Cognition in adult patients with newly diagnosed non-lesional temporal lobe epilepsy

Agnes Balint Bjørke a,b,c,* Ylva Østby d, Simon Gevert Grah d, Pål Gunnar Larsson e, Ketil Berg Olsen e, Marianne C. Johansen Nævra e, Geir Andre Ringstad f, Atle Bjørnerud g, Leif Gjerstad c, Erik Taubøll a,c, Kjell Heuser a

a Department of Neurology, Division of Clinical Neuroscience, Oslo University Hospital, Rikshospitalet, Oslo, Norway
b Department of Neurology, Division of Neurology, Rheumatology and Habilitation, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway
c Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
d Institute of Psychology, Faculty of Social Sciences, University of Oslo, Oslo, Norway
e Section of Clinical Neuropsychology, Department of Neurosurgery, Division of Clinical Neuroscience, Oslo University Hospital, Rikshospitalet, Oslo, Norway
f Department of Radiology, Division of Radiology and Nuclear Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway
g The Intervention Centre, Oslo University Hospital, Rikshospitalet, Oslo, Norway

Article info

Article history:
Received 28 October 2020
Revised 29 December 2020
Accepted 29 December 2020
Available online 2 February 2021

Keywords:
Adults
Cognition
Executive functions
Memory
Neuropsychology
Temporal lobe epilepsy

Abstract

Objective: To evaluate whether cognitive performance is affected in newly diagnosed temporal lobe epilepsy (TLE) and to determine the most vulnerable cognitive domains.

Methods: In this baseline longitudinal study, differences in memory and non-memory cognitive functions were assessed using comprehensive neuropsychological test batteries in 21 adult patients with newly diagnosed non-lesional TLE and individually matched controls. In addition, the analyses included ratings of self-perceived emotional status.

Results: The patients performed more poorly than the control group regarding delayed visual memory (p = 0.013) and executive function tasks related to switching (Trail Making Test and verbal fluency shifting; p = 0.025 and p = 0.03, respectively). We found no differences in verbal learning and memory, attention/working memory/processing speed, and other executive functions.

Significance: Our results show that patients with TLE often have specific cognitive deficits at time of diagnosis, even in the absence of structural brain abnormalities. This supports the hypothesis that memory dysfunction is linked to an underlying pathology rather than to the effect of recurrent seizures, long-term use of anti-seizure medication, or other epilepsy-related factors. As certain executive functions are affected at an early stage, the pathology may involve brain regions beyond the temporal lobe and may comprise larger brain networks. These results indicate the need for greater awareness of cognition at the time of diagnosis of TLE and before initiation of treatment, and integration of neuropsychological assessment into early routine clinical care.

Citation

OBJECTIVES: To evaluate whether cognitive performance is affected in newly diagnosed temporal lobe epilepsy (TLE) and to determine the most vulnerable cognitive domains.

METHODS: In this baseline longitudinal study, differences in memory and non-memory cognitive functions were assessed using comprehensive neuropsychological test batteries in 21 adult patients with newly diagnosed non-lesional TLE and individually matched controls. In addition, the analyses included ratings of self-perceived emotional status.

RESULTS: The patients performed more poorly than the control group regarding delayed visual memory (p = 0.013) and executive function tasks related to switching (Trail Making Test and verbal fluency shifting; p = 0.025 and p = 0.03, respectively). We found no differences in verbal learning and memory, attention/working memory/processing speed, and other executive functions.

SIGNIFICANCE: Our results show that patients with TLE often have specific cognitive deficits at time of diagnosis, even in the absence of structural brain abnormalities. This supports the hypothesis that memory dysfunction is linked to an underlying pathology rather than to the effect of recurrent seizures, long-term use of anti-seizure medication, or other epilepsy-related factors. As certain executive functions are affected at an early stage, the pathology may involve brain regions beyond the temporal lobe and may comprise larger brain networks. These results indicate the need for greater awareness of cognition at the time of diagnosis of TLE and before initiation of treatment, and integration of neuropsychological assessment into early routine clinical care.

1. Introduction

Cognitive impairment is a major complicating feature of epilepsy, adversely influencing several aspects of daily functioning [1–3]. Patients with temporal lobe epilepsy (TLE) often display cognitive dysfunction, particularly affecting memory, but also a range of other abilities such as language, attention, and higher level problem-solving skills [1,4–6]. Lesional etiology is associated with more pronounced cognitive dysfunction than non-lesional cases, even at early stages [7,8], and chronic TLE, especially if unsuccessfully treated, may be associated with cognitive decline [5,6,9,10].

Most knowledge on cognition in TLE has been obtained from investigations of severely affected patients and from those with late stages of the disease [5,6,9–16], making it difficult to ascertain the natural course of cognitive dysfunction or cognitive decline in this condition. There are only a few studies on cognition in new-onset epilepsies, including TLE [1,17–21], and even fewer have been conducted in patients with non-lesional TLE [22].

This absence of information means that when cognitive alterations occur, it is unknown whether they are due to the epilepsy per se, an underlying complex brain pathology, recurrent seizures,
ongoing epileptic activity over time, adverse effects from long-term use of anti-seizure medication (ASM), or a combination [23]. The extent to which cognitive functions decline during the course of the disease is also uncertain.

