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Short Communication

Working Memory Deficit in Patients with Temporal and Frontal Lobe Epilepsy

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Submitted: 06 September 2017

Accepted: 26 September 2017

Published: 28 September 2017

ISSN: 2573-1289

OPEN ACCESS

Keywords
- Temporal lobe epilepsy
- Frontal lobe epilepsy
- Working memory
- Phonological loop
- Visuo-spatial sketchpad
- Central executive

Abstract

Working memory problems in epilepsy patients that are described in literature are controversial and it remains a subject of ongoing debate. The aim of the present study is to conduct neuropsychological analysis of working memory components in patients with temporal lobe and frontal lobe epilepsy. In quasi-experiment the independent variable is the epilepsy diagnose, presented in three levels: 1) Epilepsy not present; 2) frontal lobe epilepsy (FLE); 3) temporal lobe epilepsy (TLE); the dependent variables are components of working memory: central executive, phonological loop and visuo-spatial sketchpad.

The experiment involved the patients with focal epilepsy diagnosed according to international classification: 21 patients with FLE; 15 patients with right TLE; 17- with left TLE. Control group consisted of 80 healthy individuals. Both groups were aged 18-45. For the experiment were selected verbal/nonverbal and meaningful/meaningless tasks that evaluate different components of working memory.

The results indicated, that working memory is impaired in both, frontal and temporal lobe epilepsy individuals. In patients with TLE verbal and non-verbal working memory are both affected. Visuo-spatial sketchpad is much impaired in patients with TLE compared toFLE individuals. Unlike FLE group, in patients with TLE, the deficit of central executive is caused by the disruption of functioning of verbal salve system.

ABBREVIATIONS

TLE: Temporal Lobe Epilepsy; FLE: Frontal Lobe Epilepsy; INN: Institute of Neurology and Neuropsychology

INTRODUCTION

Working memory holds limited amount of information for short period for manipulation while individual is thinking and reasoning [1]. The most vital component of working memory is central executive, which monitors and manipulates with the information. Central executive has its slave systems, "phonological loop" and "visual-spatial sketchpad", that serve as temporary storage systems. "Phonological loop" stores verbal information, while "visual-spatial sketchpad" deals with nonverbal material [2].

The traditional view, suggesting long-term and short-term memory as anatomically and functionally different systems has been questioned by the recent studies, which consider temporal lobe, alongside with frontal lobe as the anatomical basis of working memory [3-7]. The question about particularly what specific roles do these regions play in the process of working memory, yet remain the subject of scientific debate. Some studies reported, that working memory is localized in frontal lobe [8-15] and thereby its disruption is prevalent FLE patients [16,17]. The majority of latest researches showed that in patients with TLE, working memory is affected [18-24]; although some of the studies still deny the disruption of working memory in TLE [25-27]. The aim of the present study is to analyze working memory components in patients with focal FLE and TLE. The hypotheses of the study are: 1. Working memory deficit is present in both FLE and TLE; 2. both, phonological loop and visuo-spatial sketchpad are affected in TLE; 3. Central executive deficits in TLE is related to the disruption of working memory slave systems.

MATERIALS AND METHODS

Study group

Cohort of fifty-three consecutive patients with epilepsy, without any other neurological deficit/co-morbid diagnose, admitted during the fifteen months (January 2015 to March 2016), at the Institute of Neurology and Neuropsychology (INN), within the National Epilepsy State Program, Tbilisi, Georgia, were recruited. In all cases the epilepsy syndromes were diagnosed according to the ILAE classifications of the seizures and epilepsies [28], by the consultation of an epileptologist, using standard

EEG recordings (Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology, 1999). All patientsof the study group had previously been diagnosed and treated for epilepsy.Inclusion criteria: 1. diagnoses of frontal or temporal lobe epilepsy, 2. aged: 18-45. Exclusion criteria: 1. Other neurological diseases, 2. Mental retardation, 3. Other chronic diseases,

Control group

Eighty adults matched to thegender, age and educational level (no less then 9 grades) of the study group were selected among volunteers who expressed willingness to participate into study. Inclusion criteria: 1. aged 18-45 years. Exclusion criteria: 1. history of neurological diseases, 2. mental retardation, 3. any chronic illness that could interfere neuropsychological assessment.

Neuropsychological study instrument and procedures

Quasi experiment invlovled 133 individuals fromstudy (n=53) and control (n=80) groups. ; We created a new measure of working memory. This is a new and original way to assess working memory. This measure was developed and derived from the theory of working memory by A. Baddeley. Accordingly we had tasks relevant to thecomponents of working memory: phonological loop, visuospatial sketchpad, verbal central executive, and non-verbal central executive. Besides, meaningful and meaningless tasks were selected for each component of working memory, to assess the role of semantics in working memory deficit. Therefore, experiment included eight tasks (Figure 1), (see the tasks used in the experiment in Table 1). Because of neuropsychological tasks have different maximum scores, they were transformed according their weight in order to allow comparisons between means. All calculation in the results section are provided on transformed scores.

