VILNIUS UNIVERSITY

Arminas
JASIONIS

Relationship of emotions, cognitive and social functions of people with epilepsy and their demographic and clinical characteristics

SUMMARY OF DOCTORAL DISSERTATION

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VILNIAUS UNIVERSITETAS

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Epilepsija sergančių asmenų emocijų, kognityvinių ir socialinių funkcijų ryšys su demografiniais, klinikiniais ir instrumentinių tyrimų duomenimis

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1. INTRODUCTION

1.1. Research problem and relevance

Epilepsy is one of the most common chronic disorders of the central nervous system (CNS): it affects 50 million people worldwide with more than twenty thousand patients in Lithuania. Epilepsy is characterized not only by recurrent seizures, but also by the cognitive, psychological, social, and neurobiological consequences of this condition. The disorder is often accompanied by mood, mental and behavioural disorders. It should be noted that epileptic seizures are often not the most tiresome problem - mood swings, memory problems, difficulties at work and social area, adverse effects of antiepileptic drugs (AED) can affect patients' lives more than epileptic seizures themselves.

Cognitive functions (CF) in epilepsy are associated with the type of epilepsy, stable or progressive brain damage, epileptic seizures, AED adverse effects, and psychological factors. There is a debate on which of these factors are the most influential and could be adjusted before the occurrence of a cognitive deficit.

Disturbance of social communication and activities may also be resulting from CNS damage, epileptic activity, concomitant psychiatric disorders and exposure to AED. On the other hand, the external factors are no less important - support from family and close ones, proper education and social environment, absence of social stigma – all these can be positive factors reducing the risk of developing social problems.

Closely related to these problems, social cognition (SC) is a distinct cognitive domain encompassing all brain processes required for adaptation and participation in social environment. The main subdomains of SC are emotion recognition allowing to recognize and perceive other people's inner states, and theory of mind (TM) enabling

to assign certain mental states (feelings, beliefs, intentions, desires, etc.) to others and therefore understand and predict their behaviour.

Certain deficits of SC have been reported in patients with temporal lobe epilepsy (TLE). Studies have been published that reported worse SC in patients with TLE than in healthy controls. However, the most common sample of such studies is patients with frequent seizures, resistant forms of epilepsy, or patients referred for surgical treatment.

Only a few small-scale studies reported the impairment of SC in other types of epilepsy. Therefore, it is currently unknown whether these changes are restricted to certain patient groups or whether it is a more universal trait of all people with epilepsy (PWE). It is also not clear exactly which patient characteristics are associated with better or worse SC. Moreover, only several authors have attempted to relate these impairments to other scales of social functioning or quality of life, and no single study has approached the relationship between SC and the actual social life of PWE. In other words, today it is not possible to answer whether these are meaningful changes in lives of patients or just revealing findings from cognitive testing. This is also recognized by international experts in the field of cognitive epileptic disorders, who constantly emphasize the lack of scientific data on the impact of SC.

This work contributes to the development of available data on CF in epilepsy and focuses on a new field of epileptology - SC research. The results of the dissertation will provide a better understanding of the thinking and social problems of PWE, their relationship to demographic and disorder-related factors, allowing to discuss appropriate interventions that could adjust or prevent the development of cognitive disorders and social problems.

1.2. Aim and objectives of the study

The aim of this study was to assess the relationship of emotions, cognitive and social functions of people with epilepsy with their demographic and clinical characteristics.

The main objectives of this research were:

1. To compare the cognitive functions of people with epilepsy and control subjects.
2. To compare the cognitive functions of individuals with different types of epilepsy.
3. To determine in what ways the results of cognitive tests in people with epilepsy are related to demographic, clinical and paraclinical characteristics.
4. To assess how social cognitive functions are related to quality of life indicators.
5. To determine how the results of social cognitive tests are related to life achievements (education, employment and family status) of people with epilepsy.

1.3. Novelty and practical significance

Although a portion of scientific data has been collected on cognitive disorders in people with epilepsy, relatively little attention has been paid to the analysis of the factors associated with these disorders. In addition, even when poorer CF-related factors are identified, statistical analysis enabling to assess whether these factors are independently associated with cognitive impairment is rarely performed.

Studies to assess the cognitive function in PWE often include only one group of people with epilepsy (e.g., patients with TLE only, or patients referred for surgical treatment only, etc.), therefore, it remains unclear whether changes observed in one group of patients can be attributed to all PWE. On the other hand, knowledge of cognitive disorders in certain forms of epilepsy (e.g., genetic generalized epilepsy (GGE)) is based on studies in the childhood or adolescent population, so it is unclear whether their results can be automatically attributed to adult GGE and compared to patients with other types of epilepsy.

SC research is a relatively new area of studies. It has been observed that some types of epilepsy (most studies have been performed with resistant temporal lobe epilepsies (1)) are characterized by these dysfunctions. Once again, it is not clear whether these changes can be generalized to all PWE (2).

Several previous studies have found a connection between SC and scalable quality of life indicators (3–5). Wang et al. reported the relationship between SC and social impairment as measured by the social and occupational functioning scale. It should be noted that so far there has been no research in the world on the extent to which these disorders can be significant in life, i.e. how they relate to real life achievements (education, work, family formation, etc.) (6).

The results of this research are important for a better understanding of the factors associated with CF in people with epilepsy. A more accurate identification of these factors in clinical practice will allow

better and faster recognition of risk groups and the organization of intervention measures. As cognitive disorders in epilepsy can be prevented and reversed, better knowledge of specific risk factors for cognitive disorders could allow them to be adjusted, or even prevent them from developing.

Social problems are crucial for people with epilepsy, as they impede the full functioning in society and complete self-realization. One plausible cause of these problems could be SC impairment. The evaluation of these functions will reveal a population of epilepsy vulnerable to these changes, while establishing a link to subjects' life indicators will provide insight into the relevance of the problem and its impact on PWE social activities and quality of life. The identification of the demographic, clinical and paraclinical indicators most relevant to SC disorders will enable the facilitated selection of at-risk populations and the implementation of actions to prevent or at least mitigate their adverse effects.

2. MATERIALS AND METHODS

2.1. Study

A cross-sectional trial was performed in the clinic of Neurology and Neurosurgery of Vilnius university. The patient selection and evaluation process was conducted from December 2019 to August 2020 in the Center of Epileptology (Vilnius University hospital Santaros clinics). The approval of the Vilnius Regional Biomedical Research Ethics Committee (VRBREC) was obtained to conduct this study (No. 2019/12-1173-661).

2.2. Participants

The participation was offered for adult PWE during routine clinical visits in the Center of Epileptology (Vilnius University hospital Santaros clinics). Control subjects were healthy hospital visitors unrelated to the investigator or PWE.

For the purpose of the study, two groups of participant were formed: 1) people with epilepsy (Group E), and 2) healthy controls (Group C). The eligibility criteria for both groups are presented below.

