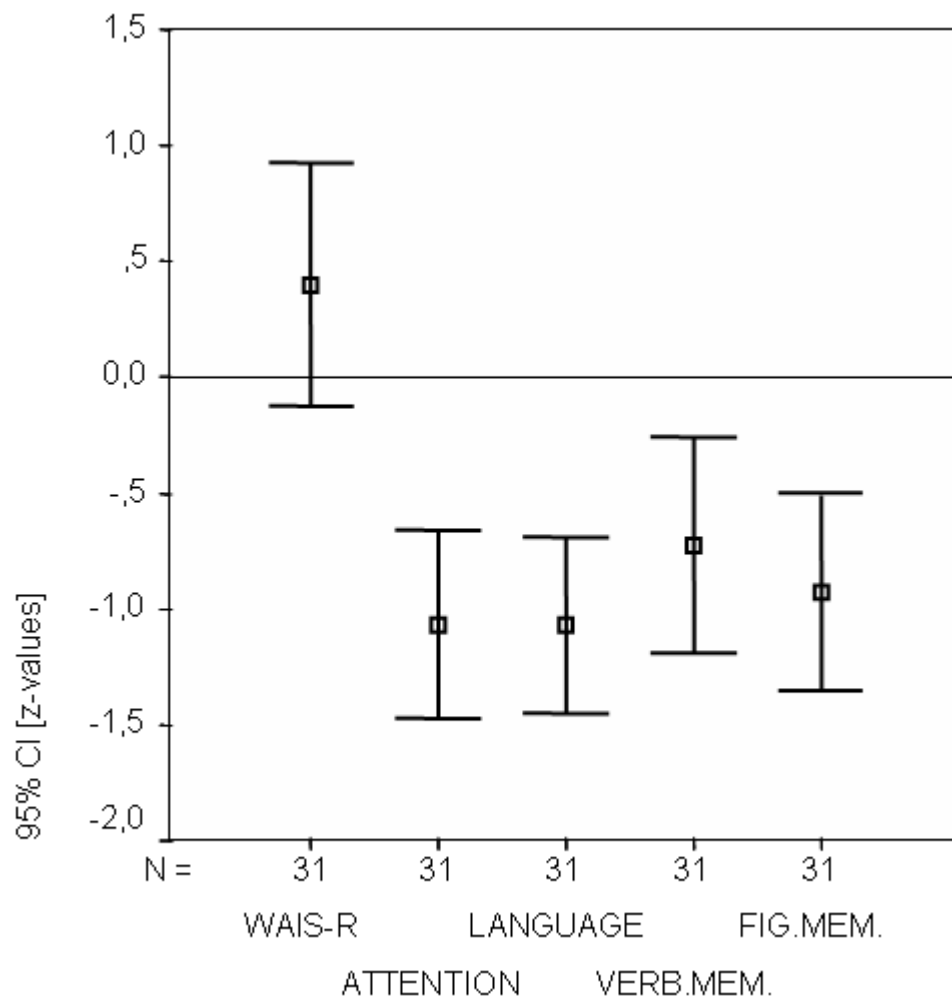


FIG 4