In order to address these knowledge gaps, and to disentangle the effects of TLE per se from other potential factors, it is essential that new-onset TLE is characterized, and that cognition is studied from a longitudinal perspective. The understanding of specific cognitive challenges at different time points during epileptogenesis and the course of the disease could also facilitate personalized treatment.

Here we assessed cognitive performance in patients with newly diagnosed non-lesional TLE and healthy, individually matched control subjects to explore whether patients show cognitive deficits already at an early stage of the disease. We also determined the most vulnerable cognitive domains.

2. Material and methods

2.1. Sample

This study is part of a longitudinal study at the Epilepsy Unit, Department of Neurology, Oslo University Hospital, with baseline data collected when the diagnosis of TLE was first established. The patients were enrolled from neurological departments in the South-Eastern Health Region of Norway. Control subjects were recruited by the patients themselves in order to provide a good match on sociodemographic variables and low between-subject variation. For this purpose, the patients were asked to identify a friend of the same age (±1 year), gender, and education level as themselves, but without epilepsy, who would be willing to act as a matched control. In cases where patients did not have the opportunity to invite their own control, the controls were recruited through advertisements at Oslo University Hospital and the University of Oslo. These controls were also individually matched to the patients by age, gender, and level of education.

Inclusion criteria for patients were newly diagnosed TLE of unknown etiology, no structural brain lesion other than mesial temporal sclerosis on 3-tesla magnetic resonance imaging (3T-MRI) scanner, and aged between 18 and 59 years. The clinical diagnosis in each case was based on seizure semiology, interictal electroencephalography (EEG) recordings, and qualitative assessment of structural MRI data according to ILAE definitions [24]. Exclusion criteria for both patients and control subjects were structural brain abnormalities (e.g., tumors, infarctions, malformations), intellectual disability, severe psychiatric disorder, progressive medical condition, alcohol or drug abuse, and former brain surgery.

Written informed consent was obtained from all participants, and the study was approved by the Regional Committees for Medical and Health Research Ethics (reference number: 2013/855/REK sør-vest A).

A total of 21 Norwegian patients with newly diagnosed non-lesional TLE and the same number of healthy, individually matched controls entered the study.

2.2. Clinical data

Data collected upon enrollment, comprised the medical history, physical examination, blood sample, standardized neuropsychological evaluation, patient-reported survey on emotional status, MRI of the brain, and recordings of blood pressure, electrocardiogram (ECG), and routine 30-minute, 27-channel resting-awake EEG. The MRI scans were acquired on a 3T whole-body scanner (Philips Ingenia®, Best, The Netherlands), and the EEGs were performed in accordance with the International 10–20 Electrode Placement System. To avoid temporary seizure-induced cognitive deficit, we ensured that patients had been seizure-free for at least 7 days prior to testing.

The MRI protocol focused both on high-resolution images for best-possible visual characterization of anatomy and pathology (sagittal T1-volume, sagittal FLAIR-volume, axial and coronal T2 2 mm, and axial Susceptibility-Weighted Imaging), as well as quantifiable measures including axial Diffusion Tensor Imaging with calculated Apparent Diffusion Coefficient maps.

All clinical data were obtained from direct interviews with the patients and control subjects, as well as from review of patient records. The clinical assessment, the neuroradiological work, and the neuropsychological evaluation were carried out by neurologist (ABB), neuroradiologist (GAR), and neuropsychologist (YØ), respectively, all with special expertise in epilepsy. The EEG data were analyzed independently by two board-certified neurophysiologists.

2.3. Neuropsychological assessment

2.3.1. General intellectual ability

Two of four subtests of the Wechsler Abbreviated Scale of Intelligence® - First Edition (WASI®-I), Vocabulary, and Matrix Reasoning, were used as a proxy measure of general intelligence (Intelligence Quotient, IQ) for group description purposes; the descriptions are given in Table 1.

2.3.2. Memory (verbal and visual)

The Norwegian translation of the Rey Auditory Verbal Learning Test (RAVLT) was used to assess verbal memory. A list of 15 semantically unrelated words was presented to each participant five times with recall trials after each presentation, followed by a new list of words (interference trial), then the immediate free-recall trial (number of words), and a 30-min delayed-recall trial. For visual memory, the Aggie Figures Learning Test (AFLT) was used. This test was developed to serve as a visual analog to RAVLT [25], consisting of 15 figures presented similarly as the word lists of RAVLT. The test has been shown to be comparable to RAVLT in terms of numbers of items recalled in healthy populations [25–27], and has been shown to be sensitive to temporal lobe surgery [25]. For the purposes of this study, the total learning scores (total number of correctly recalled figures or words cumulatively over 5 trials) and delayed-recall scores were used in further analyses.

2.3.3. Attention/working memory/processing speed

Verbal and visuospatial working memory were assessed using Digit span and Spatial span (total score, including both forward and backward span) from the Wechsler Memory Scale 3rd ed. (WMS-III). Attention and processing-speed measures were obtained from the Delis–Kaplan Executive Function System (D-KEFS) subtests Trail Making Test 2 (TMT2), and Color Word Interference Test (CWIT) part 1 (color naming) (seconds) and part 2 (color reading) (seconds) [28].