The inclusion criteria for Group E:

1. Focal or generalized epilepsy fulfilling the 2014 International League Against Epilepsy (ILAE) definition of epilepsy (7);
2. At least 6 months duration of epilepsy;
3. Subjects at least 18 but no more than 65 years of age;
4. Stable seizure frequency in the last 3 months;
5. Stable AED treatment regime in the last 3 months;
6. Subject has had a magnetic resonance imaging (MRI) exam within 24 months;
7. Native Lithuanian speaker;
8. Subject is willing and able to participate and complies with all study requirements;

9. Subject has read, understood and signed a VRBREC approved written Informed Consent form.

The exclusion criteria for Group E:

1. Acute symptomatic seizures;
2. Definite or probable psychogenic non-epileptic seizures (irrespective of the presence of epileptic seizures);
3. Status epilepticus within 6 months;
4. Discordant seizure semiology, electroencephalography (EEG) or neuroimaging data, interfering with appropriate categorization of seizure types;
5. History of any neurosurgical intervention;
6. Presence of vagus nerve stimulation or any other device intended to reduce seizure frequency or severity;
7. Resolved epilepsy (according to 2014 ILAE Definition of epilepsy) (7);
8. Progressive neurological disorder;
9. Focal neurological signs (e.g. aphasia) that could compromise subject‘s participation or interpretation of study results;
10. Mental retardation, cognitive impairment or dementia (irrespective of the severity);
11. Need for assistance in daily living, established special needs or residing in social care institution;
12. History of significant psychiatric disorder according to 10^{th} version of International Classification of Diseases (ICD-10) or 5^{th} version of Diagnostic and Statistic Manual (DSM-V) (8);
13. Dependence or harmful use of alcohol or psychoactive substances within 12 months;
14. A history or clinical evidence of significant chronic disorders that could compromise subject‘s participation or interpretation of study results or Chalson Comorbidity Index (CCI) >1 (except for age) (9).

The inclusion criteria for Group C:

1. Subjects at least 18 but no more than 65 years of age;
2. Native Lithuanian speaker;
3. Subject is willing and able to participate and complies with all study requirements;
4. Subject has read, understood and signed a VRBREC approved written Informed Consent form.

The exclusion criteria for Group C:

1. History of epilepsy;
2. History of any other chronic neurological disorder;
3. History of any neurosurgical intervention;
4. History of any episodes of loss of consciousness;
5. Focal neurological signs revealed during the examination;
6. Mental retardation, cognitive impairment or dementia (irrespective of the severity);
7. Need for assistance in daily living, established special needs or residing in social care institution;
8. History of significant psychiatric disorder according to ICD-10 or DSM-V (8);
9. Dependence or harmful use of alcohol or psychoactive substances within 12 months;
10. A history or clinical evidence of significant chronic disorders that could compromise subject‘s participation or interpretation of study results;
11. Concomittant use of any medications;
12. Significant connection with the investigator or patients with epilepsy.

Based on the type of epilepsy, two subgroups were separated in group E: subjects with generalized epilepsy (GE) and focal epilepsy (FE). In this subgroup, a distinction between subjects with mesial temporal lobe epilepsy (TE) and neocortical epilepsies (NE) was made (Figure 1).

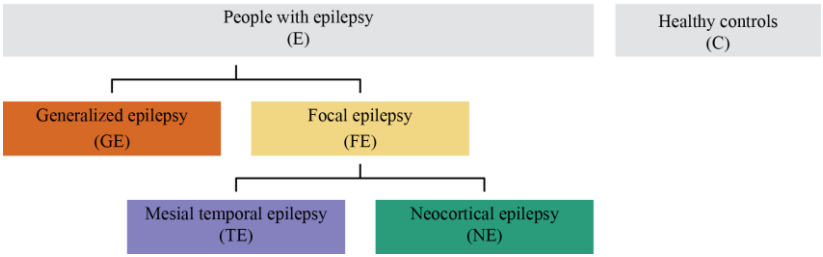

Figure 1. Study groups

At the beginning of the selection visit of each subject, the required demographic and clinical information was collected through structured interview, and the results of paraclinical studies were accessed (Table 1).

Table 1. Variables collected about study participants

Demographics	**Clinical data**	**Paraclinical and pharmacological data**
Gender	Comorbidities	**MRI data:**
Age	Related medications	Abnormalities
Place of residence	Addictions	Relation to seizures
Duration of education	**Epilepsy:**	**EEG data:**
Level of education *(ISCED-11)*	Duration of epilepsy	Epileptiform activity (lateralization, localization)
Work status	Age at seizure onset	Pathological slowing (lateralization, localization)
Occupation *(ISCO-08)*	**Seizures:**	**Pharmacological data:**
Driving status	Seizure types	Types of AED
Family status	Seizure frequency	Number of AED
Number of children	Seizure severity	AED load

Abbreviations: AED – antiepileptic drugs, EEG – electroencephalography, ISCED-11 – The International Standardized Classification of Education, ISCO-08 – The International Standard Classification of Occupations, MRI – magnetic resonance imaging.

Collected demographic variables included gender, age, education (total duration of education and level of education attained), place of residence, occupation (employment, workload and position), driving status. The level of acquired education was assessed in compliance with the International Standard Classification of Education ISCED-11 (10). The positions held were classified according to 2008 International Standard Classification of Occupations ISCO-08 (11). Finally, the subjects were asked to indicate their family status and the number of children.

General medical data was collected including comorbidities, related medications and addictions. Information on epilepsy (age at seizure onset, duration of epilepsy, medications and their doses) was analyzed. Occuring seizures were specified and categorized according to ILAE classification of epilepsies (12). The frequency of each seizure type was converted to a rank scale of seizure frequency (seizures occuring: 1 - less than once a year; 2 - more than once a year; 3 - more than once a month; 4 - more than once a week; 5 - daily or several times a day). The severity of each type of seizure was assessed using the National Hospital Seizure Severity Scale (NHS-3) (13).

The results of instrumental studies were obtained from medical documents. In EEG records, the presence of pathological slowing (PS) and epileptiform activity (EA), its lateralization, and localization were noted. MRI protocols were analysed for presence, type, lateralization, and localization of pathological foci. The concordance of MRI lesions with epileptic seizures was also assessed.

The subjects were interviewed about AED used, the information was clarified in the medical documents. For the purposes of the study, the number of AED used, preparations and their doses, and the calculated AED load were recorded. AED load is the sum of ratios of each medication's patient's daily dose (PDD) of each medication to the defined daily dose (DDD) set by the World Health Organization (WHO), i. e.

$\sum_{i=1}^{n} x = x_1 + x_2 + \cdots + x_n$,

where $x = \frac{PDD}{DDD}$, and 1, 2,..., n – 1st, 2nd, ..., nth AED.