ETHICAL ISSUES

Informed consent were obtained from each participant before inclusion into the study. Study was scrutinised and approved by the institutional ethics committee.

STATISTICAL ANALYSIS

Descriptive statistics were used for demographic variables. We performed a two-sample t-test, one way ANOVA with Tukey's post hoc analysis and paired simple t-test to detect differences between means scores of neuropsychological tasks across different clinico-demographic characteristics. We used multiple linear regression to detect association between neuropsychological task performance and epilepsy characteristics. Stepwise method was used to test the model. We calculated the non-standardized beta (β) coefficient. Adjusted R squared value was calculated. Probability less than 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS (IBM SPSS Statistics, Version 21.0, Armonk, NY).

RESULTS

In total 53 participants with epilepsy were enrolled into the study [male, n=36 (68%); female, n=17 (22%)]. Among them were 17 (32%) individuals were with left temporal lobe, 15 (28%) with right temporal lobe and 21 (40%) individuals with frontal lobe epilepsy. The age of the patients varied between 18 and 45 (mean: 28 years; SD: 8.1). Among them 28 individuals were with secondary education, and 25 of them with higher education. Among eighty controls 53 (66%) were male, and 27 (24%) were female. Mean age was 24 (SD: 5.724). Among them 41 individuals were with secondary education, and 39 of them with higher education. Table 2 shows distribution of clinical data among FLE and TLE groups.

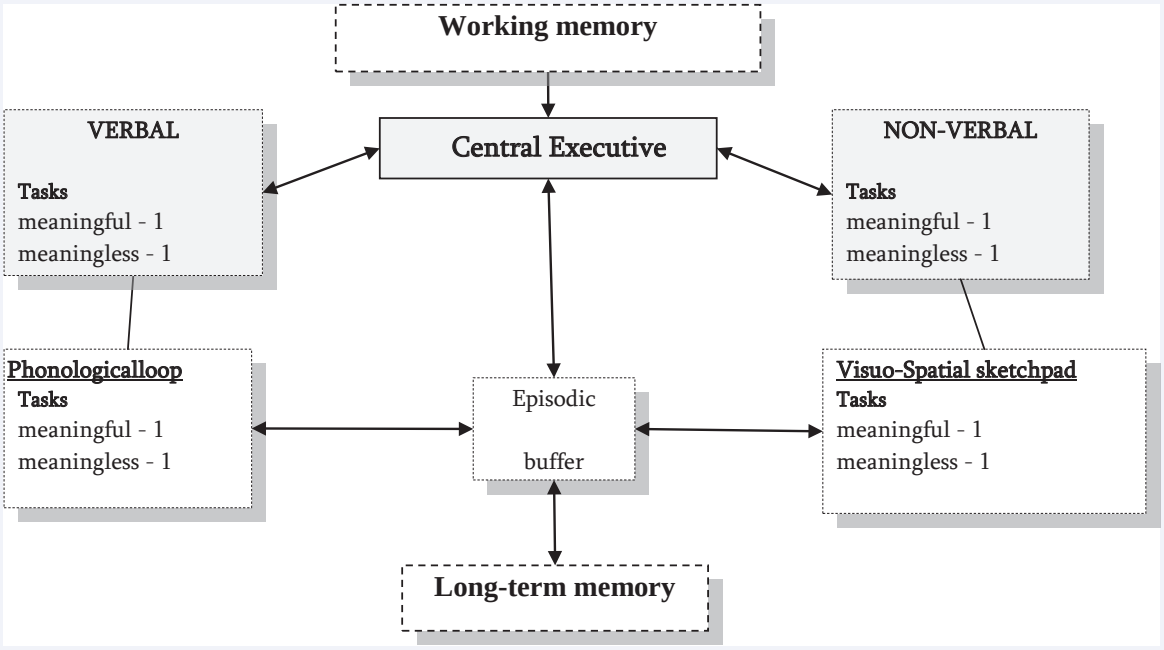

Figure 1 Flow chart on study disign and assignments by modalities.

Table 1: Tasks used in the experiment.