2.3.4. Executive functions (verbal fluency, inhibition, and shifting)

Subtests from three domains from the D-KEFS, a compilation of neuropsychological tests used to measure a variety of verbal and nonverbal executive functions were used: verbal fluency tests with separate scores for phonetic fluency (number of words on the F-A-S test), semantic (categorical) fluency, and modified switching verbal fluency (number of words of fruit and furniture); TMT number-letter-switching (TMT4) (seconds), and CWIT inhibition (CWIT3) (seconds) and inhibition/switching (CWIT4) (seconds) [28].
2.4. Self-reported emotional well-being

Emotional-status score was calculated based on the emotional well-being subscale (5 items) of the QOLIE-89 (Quality of Life in Epilepsy Inventory-89), asking specifically about how the patients have felt during the past 4 weeks, using an analog scale ranging from 1 (all of the time) to 6 (none of the time).

2.5. Statistical analyses

In order to ensure control groups were well matched with patients, age, education level, and IQ were compared using paired-samples t-tests. Descriptive statistics were calculated for all variables. Descriptive analysis included frequency and proportions for categorical variables, with means with standard deviation (SD) and ranges, or medians with ranges, for continuous variables. Groups were compared using Pearson’s chi-squared test, Kruskal–Wallis test, or t-test, as appropriate.

Neuropsychological test scores were analyzed with paired-samples t-tests, comparing each patient with the matched control on each variable of the neuropsychological assessment (all raw scores). Clinical cutoff for memory scores were defined as 1 SD below the age-corrected mean. In the case of RAVLT, raw scores were converted to z-scores using the meta-norms given in Schmidt, 1996 [29]. For the AFLT, there are, to our knowledge, no published age-corrected norms. Instead, we set the clinical cutoff

### Table 1

| Demographic and clinical characteristics of patients with newly diagnosed, non-lesional temporal lobe epilepsy and healthy control subjects. |
|---------------------------------------------------------------|
| **Patients** | **Control subjects** | **P-value*** |
| Age (years), mean (SD) [range] | 31.76 (11.67) | 31.71 (11.59) | 0.803 |
| [19–58] | [19–58] | |
| Gender (male/female), n (%) | 7/14 (33/67) | 7/14 (33/67) | 0.410 |
| Intelligence Quotient (IQ) (WASI-I), mean (SD) [range] | 113.48 (11.24) | 116.19 (9.52) | 0.229 |
| Vocabulary (T-score) | 58.19 (5.41) | 60.14 (5.84) | |
| [43–67] | [47–71] | |
| Matrix reasoning (T-score) | 56.81 (10.05) | 58.10 (6.49) | 0.665 |
| [20–66] | [47–68] | |
| Dominance, n (%) | Right-handed | 20 (95) | 17 (81) | 0.153 |
| Left-handed | 1 (5) | 4 (19) | | 0.259 |
| Epilepsy in first degree family members, n (%) | No | 19 (90) | 19 (90) | 0.549 |
| Yes | 2 (10) | 2 (10) | | |
| Structural etiology | No | 1 (5) | 1 (5) | 0.054 |
| Febrile seizures, n (%) | No | 19 (90) | 20 (95) | 0.054 |
| Yes | 2 (10) | 1 (5) | | |
| Seizure type, n (%) | Focal aware seizure | 3 (14) | | |
| Focal impaired awareness seizure | 3 (14) | | |
| Focal aware seizure and focal impaired awareness seizure | 7 (33) | | |
| Bilateral tonic-clonic seizure with focal onset | 8 (38) | | |
| Focal aware seizure and bilateral tonic-clonic seizure | 3 (14) | | |
| Focal impaired awareness seizure and bilateral tonic-clonic seizure | 5 (24) | | |
| Use of anti-seizure drug by inclusion in the study, n (%) | No | 7 (33) | | |
| Under titration | 6 (29) | | |
| Yes (therapeutic dosage) | 8 (38) | | | 0.753 |
| Magnetic Resonance Imaging (3 Tesla) findings, n (%) | Normal | 9 (43) | 8 (38) | |
| Abnormalities not associated with epilepsy* | 12 (57) | 13 (62) | | |
| Non-specific | 15 (71) | 12 (57) | | |
| Small non-specific white matter hyperintensities | 13 (62) | 10 (48) | | |
| Small white matter gliosis (1 or 2) | 2 (10) | 2 (10) | | |
| Specific | 1 (5) | 2 (10) | | |
| Arnold-Chiari malformation I | 0 (0) | 1 (5) | | |
| Small arachnoid cyst (1–3) | 1 (5) | 1 (5) | | |
| Mesial temporal sclerosis | 0 (0) | 0 (0) | | |
| 27-channels electroencephalography findings, n (%) | Normal | 5 (24) | | |
| Abnormalities** | 16 (76) | | |
| Non-specific | 10 (48) | 7 (38) | | |
| Abnormal theta rhythms | 2 (10) | | |
| Sharp waves, suspected epileptiform activities | 7 (38) | | |
| Epileptiform | | | |
| Focal spike discharges | 10 (48) | | | 0.039 |
| Self-reported emotional well-being, mean (SD) [range] | 67.81 (19.29) | 78.86 (11.67) | 0.039 |
| [20–92] | [56–96] | |

SD = Standard Deviation.

WASI-I = Wechsler Abbreviated Scale of Intelligence, first edition.

* Four patients and one control subject had several abnormalities.