2.3. Methods

During the selection visit, the subjects were informed about the necessary preparation for the testing. Those who agreed to participate were asked to sleep for at least 7 hours the night before testing, not to use sedative substances that are not normally used AED, overeat or drink more caffeinated beverages than usual (14). The subjects underwent cognitive testing according to the prepared cognitive test battery (Table 2), as well as completed scales assessing their anxiety, depression, quality of life, and adverse medication effects (Table 3). Cognitive testing was performed in the first half of the day in a separate quiet room. The subjects could not have experienced a tonic-clonic seizure (TCS) for at least 3 days prior to the testing visit or focal seizure with loss of awareness for at least 1 day, otherwise the date of the visit was postponed. The average duration of the testing was three to four hours.

Table 2. Tests included in the cognitive test battery

Cognitive domain	**Instruments**	**Score range**
Attention	Trail making test A (TMT-A)	0 - 300
	Trail making test B (TMT-B)	0 - 300
	Digit span forward (DSF)	2 - ∞
Working memory	Digit span backward (DSB)	2 - ∞
Verbal fluency	Phonemic verbal fluency (PVF)	0 - ∞
	Categorical verbal fluency (CVF)	0 - ∞
Verbal memory	Short story recall (SSR):	
	- immediate recall (SSR-I)	0 - 24
	- delayed recall (SSR-D)	0 - 24

Cognitive domain	Instruments	Score range
Non-verbal memory	Rey-Osterrieth complex figure test (ROCFT):	
	- immediate recall (ROCFT-I)	0 - 36
	- delayed recall (ROCFT-D)	0 - 36
	Cambridge Face Memory Test (CFMT)	0 - 18
Executive functions	Iowa Gambling Task (IGT)	0 - 100%
Social sognition	Reading the mind in the eyes test (RMET)	0 - 36
	Happé strange stories test (HST)	0 - 16
	Faux pas recognition test (FPRT)	
	- Correct *faux pas* stories	0 - 6
	- Correct control stories	0 - 3
	- Total score	0 - 36
	- Subscores:	
	(1-2) *Faux pas* detection	0 - 12
	(3) Understanding inappropriateness	0 - 6
	(4) Intentions	0 - 6
	(5) Beliefs	0 - 6
	(6) Empathy	0 - 6

Table 3. Other scales and questionnaires used in the study

Field of assessment	Instrument	Score range
Anxiety	GAD-7	0 - 21
Depression	NDDI-E	6 - 24
AED tolerability	LAEP	25 - 100
Quality of life	QOLIE-31P	0 - 100

Abbreviations: AED – antiepileptic drugs, GAD-7 – 7 item Generalized anxiety disorder scale, LAEP – Liverpool Adverse Events Profile, NDDI-E – Neurological Disorders Depression Inventory for Epilepsy, QOLIE-31P – Quality of Life in Epilepsy inventory.

Below is a brief description of the tests and scales used in the study.

Trail making test (15). In the first part (TMT-A), subjects are presented with a sheet of paper with circles numbered from 1 to 25. After explaining the task and a short training test, the subjects are

asked to connect the circles in sequence as soon as possible (1 ... 2 ... 3 ..., etc.). In the second part (TMT-B), the subjects are given sheets with printed circles with 25 numbers and letters to be joined in alternating ascending and alphabetical order (1 ... A ... 2 ... B ..., etc.).

Digit span test (16) consists of two parts: digit span forward (DSF)) and digit span backward (DSB) tests. In the first part, a sequence of digits which, after hearing, must be repeated by a subject in the same order as they heard it. In the second part, they are asked to repeat it in the opposite order to what was read by an investigator. When repeated correctly, an ever-increasing sequence of digits is given. If the sequence is repeated incorrectly twice, the test is terminated. The result of each task is the number of elements in the longest correctly repeated sequence.

Phonemic verbal fluency (PVF). During the test, subjects should list as many common nouns as possible from a single letter in 1 minute. Before testing, the subjects are introduced to the performance process, and their answers are marked on a piece of paper by a researcher. The test result is the number of common nouns given in 1 minute (17).

Categorical verbal fluency (CVF). In categorical (semantic) verbal fluency tasks, subjects are asked to list as many different words within a category as possible per unit of time. In this study, the subjects are asked to list as many different animals as possible in 1 minute. The test result is the number of animals listed in 1 minute (17).

Short Story Recall (SSR). The subjects are read Anna Thompson's story from Wechsler Memory Scale – third edition (WMS-III) (18), which consists of 24 semantic elements. The test result is the number of items correctly indicated during immediate recall (SSR-I), and after 30 minutes (delayed recall, SSR-D). The difference between the elements recalled during delayed and immediate retelling (ΔSSR = SSR-D - SSR-I) reflects the forgetting of verbal information.

Rey-Osterrieth complex figure test (ROCFT) (19). Subjects are presented with a printed complex geometric figure consisting of

18 different geometric elements and asked to memorize it. They are asked to draw a figure from memory immediately (immediate recall (ROCFT-I)) and 30 minutes after memorizing (delayed recall (ROCFT-D)). The difference between delayed and immediate recall (ΔROCFT = ROCFT-D - ROCFT-I) reflects the forgetting of nonverbal information.

Iowa gambling task (IGT) (20). Subjects are presented with four decks of cards (A-D) on a computer screen, and during each move, the subjects must select one of the decks. At the beginning of the game, the subjects have 2,000 virtual dollars, while by opening cards from different decks, they may lose or win a certain amount of money - in order to do so, they have to understand which decks of cards are 'successful' in the long run.

Cambridge face memory test (CFMT) (21) is intended to assess facial recognition. During the test, a subject is presented with a computerized human left, right, and frontal face images, and is asked to memorize the face. Immediately afterwards, three different faces are presented, and the subject must indicate which one they have just memorized. The primary purpose of this test was screening of prosopagnosia since it can be easily overlooked in stardard neurological examination.

Reading the mind in the eyes test (RMET) (22). The test consists of 36 black-and-white photographs of different peoples' upper parts of the face (including a forehead, eyebrows, eyes, and nose). From the subtle facial expression, subjects must predict and choose one of the four descriptions of the mental state of a depicted person.

Happé strange stories test (HST) (23). During this study, the Lithuanian adapted and validated version of HST test was used, which presents 8 stories. After reading each story, a question is asked about the motives of actions of characters. The subject is expected to notice and name an implied lie, double bluff, deception, persuasion, 'white' lie, or false belief of the characters.

Faux pas recognition test (FPRT) is intended to evaluate *faux pas* cognition function (24). The Lithuanian adapted and validated version of FPRT test consisting of nine stories (6 *faux pas* and 3 control stories) was used in this study. After reading each story, a subject is asked if, in their opinion, someone said something inappropriate (conducted *faux pas*). If answered positive, additional questions are asked. The first two questions assess whether the subject recognized *faux pas*. The third question tests the understanding of inappropriateness (why it is inappropriate), the fourth - understanding of a character's intentions (why the character said it), the fifth - understanding of the character's beliefs (what facts are known to the character), the sixth - empathy (how the character might feel).

