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# Cognitive changes in people with temporal lobe epilepsy over a 13-year period

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ABSTRACT

*Objectives:* The aims of our study were to evaluate cognitive decline in people with temporal lobe epilepsy over a period of 13 years and to determine what clinical and treatment characteristics may have been associated with these.

*Materials and methods:* Thirty-three individuals with temporal lobe epilepsy underwent the same neuropsychological assessment of verbal and nonverbal memory, attention, and executive functions using the same cognitive test battery as one used 13 years ago. Long-term verbal and nonverbal memory was tested four weeks later. Results were compared with those carried out 13 years earlier.

*Results:* There was no significant change in verbal and verbal–logical memory tests; however, nonverbal memory worsened significantly. Long-term verbal memory declined for 21.9% of participants, long-term verbal–logical memory for 34.4%, and long-term nonverbal memory for 56.3%. Worsening of working verbal and verbal–logical memory was associated with longer epilepsy duration and lower levels of patients' education; worsening of verbal delayed recall and long-term verbal–logical memory was associated with higher seizure frequency. Decline in long-term nonverbal memory had significant association with a longer duration of epilepsy. The worsening of reaction and attention inversely correlated with the symptoms of depression.

*Conclusion:* Over a 13-year period, cognitive functions did not change significantly. Good seizure control and reduced symptoms of depression in this sample of people with temporal lobe epilepsy were associated with better cognitive functioning. The predictors of change of cognitive functions could be complex and require further study.



## 1. Introduction

Impairment of memory, attention, and other cognitive functions is common among people with epilepsy (PWE), which poses a negative impact on their quality of life, work, and learning abilities [1–4]. Studies have compared cognitive functions in healthy people and those with epilepsy [5–9]. Many studies also discuss the influence of demographic (age of onset, etiology, and duration of epilepsy) and functional (the total number and frequency of seizures, mood changes, and treatment) factors on cognition [7–9]. The effect of epilepsy on cognitive functions is best understood in temporal lobe epilepsy (TLE), which is known as a focal epilepsy associated with frequent and recurring seizures and is highly resistant to antiepileptic drugs (AEDs) [9–13]. Impairment of memory and other cognitive functions in people with epilepsy is observed while they are aging, but it is not clear whether this deterioration is determined by the early onset of the disease, poorly controlled seizures, and anatomical brain damage or due only to natural aging [5,14,15]. It is shown that speed and reaction of cognitive functions 'normally' deteriorate by about 20% at the age of 40, and at the age of 80, the decline is up to 40–60% [16]. Over a 20-year period, delayed recall declines by 25%; over 40 years, it declines by half [17].

Despite many studies focusing on cognitive functions of patients with TLE, there is still a lack of research showing how cognitive functions vary over time and whether good seizure control may slow the deterioration of cognitive functions in patients with epilepsy.

Thirteen years ago, we evaluated cognitive functions in patients with TLE and healthy controls, and published the findings in 2006 [9]. Our study revealed that, in individuals with epilepsy, memory and other cognitive functions were impaired in comparison with that of the healthy age- and sex-matched control group. Worse delayed recall and long-term memory were associated with frequent seizures, older age, and abnormal interictal EEG [9]. In this study, we aimed to retest patients with temporal lobe epilepsy and evaluate how their cognitive functions have changed in 13 years. We also tried to determine clinical and treatment characteristics that may have led to these changes.

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## 2. Materials and methods

### 2.1. Subjects

Participants of the research were patients with TLE who were investigated 13 years ago. Additional criteria for patients considered suitable for investigation were as follows: (1) no medications other than AEDs, (2) no epilepsy surgery, (3) no psychiatric background, and (4) no extensive or progressive cerebral lesions. Confirmation of TLE and determination of seizure type were based on clinical manifestations during seizures, localizing EEG abnormalities, and/or neuroimaging findings (MRI).

### 2.2. Methods

#### 2.2.1. Standard procedures

The study was approved by the hospital's bioethics committee. All subjects gave their informed consent to participate in the study. Patients underwent a full neurological examination and brain MRI before the study. Neuroimaging revealed temporal lobe lesions in only 11 patients; therefore, we did not classify patients on the basis of laterality of seizures or type of structural abnormality. Interictal epileptiform activity was evaluated with standard interictal EEG recording, which preceded the neuropsychological tests. Patients were classified according to the duration of epilepsy, age at the onset of epilepsy, seizure type, mean seizure frequency before recruitment, and the presence of epileptiform discharges on interictal EEG. The duration of epilepsy reflected the age span from the beginning of habitual seizures to the age at this neuropsychological testing. The age at the onset of epilepsy was the age of the patient when the epilepsy manifested. The frequency and type of seizures were recorded after reviewing patients' medical diaries and clarifying uncertainties through discussions with the patients. Seizure frequency was estimated as the mean frequency of habitual seizures per month during the year preceding recruitment. On the basis of the mean baseline frequency of seizures, patients were divided into three groups: 1) no seizures at all, 2) less than 4 seizures per month, and 3) four and more seizures per month. Patients who had both focal seizures (aware and with impairment of awareness) were categorized as the group with 'focal seizures'. Patients who had focal and focal-to-bilateral tonic–clonic seizures were referred to as the group with 'focal-to-bilateral tonic–clonic seizures'.