** Four patients had both nonspecific and epileptiform abnormalities.

*** P-values are calculated using Pearson’s chi-squared test (n (%)), t-test (mean (SD) [range]), or Kruskal–Wallis test (median (range)), as appropriate.
to 1 SD below the mean of the control group, which was 45 or fewer figures on total learning score and 11 or fewer figures on delayed-recall. Clinical cutoffs for all other scores (D-KEFS, digit, and spatial span) were based on published norms and were set at 1 SD below the normative mean, i.e., a scaled score of 6 or below. We noted that the mean scores of our controls were higher than the norms usually applied. The number of people with a scaled score below clinical cutoff was calculated for patients and control subjects, but the results were not submitted to statistical analyses. Cognitive domains in patients were also analyzed at the group level regarding age at seizure onset of potential seizure-like episodes (before or after 18 years of age) by independent sample t-test.

Although several neuropsychological tests were used, and thus multiple statistical tests were employed, we decided not to correct for multiple comparisons using Bonferroni criteria; the sample is small, and we expect small effect sizes at this stage of TLE, and wanted to avoid type II errors. We included only a few scores from each test to limit the number. The results should be considered with this limitation in mind.

The possible influence of ASM use on neuropsychological test results was determined by one-way ANOVA with post hoc Tukey HSD tests, using test scores as dependent variables and ASM use as independent variable (three groups: no medication, under titration, on therapeutic dosage).

The relationship between reduced cognitive performance and emotional status was tested in both patient and control groups using Pearson’s correlation coefficients between neuropsychological test scores and the emotional well-being subscale of QOLIE-89.

All statistical analyses were performed using SPSS (IBM Corp. Released 2017. IBM® SPSS® Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp.). Statistical significance was set at p < 0.05. As effect size statistics, Cohen’s d was used, which presents the difference between groups in terms of SD units, using the following guidelines for interpretation: 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect.

### Table 2

| Neuropsychological tests                  | Patients       | Control subjects | T-value* | P-value** | Cohen’s d |
|------------------------------------------|----------------|-----------------|----------|-----------|-----------|
| Visual learning and memory               |                |                 |          |           |           |
| AFLT learning                            | 45.76 (12.79)  | 51.33 (5.37)    | 2.016 (20)| 0.057     | 0.44      |
| AFLT delayed recall                      | 11.52 (3.41)   | 13.52 (1.40)    | 2.739 (20)| 0.013     | 0.59      |
| Verbal learning and memory               |                |                 |          |           |           |
| RAVLT Learning                           | 56.14 (9.91)   | 57.81 (6.76)    | 0.609 (20)| 0.549     | 0.13      |
| RAVLT delayed recall                     | 11.33 (3.34)   | 12.52 (2.20)    | 1.203 (20)| 0.243     | 0.26      |
| Attention and executive functions        |                |                 |          |           |           |
| TMT 4                                    | 69.75 (29.49)  | 52.40 (18.72)   | –2.429 (19)| 0.025     | –0.54     |
| CWIT 3                                   | 52.33 (13.70)  | 47.38 (7.79)    | –1.458 (20)| 0.160     | –0.26     |
| CWIT 4                                   | 58.05 (11.66)  | 52.33 (8.59)    | –1.857 (20)| 0.078     | –1.52     |
| Verbal fluency switching                 | 14.76 (3.14)   | 16.52 (2.48)    | 2.341 (20)| 0.030     | 0.51      |
| Digit span                               | 15.90 (3.08)   | 16.86 (3.85)    | 0.791 (20)| 0.438     | 0.17      |
| Spatial span                             | 17.00 (2.86)   | 17.48 (2.06)    | 0.621 (20)| 0.542     | 0.14      |
| Verbal fluency                           |                |                 |          |           |           |
| Categories                               | 47.05 (11.24)  | 50.95 (10.38)   | 1.219 (20)| 0.237     | 0.27      |
| Phonetic                                 | 44.00 (10.70)  | 46.67 (8.93)    | 0.843 (20)| 0.409     | 0.18      |
| Processing speed                         |                |                 |          |           |           |
| TMT 2                                    | 24.00 (7.75)   | 22.25 (8.11)    | –0.738 (19)| 0.469     | –0.17     |
| CWIT 1                                   | 29.62 (5.33)   | 26.90 (2.95)    | –2.017 (20)| 0.057     | –0.44     |
| CWIT 2                                   | 22.00 (3.24)   | 20.48 (3.14)    | –1.657 (20)| 0.113     | –0.36     |

AFLT = Aggie Figures Learning Test.
CWIT = Color-Word Interference Test (seconds).
Df = Degrees of freedom.
RAVLT = Rey Auditory Verbal Learning Test.
SD = Standard Deviation.
TMT = Trail Making Test (seconds).
* T-values are calculated using paired-samples t-tests (df).
** P-values are calculated using paired-samples t-tests (mean (SD)).

### 3. Results

#### 3.1. Clinical and demographic variables

Among participants (n = 21 patient-control pairs), 14 (67%) were females and 7 (33%) males. Median age at diagnosis was 32 years (19–58 years). Age, education level (>13 years of education for all participants), and IQ in the patient and the control groups were comparable, confirming an efficient matching method. Physical and neurological examination, hematological and biochemical parameters, and ECG were normal in all study participants. Further demographic characteristics and clinical data are summarized in Table 1.