Neurological Disorder Depression Inventory (NDDI-E). This is a questionnaire that assesses the depressiveness of subjects. Six statements describing the inner state of the last 2 weeks are presented (25).

General Anxiety Disorder 7 (GAD-7). This is a seven-elemet scale to assess the severity of anxiety experienced by subjects in the last 2 weeks (26).

Liverpool Adverse Event Profile (LAEP). The questionnaire is intended to evaluate subjective tolerability of AED – it consists of 23 items of listed adverse drug effects and 2 blank items left for individually concerning symptoms. Subjects are to indicate the presence and severity of each symptom in the last 4 weeks. The higher results reflect poorer AED tolerance (27).

Quality of Life in Epilepsy (QOLIE-31P) version 2.0. The scale consists of 31 items and assesses various health-related areas of quality of life in epilepsy: seizure worry, emotional well-being, energy/fatigue, cognitive functioning, medication effects, social functions and overall quality of life. The assessment is based on the well-being of the last four weeks (28).

2.4. Statistical data analysis

Microsoft Excel 2017 was used for data entry, IBM SPSS 26.0 - for statistical analysis. Jamovi 2.0.0 and R 4.1.0 software were used for graphical data presentation. Illustrations were drawn with Adobe InDesign CC 2018.

Data distribution was assessed by calculating a histogram asymmetry coefficient (skewness) and excess coefficient (kurtosis) and by graphically evaluating Q-Q curves. Correspondence of the normal Gaussian distribution was assessed by calculating the Shapiro-Wilk coefficient.

The arithmetic mean and standard deviation (M ± SD) served as descriptors of normally distributed quantitative data while for non-normally distributed data center and scatter parameters were median and interquartile range (Md ± IQR). For data that are usually expressed as mean (e.g., age) the tables present both center and scatter characteristics for clarity. Qualitative variables are given as absolute numbers and percentages (N (%)).

Student's t test was used to compare means of the continuous variables between the two groups, and analysis of variance (ANOVA) or Welch's correction (Levene's criterion was used to assess the equality of variances) - among more than two groups. Tukey or Bonferroni's *post hoc* analysis methods were employed to clarify the differences between the groups. The Mann-Whitney U test was applied to compare the differences between continuous, non-normally distributed or ordinal variables between the two groups, and Kruskal-Wallis H test - among more than two groups. Fisher's least significant difference (Fisher LSD) methodology was used for adjusting differences in groups. The association between categorical variables was assessed using Fisher's exact test and Spearman's chi-square (χ^2) test. The Pearson r correlation coefficient served as a measure of correlation of two continuous normally distributed variables distributed, while the correlation of the non-normally distributed or

ordinal variables was judged according to the Spearman's rho (r_S) coefficient.

Regression analysis was employed to determine variables that independently estimate the values of the quantitative variable. The modeling of the multiple linear regression equation included relevant significantly related variables. Qualitative variables were also included after conversion to binary dummy variables. The variables were included in a stepwise manner. In case of apparent multicollinearity, variables with a higher correlation coefficient were chosen. Durbin-Watson statistics served as a measure of autocorrelation, while collinearity diagnostics and calculation of variance inflation factors (VIF) were used to detect multicollinearity. When calculating non-parametric dependent variables, the distribution of random errors was evaluated at the end. When describing properties of the regression equation, the coefficients of determination R^2 or, where necessary, the adjusted R^2, ANOVA *F* values and p values of statistical significance are presented. Standardized β coefficients and p values of significance are given when describing properties of independent variables.

To identify which independent variables determine the dependent nominal variable, a binary logistic regression analysis was performed, and which independent variables determine the rank variable, a rank-ordered logistic regression was analysed.

In assessing the hypotheses, differences were seen as statistically significant throughout if the probability of type I error (α) was less than 0.05.

3. RESULTS

3.1. Demographic characteristics

One hundred eleven participants were included, 69 (62.16 %) were female. Mean age of the subjects was 31.68±10.86 years.

Eighty one subject had epilepsy and constituted study group E while 30 subject were healthy controls (study group C). These two groups were comparable by means of age (U = 1076; p = 0.36), duration of education (t = -1.14; p = 0.26), level of education (U = 1034; p =0.44), distribution by gender (χ^2 = 0.02; p = 0.88) or residence (χ^2 = 0.36; p = 0.83) (Table 4). Twenty-seven (33.33 %) participants in the epilepsy group had generalized epilepsy while 54 (66.67 %) were diagnosed focal epilepsy (25 (30.86 %) - mesial temporal epilepsy (TE group) and 29 (35.8 %) - neocortical epilepsies (NE group).

Table 4. Demographic characteristics of study participants

	Group E (N = 81)	**Group C** (N = 30)	p
Age (y) [1]	30±14	27.5±19	0.36
Gender			
Female	50 (61.7 %)	19 (63.33 %)	0.88
Male	31 (38.3 %)	11 (36.67 %)	
Education			
Duration of education (y) [2]	13.73±2.9	14.4±2.29	0.26
ISCED-11 [1]	4±3	4±3	0.44
Residence			
Town	48 (59.3 %)	16 (53.33 %)	0.83
Small town	20 (24.7 %)	9 (30 %)	
Village	13 (16 %)	5 (16.67 %)	

Explanations: qualitative data presented as number (percentage), [1] – median ± interquartile range, [2] – mean ± standard deviation. Abbreviations: ISCED-11 – International Standard Classification of Education, y – years.

3.2. Clinical and paraclinical characteristics

Duration of epilepsy. Mean age at seizure onset was 16.6±10.58 years, while duration of epilepsy was 15.15±9.57 years (range 0.5 to 40). No significant differences among epilepsy groups were detected ([onset age] F = 1.84; p = 0.17; [duration of epilepsy] F= 2.82; p = 0.07).

Seizure types. Tonic-clonic seizures (TCS) were most common in GE group (92.6 %), however**,** 48.15 % were experiencing myoclonia and 37.04 % had absences. Most common seizure type in group TE were focal seizures with loss of awareness (80 %), focal seizures without loss of awareness (52 %) and bilateral TCS (64 %). Subjects in group NE were experiencing focal seizures without loss of awareness (65.52 %), focal seizures with loss of awareness (51.72 %) and bilateral TCS (69 %).

Seizure frequency ranged from less than yearly seizures (rank 1) to daily seizures (rank 5). Median seizure frequency was 3±2 (monthly seizures). Total seizure frequency was different among epilepsy groups (H = 7.57; p = 0.02): subjects in groups TE and NE had more frequent seizures than individuals in group GE (p = 0.007 and p = 0.02 respectively). The frequency of TCS and other seizures did not differ among the groups ([TCS] H = 0.05; p = 0.97; [non-TCS] H = 2.47; p = 0.29).