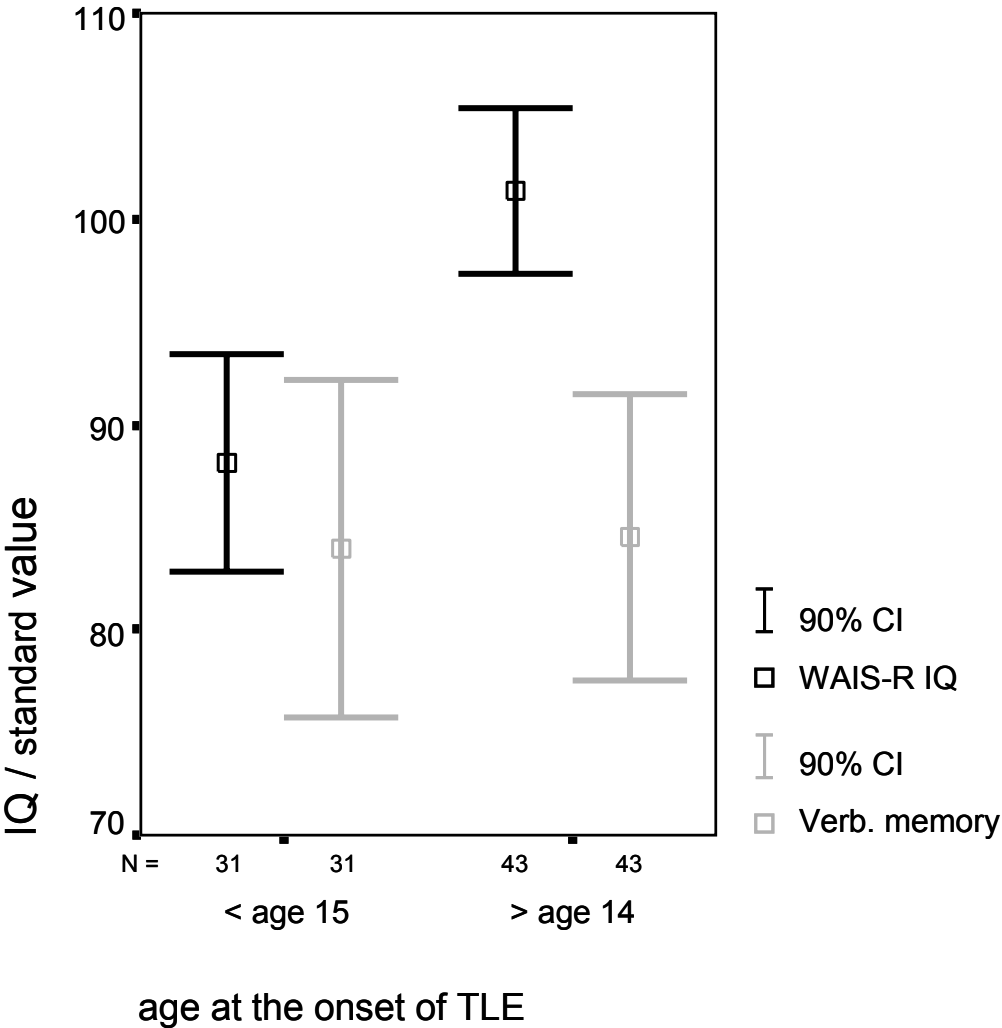


FIG 5

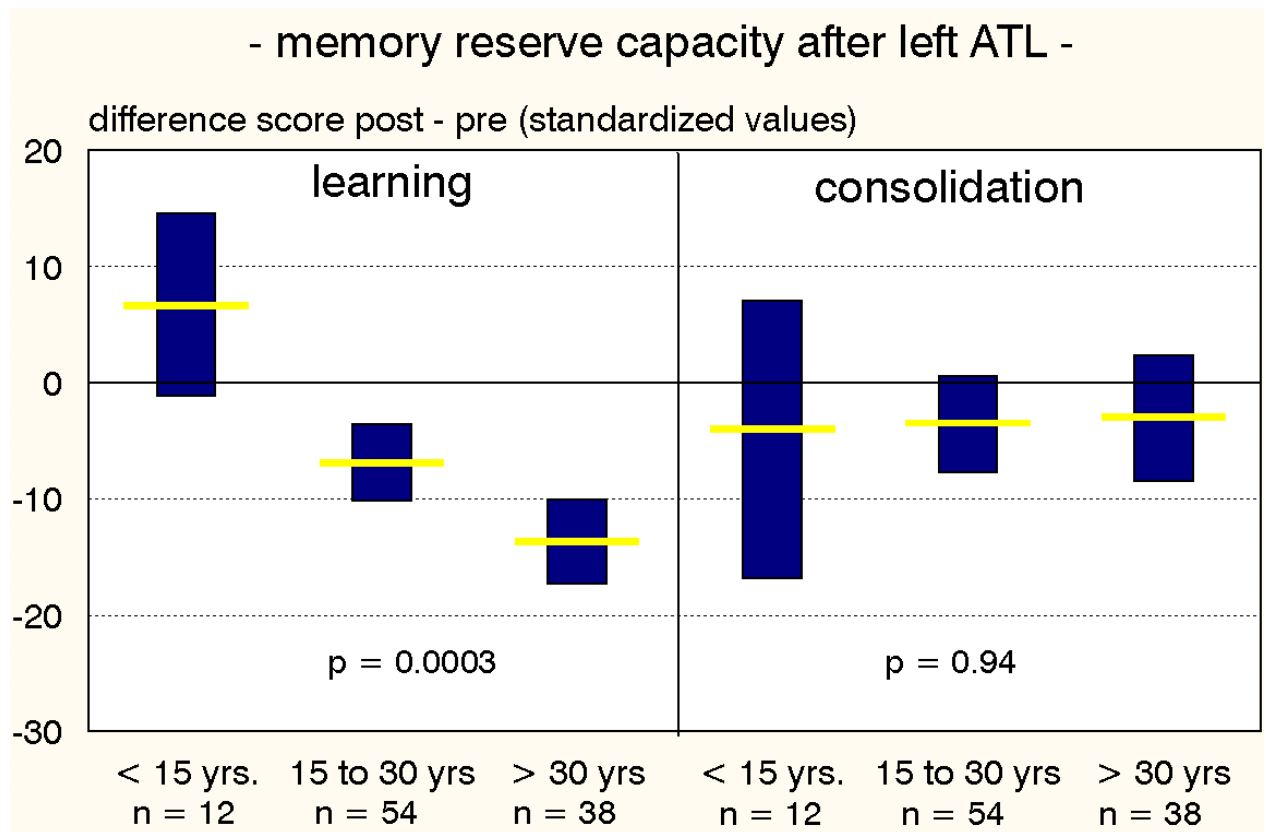