#### 3.2. Cognitive functioning

The results of the paired-samples t-tests, using neuropsychological test scores (raw scores) as dependent variables, are shown in Table 2. There were statistically significant differences between patients and healthy controls on visual delayed recall tests (AFLT delayed recall), TMT4 completion time, and verbal fluency shifting (Table 2; Fig. 1). We also found a tendency toward reduction, with p < 0.10, for visual learning (AFLT total learning score), CWIT inhibition/shifting, and CWIT color naming.

When looking at the results in terms of effect sizes, the differences between patients and controls seem more pronounced and extends to several neuropsychological tests than could be verified by calculating statistical significance, particularly regarding CWIT inhibition and CWIT inhibition/shifting. Although conclusions based on this should currently be treated with caution, future studies with larger cohorts might confirm our findings.

#### 3.3. Clinically significant cognitive deficits

A clinically significant deficit was defined by a result of more than one SD below the normative mean. Eight patients (38%) and
only one of the controls (5%) scored in this range on tests of delayed visual memory recall. In delayed verbal-memory recall tests, three patients (14%) showed results indicating impairments of clinical significance, whereas this was not seen with any of the controls. For the WMS and D-KEFS tests, 0–3 patients and 0–1 controls, respectively, had scores that may represent such deficits.

3.4. Impact of epilepsy-related factors on cognitive functions

3.4.1. Epilepsy-like symptoms before seizure onset

Newly diagnosed TLE was an inclusion criterion for patients. In our sample, patients were included directly after the diagnosis was established, with a median of 2 months (0–10 months). However, in retrospect, several patients (19 of 21) had previously experi-
enced subtle symptoms of potential seizures at a median time of 7 years (0–26 years) before the diagnosis was established. It is emphasized that these are very uncertain indications from patients, and there is no evidence that these symptoms were epileptic in nature. In the patient group as a whole, 48% (n = 10) started experiencing potential seizure-like episodes before the age of 18 years, while 52% (n = 11) experience these in adulthood. We did not detect a significant difference in any of the cognitive domains between patients with seizure-like episodes of early or late onset, indicating an absence of, or only minor, effects of such episodes before diagnosis on cognitive function.

3.4.2. Use of anti-seizure medication (ASM)

Although patients were enrolled directly after the diagnosis was established, some had already started taking ASM when entering the study; 29% of patients (n = 6) had the first-choice drug under titration and 38% (n = 8) had achieved therapeutic dosage of their first ASM (Table 1). The medications in use included lamotrigine (n = 9), levetiracetam (n = 2), valproate (n = 1), oxcarbazepine (n = 1), and carbamazepine (n = 1). In order to assess whether use of ASM may have influenced the neuropsychological test results, we compared the test performances of patients not using medication (n = 7), patients with ASM under titration (n = 6), and patients on therapeutic dosage of ASM (n = 8). Only the three tests with statistically significant group differences in the main analysis were submitted to sub-group analyses (one-way ANOVA). All three groups performed similarly in the AFLT (visual memory) delayed recall with scores of 11.6, 12.0, and 11.1, respectively, indicating no influence of ASM on performance (F = 0.10, p = 0.902). Furthermore, there was no difference in test scores between the three medication groups on TMT4 (mean scores of 68.0, 69.3, and 71.9, respectively; F = 0.03, p = 0.973). However, patients who had reached full dosage ASM performed significantly poorer in verbal fluency shifting (mean score: 12.1) than unmedicated patients (15.3) (F = 10.86, p = 0.001). Post hoc Tukey HSD tests confirmed that the group on full ASM had statistically lower scores than both the group with no ASM (p < 0.05) and the group with ASM under titration (p < 0.01). Patients undergoing titration, however, achieved higher scores (17.7) than unmedicated patients, making the results difficult to interpret.

3.4.3. Self-reported emotional well-being

Patients reported significantly poorer emotional well-being than control subjects (Table 1). In order to assess whether the neuropsychological test results were influenced by the patients’ greater subclinical depressive symptoms and negative mood states, we performed correlation analysis between self-reported emotional scores and the results of the three measures that were significant in the main analysis. No statistically significant correlations between self-reported emotional well-being and delayed visual recall (r = 0.11, p = 0.63), TMT4 (r = -0.12, p = 0.62) or verbal fluency switching (r = -0.11, p = 0.65) were identified.

4. Discussion

To our knowledge, this is the first study to conduct extensive neuropsychological assessment of adult patients with newly diagnosed non-lesional TLE. The primary finding is that patients with TLE, already at the time of diagnosis, and even without any evidence of structural brain abnormalities in 3T MRI, display cognitive deficits, particularly within the domains of memory but also certain executive functions. These findings may indicate that cognitive symptoms are not necessarily precipitated by epilepsy, but may develop independently, or alongside. Furthermore, the question arises whether other brain regions, beyond the temporal lobe, are involved in the cognitive problems seen in TLE. Finally, our results substantiate the need for neuropsychological evaluation and monitoring already during initial meetings with the patient.

4.1. Potential causes of cognitive alterations in newly diagnosed non-lesional TLE

Previous studies have indicated a set of different factors that appear to be associated with cognitive deficits in epilepsy and TLE, these are discussed below. However, most studies are limited by methodological challenges such as heterogeneity of patient cohorts [7,8,30–32], high proportion (46%) of participants with more than one year of disease before enrollment [7], lack of control group [8,30,31] or insufficient matching criteria (low case/control ratio, few matching parameters) [7], or use of nonspecific or short-version neuropsychological test instruments or studying only a single/few cognitive domain(s) [8,31,33].