Seizure severity ranged from 1 to 26 points of NHS-3 scale. Mean severity of seizures was 12.63±5.24 points and significant differences among epilepsy groups were detected (F = 3.15; p = 0.04) - GE subjects had more severe seizures than TE (p = 0.04). While the severity of TCS was comparable among the groups (F = 0.48; p = 0.62), the severity of other seizures differed (H = 17.93; p < 0.001): individuals in groups NE and TE experienced more severe seizures than those in group GE (p < 0.001 and p = 0.006 respectively).

Etiology of epilepsy. Different etiology was noted among the groups (χ^2 = 73.38; p < 0.001): all epilepsies in group GE were presumed to have genetic origin, while structural pathology was

leading etiology in group TE (48 %), and unknown cause was most common in group NE (69 %). The most common syndromes in group GE were juvenile myoclonic epilepsy (11 (44 %)), juvenile absence epilepsy (4 (16 %)) and epilepsy with generalized tonic-clonic seizures alone (9 (36 %)). Among subjects with focal epilepsies (N = 54) leading causes were hippocampal sclerosis (N = 7), focal cortical dysplasia (N = 3), vascular malformations (N = 3) and epilepsy-related tumours (N = 3).

MRI abnormalities were detected for 31 (38.3 %) PWE, 22 of them (27.16 % of all participants) were presumed to be seizure-related.

EEG. PS was detected in 15 (18.5%), while EA was present in 79 (97.5 %) EEG records. None of the subjects in GE group had PS, however it was present in the records of 9 (36 %) group TE and 6 (20.7 %) group NE subjects. This difference among the groups was significant ($\chi^2 = 11.29$; $p = 0.004$). EA was present in all records of patients in groups TE and NE, and 25 (92.6 %) individuals in group GE ($\chi^2 = 4.1$; $p = 0.13$).

Pharmacological properties. Seventy-seven (95 %) PWE were treated with at least one AED. Monotherapy was prescribed for 32 (39.5 %) PWE while multiple AED were taken by 45 (55.6 %) individuals. Median number of used AED was 2±2 and AED load was 1.33±1.8. The proportion of PWE treated with monotherapy and polytherapy was comparable ($\chi^2 = 4.75$; $p = 0.09$), yet significant difference of the number of AED and AED load were noted among the groups ([number of AED] $H = 8.26$; $p = 0.02$; [AED load] $H = 13.62$; $p = 0.001$). Participants in the group GE used less medication than those in other groups ([number of AED] GE < TE, $p = 0.006$; GE < NE, $p = 0.02$; [AED load] GE < TE, $p = 0.002$; GE < NE, $p = 0.002$). Most commonly prescribed AED were levetiracetam (44 (54.3 %)), lamotrigine (37 (45.7 %), valproate (25 (30.9 %) and topiramate (16 (19.8 %). The tolerability of AED was comparable among the groups ($F = 1.27$; $p = 0.29$).

3.3. Evaluation of emotional state

Depressive symptoms as measured by NDDI-E score were more pronounced in PWE than healthy controls . GAD-7 score was also higher in PWE suggesting higher level of measured anxiety among participants with epilepsy (Table 5).

Table 5. Results of screening scales for anxiety and depression

Scale	**Group E** (N = 81)	**Group C** (N = 30)	Statistics, p value
GAD-7	6±8	2±4	$U = 529$; $p < 0.001$
NDDI-E	11±6	7.5±3	$U = 525{,}5$; $p < 0.001$

Explanations: quantitative data presented median ± interquartile range. Abbreviations: GAD-7 – Generalized Anxiety Disorder 7-item scale, NDDI-E – Neurological Disorders Depression Inventory for Epilepsy.

The single variable independently associated with GAD-7 score was duration of education ($R^2 = 0.06$; $\beta = -0.25$; $p = 0.03$) while NDDI-E score was best estimated ($R^2 = 0.22$; $p < 0.001$) by town residence ($\beta = -0{,}34$) and number of prescribed AED ($\beta = 0.31$).

3.4. Evaluation of cognitive functions

3.4.1. Attention, working memory and executive functions

The results of attention, working memory and executive functions were significantly worse in PWE than their healthy counterparts (Table 6).

Table 6. Results of attention, working memory and executive functions tasks

Test	**Group E** (N = 81)	**Group C** (N = 30)	Statistics, p value
TMT-A	35±21	23±17	$U = 520$; $p < 0.001$
TMT-B	90±58	69±41	$U = 652$; $p < 0.001$
DSF	6±1	7.5±2	$U = 347.5$; $p < 0.001$
DSB	4±1	6±2	$U = 392.5$; $p < 0.001$
IGT	48±15	54.5±19	$U = 701.5$; $p = 0.05$

Explanations: quantitative data presented as median ± interquartile range. Abbreviations: DSB – Digit span backward, DSF – Digit span forward, IGT – Iowa Gambling Task, TMT-A – Trail making test A, TMT-B – Trail making test B.

Independent variables associated with TMT-A score were ($R^2 = 0.26$; $p < 0.001$) duration of education ($\beta = -0.35$) and duration of epilepsy ($\beta = 0.34$), while TMT-B score ($R^2 = 0.52$; $p < 0.001$) was estimated by the use of benzodiazepines ($\beta = 0.45$), duration of education ($\beta = -0.32$) and seizure frequency ($\beta = 0.23$). Measures of working memory were best estimated by the duration of education and number of prescribed AED: DSF ($R^2 = 0.4$; $p < 0.001$) – [duration of education] $\beta = 0.41$, [number of AED] $\beta = -0.37$); DSB ($R^2 = 0.27$; $p < 0.001$) – [duration of education] $\beta = 0.39$, [number of AED] $\beta = -0.25$).

3.4.2. Verbal fluency

PWE performed both fluency tasks poorer when compared to healthy controls (Table 7).

Table 7. Results of verbal fluency tasks

Test	**Group E** (N = 81)	**Group C** (N = 30)	Statistics, p value
PVF	10.48±4.4	15.83±3.86	$t = -5.87$; $p < 0.001$
CVF	17.86±6.3	22.53±6.02	$t = -3.5$; $p = 0.001$

Explanations: quantitative data presented as mean ± standard deviation. Abbreviations: CVF – categorical verbal fluency, PVF – phonemic verbal fluency.

Duration of education (β = 0.39), the use of topiramate (β = -0.23) and female gender (β = 0.25) emerged as variables independently associated with PVF score (R^2 = 0.27; p < 0.001) while the only independent variable estimating CVF score was the duration of education (R^2 = 0.19; p < 0.001; β = 0.45).

3.4.3. Verbal memory

PWE recalled less elements from the presented Short story immediately and after 30 minutes when compared to healthy controls. The number of forgotten elements was also higher in the former group (Table 8).