To take into account the possible influence of anxiety and depression on the cognitive evaluation, patients were assessed using the Lithuanian version of the Hospital Anxiety and Depression (HAD) scale [18]. We counted those scoring 0–7 points on the HAD scale as being without anxiety or depression signs; those with 8 or more points were counted as showing signs of anxiety or depression.

Before starting the tests, all the patients were asked to evaluate their memory subjectively from 0 to 10 points, with 0 being the worst and 10 being the best memory.

#### 2.2.2. Neuropsychological evaluation

Two separate outpatient visits were scheduled for neuropsychological testing and evaluation of delayed recall and long-term memory. The same investigator performed neuropsychological measurements for all patients on both occasions. Neuropsychological testing of patients was never performed in the postictal period (within 12h after the last seizure).

During the first meeting, we tested psychomotor reaction speed, attention, verbal memory, verbal–logical memory, nonverbal memory, working memory, and delayed recall. All the patients were evaluated with a battery of 11 standardized cognitive tests which were used 13 years ago: word list learning (Lithuanian equivalent to the Rey Auditory Verbal Learning Test (RAVLT)), immediate and delayed recall of a short verbal–logical story (VLS), Rey–Osterrieth complex figure test (ROCFT), digit span forward (DS-1) and backward (DS-2), word pair association test (WPAT), verbal recognition (WR), Trail Making Tests A (TMT-A) and B (TMT-B), block tapping test (BTT), and digit symbol substitution test (DSST).

Delayed recall of the word list (RAVLT-7), VLS (VLS-2), and ROCFT (ROCFT-2) were tested 30 min after word list learning (five attempts to learn list A plus one attempt to learn distractive list B; each list contained 15 words), immediate recall of the VLS, and copying of a complex figure. Word list recall was scored as the number of words recalled from list A without a reminder. Verbal–logical story recall was scored as the sum of points given for 24 units of VLS (2 points for each correctly recalled unit, 1 point for each partially recalled unit; maximum score = 48 points). Nonverbal recall was scored as the sum of elements recalled on the ROCFT (2 points for each correct and properly placed element, 1 point for each distorted or incomplete properly placed element or correct poorly placed element, and 0.5 point for each distorted or incomplete poorly placed element; maximum score = 36 points).

Patients were asked to use the stable dose of earlier prescribed AEDs, to avoid the use of other medications, and to complete the seizure diary as they did earlier. Visit 2 was scheduled 4 weeks later. During the second meeting, we tested long-term verbal (RAVLT-8), verbal–logical (VLS-3), and nonverbal (ROCFT-3) memory. At visit 2, patients were asked to recall word list A from the RAVLT, the VLS, and the Rey–Osterrieth complex figure (without reminder) to evaluate long-term verbal and nonverbal memory capability. The interval of 4 weeks was chosen on the assumption that it should be long enough for memory consolidation and that we did not change the procedure performed 13 years ago. The decay in memory was estimated for each patient by calculating scores for the RAVLT, VLS, and ROCFT at visit 2 as percentages of the corresponding scores for delayed recall at visit 1: % test (RAVLT, VLS, ROCFT) = long-term recall score (visit 2) / delayed recall score (visit 1) × 100%.

All of the test results were compared with the results of the same patients tested with the same test battery used 13 years earlier.

### 2.3. Statistical analysis

Means (SD) were calculated for continuous variables and absolute values, and percentages were calculated for categorical variables in the patients with epilepsy. Differences in continuous variables between the groups were estimated with independent-samples *t*-test or Mann–Whitney U test (two groups) and Kruskal–Wallis test with a Dunn's post hoc test when necessary (more than two groups). Differences between baseline and follow-up results were compared with dependent-samples *t*-test or Wilcoxon signed-rank test. Correlation analysis employed the Pearson (for parametric values) and Spearman (for nonparametric values) coefficients as appropriate. The dependence of demographic and clinical factors (age, sex, education, disease duration, seizure frequency, number of AEDs, anxiety, and depression) on long-term memory decay was evaluated by stepwise linear regression analysis. A $p < 0.05$ was considered to indicate a statistically significant difference; a $p < 0.1$ was considered to indicate a significant trend. Because multiple cognitive tests were administered, Bonferroni correction for multiple tests was also applied (level of significance set at 0.0022, accordingly). The data set of variables included sex, age at testing, education, age at the onset of epilepsy, duration of epilepsy, mean seizure frequency before recruitment, type and frequency of seizures between visits 1 and 2, and number of AEDs.

## 3. Results

Thirty-three patients (21 females) with TLE out of 70 who were tested 13 years earlier met the inclusion criteria and agreed to participate in this retesting. Females were younger ($U = 61$, $p = 0.015$): the mean age of females was 41.2 ± 10.1 (ranging from 30 to 66) years, and the mean age of males was 48.8 ± 7.0 (from 35 to 56) years. All but one were on an AED at a stable dose for at least 1 month preceding