4.1.1. Early-onset and long duration of epilepsy

The discussion regarding whether chronic epileptic activity is harmful to the brain is still ongoing [34]. In this context, impaired cognition has typically been linked causally to childhood-onset TLE [10], prolonged duration of epilepsy [5,6], and chronic seizure activity [5,11,12]. However, the picture may be more complex than this implies, and there is increasing evidence that epilepsy may be considered as another symptom of a complex underlying pathogenetic process, which also includes cognitive impairment [25]. The hypothesis that cognitive deficits are related to chronic epilepsy was not supported by our findings, with significant reductions in some parameters evident at the time of diagnosis and independent of age at onset. However, no definitive conclusion on this can be made as a substantial proportion of the patients showed subtle symptoms reminiscent of epilepsy prior to diagnosis.

4.1.2. Long-term use of ASM

Use of certain ASMs may result in impairments in attention and cognitive slowing [36,37], especially with polytherapy and/or elevated serum levels of these drugs. On the other hand, the positive effect of ASMs on seizure control may improve cognition and behavior [2,38].

There has been growing evidence that newly diagnosed patients with epilepsy may be cognitively compromised even before the use of ASM [7,22,31,39]. Furthermore, one study identified cognitive improvement in only a few executive tasks upon ASM withdrawal [40]. However, TMT4 and AFLT delayed recall test results, which were significantly affected in our patients, were not improved 7 months after discontinuation of ASM in that study [40]. Although our patients were enrolled directly after the diagnosis was established, some had started taking ASM (Table 1). The majority had started on lamotrigine, which seems to have minor, if any, impacts on cognition [41]. When grouping our patients by medication status, we could not identify medications as a driving force behind our main results. However, as our cohort was small, we cannot completely exclude an impact of ASM on cognition.

4.1.3. Mood disturbances

Mood disorders, such as anxiety and depression, are frequent comorbidities in patients with TLE, adversely influencing cognitive functioning [42–44]. Psychiatric comorbidities may both evolve from epilepsy or precede epilepsy, and this reciprocal relationship between these disorders suggests common pathogenic mechanisms [21,35,44].

In our study cohort, the patients reported more subclinical depressive symptoms and mood disturbance prior to enrollment than healthy control subjects. However, in accordance with previ-
ous studies [22,43], we found no association between self-reported symptoms of depression or negative mood states and cognitive impairment.

4.2. Lateralization of verbal and visual memory functions in TLE

Material-specific verbal memory deficits are associated with TLE in the language-dominant hemisphere, whereas non-verbal/visuospatial memory is suggested to be mainly lateralized in the non-dominant hemisphere [1,45]. As patients in our study performed, on average, lower on the visual memory test, but did not show any evidence of verbal memory dysfunction, the question arises of whether this cohort may consist of more right-lateralized TLE than left. However, due to the lack of ictal EEG recordings and no structural brain abnormalities on MRI, we cannot be certain of the seizure focus location. Nevertheless, based on seizure semiology and interictal EEG findings, there appeared to be as many left-lateralized as right-lateralized TLE foci in our sample. A post hoc comparison of participants grouped according to these lateralization findings showed no difference in visual or verbal memory scores.

4.3. Executive function and working-memory impairments in TLE

TLE is commonly associated with learning and long-term memory dysfunctions and impairment of material-specific episodic memory, language-based cognitive tasks, and visuospatial functions. However, there is growing evidence to suggest that, besides focal temporal lobe deficits, functions supported by the frontal lobes, like executive skills and working memory, are also compromised in TLE [20,46]. Several recent neuropsychological and imaging studies have focused on executive dysfunctions and hypothesized disrupted anatomical and functional neuronal networks integrating temporal and frontal regions [11,13,46,47]. To our knowledge, no previous study has investigated executive function systematically in patients with newly diagnosed TLE. The comprehensive neuropsychological test battery used here did not cover all frontal lobe functions. However, demonstrating that a set of executive functions are affected strengthens the previous assumptions that the disorder is not limited to the temporal lobes, but may involve larger brain networks, even at an early stage.

4.4. Need for early neuropsychological assessment and monitoring

Results from a few neuropsychological studies conducted in untreated patients with newly diagnosed epilepsies (mainly mixed epilepsy cohorts) indicate that cognitive deficits and psychiatric comorbidities occur early in the course of the disease [7,8,22,33,48], suggesting that seizures and cognitive impairment represent different symptoms of a common etiology or network-wide disturbance. As patients appear to underreport their cognitive and psychiatric deficits, these may be missed if not deliberately included in screening [49]. Thus, several recent publications emphasize the need for early neuropsychological evaluation (before the initiation of pharmacological treatment) and monitoring in both children and adults [8,50]. Patients most at risk can then be identified early and referred for more comprehensive cognitive assessment and appropriate interventions in order to prevent, limit, or reverse cognitive complications associated with TLE.

4.5. Limitations

Our study has some limitations. Nonsignificant results in this study may suggest an insufficient power of the test, due to small group size, rather than no real difference between the groups. This is also supported by effect size measures that suggest more pronounced differences between patients and controls than could be verified by testing statistical significance.