Table 8. Results of verbal memory tasks

Test	**Group E** (N=81)	**Group C** (N=30)	Statistics, p value
SSR_I [1]	14.8±4.17	18.93±2.61	t = -6.21; p < 0.001
SSR_D [1]	12.12±5.26	18.13±2.47	t = -8.14; p < 0.001
ΔSSR [2]	-2±3	-1±2	*U* = 517.5; p < 0.001

Explanations: [1] – quantitative data presented as mean ± standard deviation, [2] – data presented as median ± interquartile range. Abbreviations: SSR_I – immediate Short story recall (0 min), SSR_D – delayed Short story recall (30 min), ΔSSR – the difference between delayed and immediate Short story recall.

Variables independently associated with immediate SSR recall (R^2 = 0.29; p < 0.001) were duration of education (β = 0.4; p = 0.001) and the frequency of non-TCS seizures (β = -0.33; p = 0.004), while delayed recall was best predicted (R^2 = 0.26; p < 0.001) by ISCED-11 level (β = 0.38) and measured NDDI-E score (β = -0.27). The difference between delayed and immediate short story recall was associated to (R^2 = 0.21; p < 0.001) NDDI-E score (β = -0.4) and presence of epilepsy-related MRI abnormalities (β = -0.22). The relationship between verbal memory measures, education and the level of depression is presented in Figure 2.

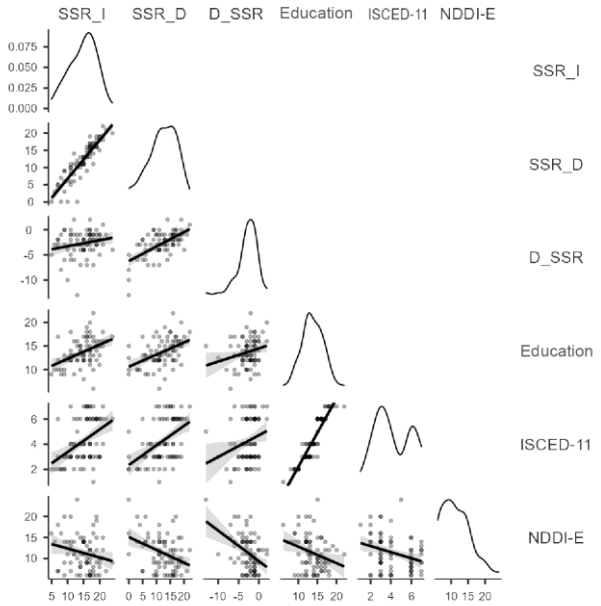

Figure 2. Relationship between Short story recall score, education and the level of depression

3.4.4. Nonverbal memory

The results of ROCFT task were significantly different as PWE performed worse than healthy controls (the results are presented in Table 9).

Table 9. Results of nonverbal memory tasks

Test	**Group E** (N = 81)	**Group C** (N = 30)	Statistics, p value
ROCFT_I [1]	23.85±6.85	31.33±2.73	t = -8.18; p < 0.001
ROCFT_D [1]	22.66±7.48	30.83±2.66	t = -8.45; p < 0.001
ΔROCFT [2]	-1±2	-0.5±1	*U* = 831.5; p = 0.01

Explanations: [1] – quantitative data presented as mean ± standard deviation, [2] – data presented as median ± interquartile range. Abbreviations: ROCFT_I – immediate recall of Rey-Osterrieth complex figure test (0 min), ROCFT_D – delayed recall of Rey-Osterrieth complex figure test (30 min), ΔROCFT – the difference between delayed and immediate recall of Rey-Osterrieth complex figure test.

Variables independently associated with immediate recall of ROCFT ($R^2 = 0.23$; $p < 0.001$) were duration of education ($\beta = 0.38$) and seizure frequency ($\beta = -0.27$). The same set of variables was the most important when estimating the score of delayed ROCFT recall ($R^2 = 0.25$; $p < 0.001$; [duration of education] $\beta=0.36$; [seizure frequency] $\beta = -0.33$). Seizure frequency was also a single variable independently associated with the difference between delay and immediate nonverbal recall ($R^2 = 0.07$; $p = 0.02$; $\beta = -0.27$). The relationship between measures of nonverbal memory, education and seizure frequency is depicted in Figure 3.

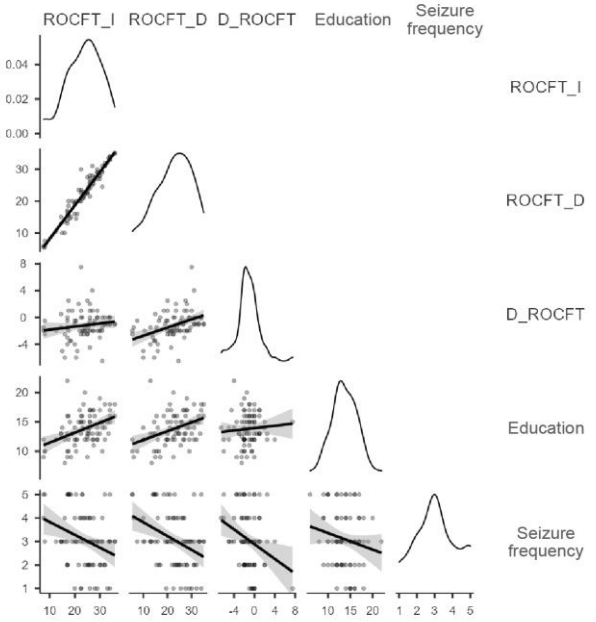

Figure 3. Relationship between Rey-Osterrieth complex figure test score, education and seizure frequency

3.5. Social cognition

3.5.1. Results of social cognitive tests

PWE scored less in RMET, HST and total FPRT than healthy controls (Table 10).

Table 10. Results of social cognitive tests.

Test	**Group E** (N = 81)	**Group C** (N = 30)	Statistics, p value
RMET	25±7	29±5	$U = 580$; $p < 0.001$
HST	12±6	14±3	$U = 614$; $p < 0.001$
FPRT total score	22±9	27±11	$U = 865.5$; $p = 0.02$
Correct *faux pas* stories	5±2	5±1	$U = 1104.5$; $p = 0.45$
Correct control stories	3±1	3±0	$U = 844.5$; $p = 0.004$
Faux pas detection	10±4	10±3	$U = 1157$; $p = 0.69$
Understanding inappropriateness	4±3	5±2	$U = 918.5$; $p = 0.05$
Intentions	2±2	4±2	$U = 489$ $p < 0.001$
Beliefs	3±2	4±2	$U = 905$; $p = 0.04$
Empathy	4±2	5±2	$U = 916.5$; $p = 0.04$

Explanations: quantitative data presented as median ± interquartile range. Abbreviations: FPRT – *Faux pas* recognition test, HST – Happé strange stories test, RMET – Reading the mind in the eyes test.