FIG 6

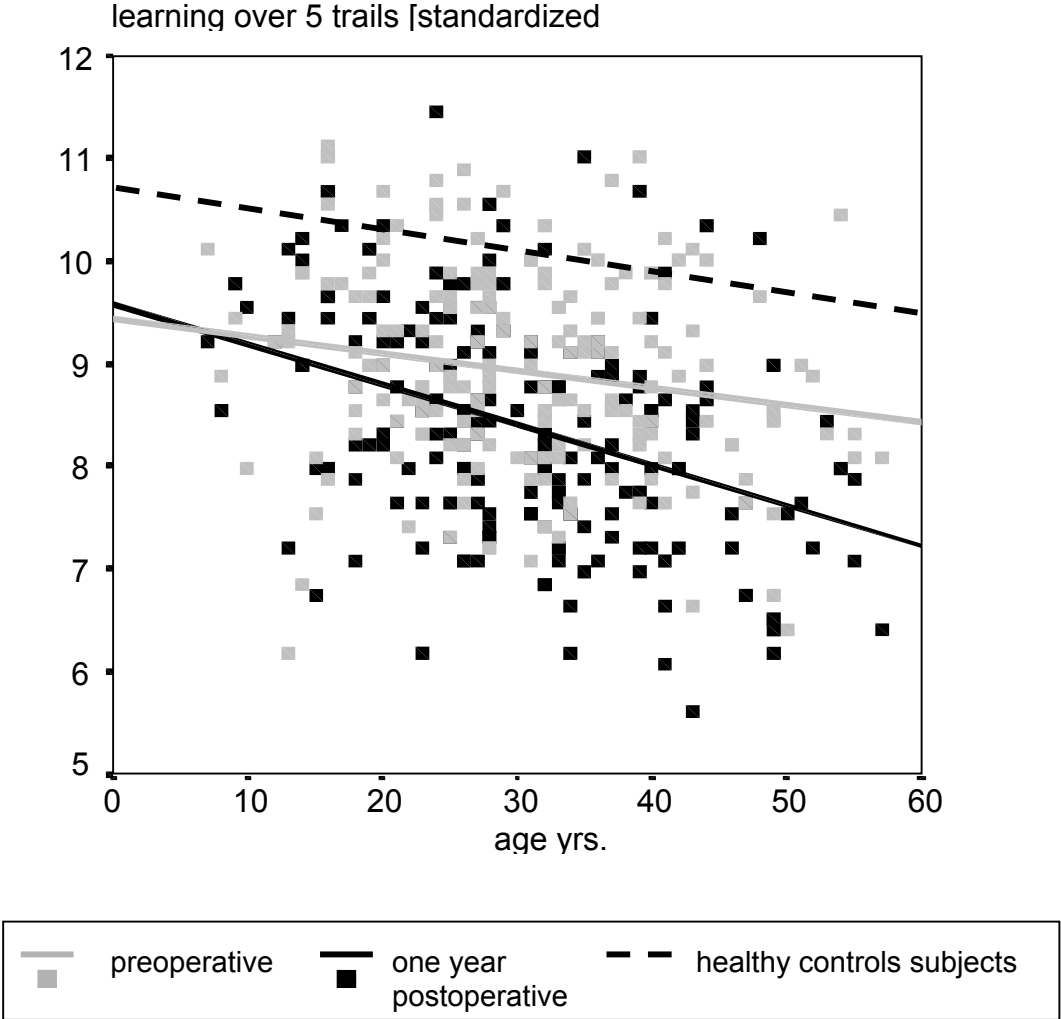


FIG 7