Both patient and control groups achieved neuropsychological test results above the population average for all functional areas, except visual learning and memory in patients, indicating a high-functioning participant cohort. This is important to consider when interpreting the results, as cognitive difficulties in patients with newly diagnosed TLE do not necessarily reflect objective failure compared with the normed average. It should also be noted that the actual test situation involves a clear external structure, and the absence of disturbing stimuli makes concentrating on the tasks easier than would be the case in everyday situations. Thus, some patients may have impaired executive functions in daily life, but these would not necessarily be evident in our neuropsychological tests.

A wide range of neuropsychological tests were used in this study, including those most frequently used and currently recommended for investigations in epilepsy [50]. However, due to time constraints, we selected a limited range of executive function tasks. Therefore, conclusions cannot be drawn from our investigations regarding whether other cognitive areas not included in our test battery are affected.

5. Conclusions

The results of our study suggest that patients with TLE may have subtle cognitive deficits already at the time of diagnosis, even in the absence of any structural abnormalities. Although TLE with hippocampal sclerosis has been extensively linked to memory disorders, the picture has been less complete for non-lesional TLE. As our patients represent a subgroup of TLE without known etiology, our results, although interpreted with caution, shed new light on the constellation of symptoms related to cognitive dysfunction. Although mesial temporal lobe structures may appear unaffected by clinical and radiological examination, the epileptic focus may still represent a functional disturbance, causing cognitive alterations. By studying this in patients who have been recently diagnosed, and therefore have a shorter history of recurrent seizures, we may be more certain that cognitive dysfunction is a co-occurring symptom of the underlying pathology of epilepsy, rather than an effect of chronic epileptic activity or associated treatment. Our study contributes to a growing understanding of the complexity of epilepsy that comprises an intricate pathogenesis involving broader cortical networks, showing commonalities with other generalized brain disorders, such as dementia and psychiatric disorders. Our views on epilepsy may need fresh thinking, as the boundaries between disease entities and classical anatomical brain areas are becoming blurred.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding source declaration

This project has been made possible by Dam Foundation, Norway, supported by the Norwegian Epilepsy Foundation (NEF), a branch of the International Bureau for Epilepsy (IBE). The funding source had no involvement in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.
Acknowledgements

We thank patients and control subjects for their participation in this on-going cohort study.