RMET score in PWE group was independently associated with the duration of education ($R^2 = 0.23$; $p < 0.001$; $\beta = 0.49$), while the ISCED-11 level of education ($\beta = 0.37$), number of AED ($\beta = -0.27$) and duration of epilepsy ($\beta = -0.21$) were associated with the HST score ($R^2 = 0.35$; $p < 0.001$). The results of social cognitive tests among subjects with different types of epilepsy are presented in Figure 4. Total FPRT did not depend of subject's gender, type or etiology of epilepsy, AED treatment, EEG or neuroimaging abnormalities. ([all] $p > 0.05$). NDDI-E score was a single independent variable associated with the total FPRT score ($R^2 = 0.06$; $\beta = -0.25$; $p = 0.03$). However,

higher determination coefficients were obtained in TE group: total FPRT score was estimated by female gender (R^2 = 0.23; β = 0.48; p = 0.015), understanding inappropriateness was predicted (R^2 = 0.43; p = 0.001) by the use of lamotrigine (β = -0.54) and duration of epilepsy (β = -0.39) while intention subscore was independently associated (R^2 = 0.53; p < 0.001) with female gender (β = 0.56) and duration of education (β = 0.49). Female gender (β = 0.42) and duration of epilepsy (β = -0.42) were predicting empathy subscore in TE group (R^2 = 0.34; p = 0.004).

3.5.2. Social cognition and quality of life

Among PWE measures of social cognition were significantly associated with quality of life variables. RMET score was significantly correlated with overall quality (r_s = 0.27; p = 0.02) and emotional well-being (r_s = 0.29; p =0.01) subscores as well as the total QOLIE-31 score (r_s = 0.31; p = 0.005). HST score correlated with the total QOLIE-31 score (r_s = 0.23; p = 0.04) only. FPRT total score was significantly associated with overall quality (r_s = 0.24; p = 0.04) and medication effects subcores (r_s = 0.29; p = 0.01) as well as total QOLIE-31 score (r_s = 0.23; p = 0.04). Inclusion of SC scores did not result in a better model fitness in quality of life regression models.

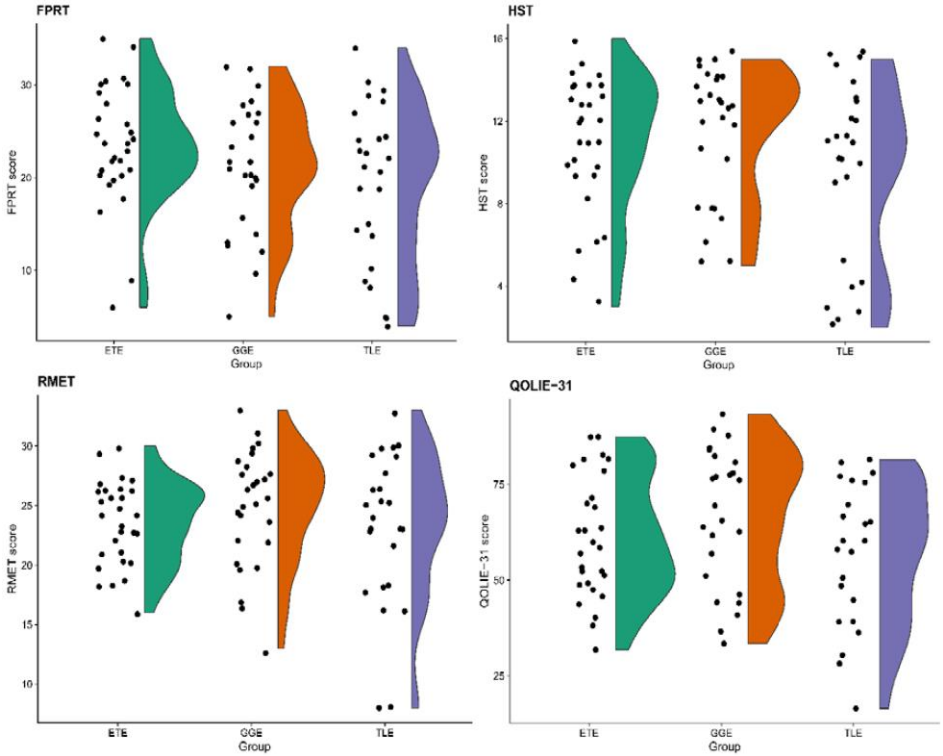

Figure 4. The results of social cognitive tasks and QOLIE-31 among the groups of PWE

3.5.3. Social cognition and life achievements

Among PWE duration of education significantly correlated with RMET and HST scores ($r_s = 0.51$; $p < 0.001$ and $r_s = 0.45$; $p < 0.001$). These tests were also significant in ordinal logistic regression model ($\chi^2 = 34.7$, $p < 0.001$) predicting the level of subject's attained ISCED-11 education level ([RMET] OR = 1.22 (95% CI = 1.09–1.36), [HST] OR = 1.2 (95% CI = 1.02–1.4)). All social cognitive tasks were associated with the achievement of tertiary education (ISCED 5 to 9) level ([RMET] OR = 1.24 (95 % CI = 1.05–1.48), [HST] OR = 1.46 (95 % CI = 1.12–1.89), [total FPRT] OR = 0.91 (95 % CI = 0.83–1.00) in a binary logistic regression model ($\chi^2 = 29.39$, $p < 0.001$).

Employed PWE performed better in RMET and HST tests when compared to unemployed participants ([RMET] $U = 416$; $p < 0.001$; [HST] $U = 363.5$; $p < 0.001$), however, the total FPRT score did not differ between these subsets of subjects ($U = 609.5$; $p = 0.11$).

No significant differences were detected when comparing SC scores between single subjects and those in a relationship. Both groups were comparable by means of RMET ($t = -1.25$; $p = 0.21$), HST ($U = 858.5$; $p = 0.51$) and FPRT ($t = -1.1$; $p = 0.27$) performance. None of the results accounted for a better model fitness in a binary logistic regression model ($\chi^2 = 4.17$; $p = 0.76$; [RMET] OR = 1.01 (95 % CI = 0.9–1.14), [HST] OR = 0.96 (95 % CI = 0.81–1.14), [FPRT] OR = 1.03 (95 % CI = 0.96–1.11)).

4. DISCUSSION

4.1. The emotional state of the subjects

The depressiveness of the subjects was independently related to the number of AED used - as a result, those who used more medications were more depressed. According to B. Schmitz, this is related to the pharmacological effects of AED, however personal factors and genetic predisposition are also important (29). It is specified that polytherapy is associated with greater stigma (30) and poorer health-related quality of life (31), so it cannot be ruled out that higher level of depressive symptoms may also be associated with poorer assessment of one's health. Like Li et al., we observed greater depressiveness of PWE living in the countryside. Li explains this finding by socio-economic factors and poorer access to personal health care services in rural areas, however, in Lithuania it may also be due to lower working capacity - our subjects living in rural areas and small towns were less likely to be employed (32). Our study found that higher anxiety in PWE was most likely due to epilepsy-unrelated factors – the anxiety rate was independently associated only with the duration of education and this accounted for only 6% of the variation.