References

[1] Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. Lancet Neurol 2004;3(11):683–72.
[2] Kwok P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001;357(9251):216–22.
[3] Fisher RS, Vickrey BG, Gibson P, Hermann B, Penovich P, Sherer A, et al. The impact of epilepsy from the patient’s perspective I. Descriptions and subjective perceptions. Epilepsy Res 2000;41(1):39–51.
[4] Zhao F, Kang H, You L, Rastogi P, Venkatesh D, Chandra M. Neuropsychological deficits in temporal lobe epilepsy: a comprehensive review. Ann Indian Acad Neurol 2014;17(4):374–82.
[5] Hermann BP, Seidenberg M, Dow C, Jones J, Rutecki P, Bhattacharya A, et al. Cognitive prognosis in chronic temporal lobe epilepsy. Ann Neurol 2006;60(1):80–7.
[6] Eygble TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004;62(10):1736–42.
[7] Pulliainen V, Kuikka P, Jokelainen M. Motor and cognitive functions in newly diagnosed adult seizure patients before antiepileptic medication. Acta Neurol Scand 2000;101(2):73–8.
[8] Witt JA, Helmstaedter C. Should cognition be screened in new-onset epilepsy? A study in 247 untreated patients. J Neurol 2012;259(8):1727–31.
[9] Hermann C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003;54(4):425–32.
[10] Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. Prog Brain Res 2002;135:429–38.
[11] Celiker Ulu S, Yuskel B, Tekin B, Sarıahmetoğlu H, Ataáli D. Cognitive impairment and drug responsiveness in mesial temporal lobe epilepsy. Epilepsy Behav 2019;96:61–8.
[12] Thompson PJ, Duncan JS. Cognitive decline in severe intractable epilepsy. Epilepsia 2005;46(11):1780–7.
[13] Eiverman KH, Resch ZJ, Quassney EE, Sabsevitz DS, Binder JR, Swanson SJ. Temporal lobe epilepsy is associated with distinct cognitive phenotypes. Epilepsy Behav 2019;96:61–8.
[14] Helmstaedter C, Elger CE. Chronic temporal lobe epilepsy: a neurodevelopmental or progressively deteriorating disease? Brain 2009;132(Pt 10):2822–30.
[15] Joket H, Ebner A. Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. J Neurol Neurosurg Psychiatry 1999;67(1):44–50.
[16] Piazzini A, Turner K, Chiari R, Morabito A, Canger R, Canevini MP. Attention and psychomotor speed decline in patients with temporal lobe epilepsy: a longitudinal study. Epilepsy Res 2006;72(2–3):89–96.
[17] Dodrill CB. Neuropsychological effects of seizures. Epilepsy Behav 2004;5(Suppl 1):S21–4.
[18] Seidenberg M, Pulsher DT, Hermann B. Cognitive progression in epilepsy. Neuropsychol Rev 2007;17(4):445–54.
[19] McDonald CR, Taylor J, Hambberger M, Helmstaedter C, Hermann BP, Scheff B. Future directions in the neuropsychology of epilepsy. Epilepsy Behav 2011;22(1):69–76.
[20] Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol 2011;7(3):154–64.
[21] Helmstaedter C, Aldenkamp AP, Baker GA, Mazzari A, Ryvlin P, Sankar R. Disentangling the relationship between epilepsy and its behavioral comorbidities - the need for prospective studies in new-onset epilepsies. Epilepsy Behav 2014;31:43–7.
[22] Taylor J, Kolamunnage-Dona R, Marson AG, Smith PE, Aldenkamp AP, Baker GA. Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment? Epilepsy Res 2010;51(1):48–56.
[23] Chassiere L. Potential causes of cognitive alterations in temporal lobe epilepsy. Behav Brain Res 2020;378:112310.
[24] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhot L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsy 2017;58(4):312–21.
[25] Majdan A, Szilas V, Jones-Gotman M. Performance of healthy subjects and patients with resection from the anterior temporal lobe on matched tests of verbal and visuospatial learning. J Clin Exp Neuropsychol 1996;18(3):416–30.
[26] Sziklas V, Jones-Gotman M. RAVLT and nonverbal analog: French forms and clinical findings. Can J Neurol Sci 2008;35(3):323–30.
[27] Miller LA, Flanagan E, Mothakunnel A, Mohamed A, Thayer Z. Old dogs with new tricks: detecting accelerated long-term forgetting by extending traditional measures. Epilepsy Behav 2015;45:205–11.
[28] Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D–KEFS). 2001.
[29] Schmidt M. Rey auditory verbal learning test: A handbook. Los Angeles, CA: Western Psychological Services; 1996.
[30] Taylor J, Baker GA. Newly diagnosed epilepsy: cognitive outcome at 5 years. Epilepsy Behav 2010;18(4):397–403.
[31] Witt JA, Werhahn KJ, Kramer G, Buckes C, Trinka E, Helmstaedter C. Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment. Acta Neurol Scand 2014;130(3):172–7.
[32] Akiá M, Kalviáinen R, Riekkinen PJ. Verbal learning and memory in newly diagnosed partial epilepsy. Epilepsy Res 1995;22(2):157–64.
[33] Akiá M, Salmenpera T, Partanen K, Kalviáinen R. Verbal memory in newly diagnosed patients and patients with chronic left temporal lobe epilepsy. Epilepsy Behav 2001;2(1):20–7.
[34] Reddy GS, Giusaani G, Sander JW. The natural history and prognosis of epilepsy. Epileptic Disord 2015;17(3):243–53.
[35] Helmstaedter C, Witt JA. Epilepsy and cognition - a bidirectional relationship? Seizure 2017;49:83–8.
[36] Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002;58(8 Suppl 5):S21–6.
[37] Ortmüsi P, Meador KJ. Cognitive side effects of antiepileptic drugs. Epilepsy Behav 2004;5(Suppl 1):S50–6.
[38] Pitkanen A, Sutula TP. Is epilepsy a progressive disorder? Prospects for new therapeutic approaches in temporal-lobe epilepsy. Lancet Neurol 2002;1(3):173–81.
[39] Witt JA, Helmstaedter C. Cognition in the early stages of adult epilepsy. Seizure 2015;26:65–8.
[40] Hessen E, Lossius ML, Reinvang I, Jerstad L. Influence of major antiepileptic drugs on neuropsychological function: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients on monotherapy. J Int Neuropsychol Soc 2007;13(3):393–406.
[41] Meador KJ, Loring DW, Ray PG, Muro AM, King DW, Perrine KR, et al. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. Neurology 2001;56(9):1177–82.
[42] Paradiso S, Hermann BP, Blumer D, Davies K, Robinson RG. Impact of depressed mood on neuropsychological status in temporal lobe epilepsy. J Neurological Neurosurgery Psychiatry 2011;4(1):80–7.
[43] Kanner AM. Epilepsy and mood disorders. Epilepsy 2007;48(Suppl 9):20–2.
[44] Wagner DD, Szilas V, Garver KE, Jones-Gotman M. Material-specific lateralization of working memory in the medial temporal lobe. Neuropsychologia 2009;47(1):112–22.
[45] Stretton J, Thompson PJ. Frontal lobe function in temporal lobe epilepsy. Epilepsy Behav 2012;26(1):1–13.
[46] ALLONE C, LO BUONO V, CORALLO F, PISANI LR, POLLICINO P, BRAMANTI P, et al. Neuroimaging and cognitive functions in temporal lobe epilepsy: a review of the literature. J Neurol Sci 2017;381:15.
[47] Kalviáinen R, Akiá M, Hellkala EL, Mervaala E, Riekkinen PJ. Memory and attention in newly diagnosed epileptic seizure disorder. Seizure 1992;1(4):255–62.
[48] Pollmann-Eden B, Aldenkamp AP, Baker GA, Brandt C, Cendes F, Coras R, et al. The relevance of neuropsychiatric symptoms and cognitive problems in new-onset epilepsy - current knowledge and understanding. Epilepsy Behav 2015;51:199–209.
[49] Helmstaedter C, Witt JA. How neuropsychology can improve the care of individual patients with epilepsy. Looking back and into the future. Seizure 2017;44:113–20.