4.2. Key variables related to cognitive functions

Demographic variables. Duration and / or level of education were related to the results of most studied CF (attention, working memory, verbal fluency, verbal and nonverbal memory). There is a bi-directional link between education and intelligence: people with higher IQ are able to study longer and gain a higher level of education, and likewise, longer education leads to higher intelligence (33). Moreover, the knowledge and skills acquired through education form a 'cognitive reserve'. Individuals with a bigger reserve may be able to withstand prolonged and more intense exposure to adverse epilepsy-

related factors until cognitive disorders occur or are detected by testing (34). This finding was replicated in PWE by various researchers, moreover, Huang et al. demonstrated that not only cognitive disorders are related to the lowest educational level, but these individuals are also most vulnerable to negative AED effects (35).

Emotional state variables. The results of this study suggest that the emotional state of patients is likely to be important not only for quality of life but also for normal cognitive functioning - the level of depression was independently related to verbal memory. Not surprisingly, concomittant psychiatric disorders might accentuate every cognitive deficit, however the memory disturbance is more related to the number of previous depressive episodes not the current emotional state, implying that depression as "a trait" might be more important (36). Returning to PWE, the results of large systematic review suggest that memory and executive disturbances are most pronounced in depressive PWE and both, immediate and delayed recall can be affected (37).

Epilepsy-related variables. The only independent static variable was epilepsy-related MRI lesions, which was associated with poorer verbal memory (delayed recall of a short story). It can be assumed that epilepsy *per se* does not lead to better or worse CF - it is far more importantly how it is controlled, as factors such as the duration of epilepsy, seizure frequency and medications were more important in predicting CF results. The duration of epilepsy was associated with poorer attention, while frequent seizures related to poorer results of attention and memory tasks. The duration of epilepsy and seizure frequency can be seen as a surrogate of the epileptic process in the brain: the duration of the disease indicates its duration, while seizure frequency reflects its intensity. Epileptic activity is known to interfere with the normal functioning of neural networks and, in critical periods, may interfere with their normal development (38). The networks responsible for CF could also be adversely affected by seizure-related metabolic changes or local neuronal damage (39).

Medications. When predicting the results of some cognitive tasks, the influence of specific medications emerged: the use of topiramate was independently associated with poorer phonemic fluency, and benzodiazepines - with attention tasks. This can be explained by the pharmacological properties of the drugs in neuronal networks responsible for CF. No less important is the number of AED used - it is negatively related to most of the tested CF and independently predicts the results of working memory tests. This corresponds to the explorations of Witt et al., who state that each subsequent AED worsens CF in an individual with epilepsy (40).

4.3. Social cognitive functions

PWE showed considerable deficits in SC when compared to their healthy counterparts. Nevertheless, the results of most tests did not differ significantly among the three PWE groups. Therefore, our data do not support the claims of other authors that SC is less disrupted in patients with other epilepsy types than TLE (41). Epilepsy-related factors were significantly associated with SC outcomes. The link between worse SC and epilepsy duration, seizure frequency and severity may be explained by greater disruption or malformation of the relevant neural networks during seizures (38). The higher number of AED is related to lower SC performance. Although a number of previous studies did not observe the association between AED treatment and SC (42,43), in our opinion, AED can affect not only the processes in the neural networks responsible for SC - a higher number of AED is an indirect indicator of ‘more severe’ epilepsy, also negatively affecting related cognitive processes - attention and executive functions.

The results of this research demonstrate that better SC results are related to higher education. This association may imply that either SC is necessary in seeking higher education, or it develops in an academic environment. Employed individuals showed better performance in SC

tasks, while in the binary regression model, the HST result independently predicted the employment of the subjects, however, with the additional inclusion of the duration of education, such association was no longer evident. This suggests that SC is indirectly linked to having a job, i. e. through an association with higher education. It is interesting to note that individuals having professions requiring simpler and more complex qualifications performed similar in SC tasks, hinting that SC is likely to be important in a variety of settings.

In this research, SC results were not related to a family status of the subjects. This suggests that high skills of SC are not necessary for interpersonal relationship. However, it cannot be ruled out that SC can be applied in romantic relationships better than during formal cognitive testing.

5. CONCLUSIONS

1. People with epilepsy have poorer attention, working memory, executive functions, verbal fluency, memory and social cognitive functions when compared to healthy individuals.

2. Cognitive functions do not differ among individuals with different types of epilepsy.

3. Demographic, clinical and paraclinical characteristics of people with epilepsy provide a reliable estimate of cognitive test results.

4. Better results of social cognition in subjects with epilepsy are associated with higher quality-of-life estimates, however they are not the factors predicting them.

5. People with epilepsy with better social cognitive functions achieve higher education, while work and family formation opportunities are not directly related to these functions.

6. PRACTICAL RECOMMENDATIONS

1. Cognitive testing of PWE is valuable as it can demonstrate clinically less evident changes in CF, and prompt to search for factors adversely affecting them.

2. The results of CF are related to the emotional state and the use of AED, therefore it is recommended to perform tests assessing the level of anxiety, depression, quality of life and AED tolerability when studying CF of PWE.

3. Both the frequency and severity of seizures are associated with poorer CF, therefore, treatment strategies aiming at remission or reduction of seizures should serve as the basis for the treatment of epilepsy.

4. Poorer CF are associated with the number and load of AED, therefore, unnecessary polytherapy should be avoided and the lowest effective dose should be prescribed in the treatment of PWE. In addition, certain medications are related with poorer results of individual CF, consequently, AED with negative psychotropic properties should be avoided.

5. Concomitant psychiatric disorders should be identified and treated as they are related with poorer CF.

6. The duration of education is related to better CF and SC and could mitigate the effect of negative factors, therefore all PWE should be encouraged to pursue education and study for as long as possible.

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1. **Jasionis A**, Jasionytė G, Mameniškienė R. Tolerability of antiseizure medicines using Lithuanian version of the Liverpool Adverse Events Profile. Epilepsy Behav. 2021;124:108371.
2. **Jasionis A**, Puteikis K, Mameniškienė R. The Impact of Social Cognition on the Real-Life of People with Epilepsy. Brain Sci. 2021;11(7):877.
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1. **Jasionis A**, Puteikis K, Mameniškienė R. Is social cognition relevant in the lives of the people with epilepsy? The 15th World Congress on Controversies in Neurology (CONy). 23-26 September 2021

2. **Jasionis A**. Faux pas recognition in unselected epilepsy population: is the deficit evident in other than temporal lobe epilepsies? International Congress on Brain, Heart and Kidney. 24 October 2020, Vilnius

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1. **Jasionis A**. Does 'the epileptic personality' exist? The 17th Summer school of Lithuanian neurologists. 14 June 2019, Panevėžys

2. **Jasionis A**. Social cognitive functions and epilepsy. Conference of Vilnius region Society of neurologists. 19 December 2018, Vilnius

3. **Jasionis A**. The invisible side of epilepsy. The 16th Summer school of Lithuanian neurologists. 9 June 2018, Marijampolė

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