Tasks	Meaningful	Meaningless
Phonological loop	**Sentence sequencing:** Participants are read out sentences and are requested to recall them immediately. After hearing sentences, participants repeated them with exact accuracy. They were presented 7 sentences in total. The number of words within the sentence increases gradually from 2 to 8. After each reproduction, sentence length is increased by one word. The task ends after 2 consecutive errors. **Scores:** Each sentence is scored 0, 1 or 2 points. The maximum score is 14.	**Letter sequencing:** Participants are read letters that are not sorted in alphabetical order and are requested to reproduce them immediately in their original order. The number of letters is increased from 2 to 8. Each set size is given two times. Each time participants are presented different sequence of letters. The presentation of the letters is ceased after two consecutive errors. Therefore, there is 14 presentation in total **Scores:** Each presentation is scored 0, 1 or 2 points. Maximum score is 28.
Visuospatial sketchpad	**Image sequencing:** Participants are given a sequence of colored images for 10 second. They are asked to remember and recall these images in their original order by pointing them on the picture which contains 18 images. For the first presentation the number of images is 2 and it increases after each presentation by one image. The maximum number of images is 8 and there are 7 presentations in total. **Scores:** Each presentation is scored with 0, 1 or 2 score. Therefore, the maximum score for this task is 14.	**Block sequencing:** The first part of visual memory subtest of Wechsler memory scale. This task requires special material - 8 red blocks printed on a paper, that researcher points at in particular order. Participant is asked to recall the blocks in the original order. The sequence length is increased by one from 3 to 8 units. Each number of blocks is presented twice. Task ends after two consecutive errors. **Scores:** We score it with 0, 1 or 2 points. There are 14 presentations in total. Maximum score is 28.
Verbal central executive	**Reproducing the last/first word of the sentence**. Three sentences were read out to participants consecutively. After that, they were asked to repeat either the last or the first word of each sentence. After each presentation the number of words in the sentence were increased by one from 2 to 7. The task ends after 2 consecutive errors. There is 6 presentation in total each presentation involve 3 sentence. **Scores:** Each presentation is scored 0, 1 or 2 points. Maximum score is 36.	**Sorting letters in alphabetical order.** Researcher reads letters to participants in non-alphabetical order. Participants are requested to sort these letters in alphabetical order. The sequence length is increased by one item from 2 to 7. Each set size is presented twice. Each set of letters is different. Test ends after two consecutive mistakes in the same size sets. **Scores:** Each presentation is scored with 0 and 1 points. There are 12 presentations in total, therefore the maximum score is 12 points.
Non-verbal central executive	**Showing the colors of the objects.** Images are displayed to participants for 10 seconds, which they have to remember in the given order. Pictures in this task are colorless. Besides, the objects on the pictures have single color in natural environment. After remembering, participants are given paper of colors (sheet with 9 colors on it) and are asked to show the colors of the remembered object in order. The number of pictures increases gradually from 2 to 7. The task is stopped after two consecutive mistakes. There are 12 presentations in total. **Scores:** Each presentation is scored with 0.1 or 2 points. The maximum score is 24.	**Reverse block sequencing.** Second part of the visual memory subtest of the Wechsler's memory scale. The researcher points at the blocks in certain order and sequence blocks shown by the researcher must be restored backwards. Sequence length is increased by one item from 2 to 7. Each set size is given two times. **Scores:** The evaluation is similar to the Wechsler memory scale test with 0 or 1 point. There are 12 presentations in total and maximum score is 12.

Table 2: Distribution of various clinical variable across FLE and TLE.

Variables	FLE (n=21)	TLE (n=32)	p- value
Age of onset, month; mean; (SD); [min; max]	11.8; (10.7); [1; 41]	15.0; (8.1); [1; 30]	0.363
Epilepsy duration, month; mean; (SD); [min; max]	18.2; (10.3); [1; 41.5]	10.2; (6.1); [3; 25]	0.017
Polytherapy; n (%)	8 (38)	2 (6)	0.003
MRI done; n (%)	10 (48)	24 (75)	0.332
Any abnormalities	7 (70)	12 (50)	0.578

Analysis of variance shoved that there is significant difference in mean working memory scores across study groups ($p<0.001$). Post hoc analysis revealed that working memory score in control group (70.3) is higher compared to that of TLE (50.2) ($p<0.001$), and FLE (52.7) ($p<0.001$) patients. However, no difference was observed between FLE and TLE groups. Mean scores of each components of working memory: phonological loop, visuo-spatial sketchpad (1), verbal and nonverbal central executive is higher in control group compared to TLE and FLE patients (Table 3). TLE and FLE patients showed significantly lower mean scores in both, slave systems and central executive of working memory, compared to the control group (Figure 2). The comparison of experimental groups showed that the mean score of meaningless visual-spatial sketchpad task in TLE group (54.36) was significantly lower, than in FLE group (65.64) ($p<0.006$).

In TLE group, mean score of visuo-spatial sketchpad tasks (49.8) was significantly lower than that of phonological loop (69.24) ($p<0.001$), while in FLE group, the mean score of phonological loop task (54.4) was lower compared to the mean score of visuo-spatial sketchpad task (65.64) ($p= 0.009$). Patients with FLE performed worse in meaningful visuo-spatial sketchpad than in meaningless visuo-spatial sketchpad ($P = 0.005$).

We performed multiple linearregression to delineate best predictor model for verbal executive tasks. Onset age, epilepsy duration, sex, polytherapy, focal and secondary generalized

Table 3: Distribution of working memory component tasc scores (meaningful and meaningless tasks together by each component) by modalities*.

Dependent variable	Experimental and control groups	Mean	p - value
Phonological loop tasks	TLE	60.9	
	FLE	64.4	0.431
	Controls	84.3	
	FLE	64.4	0.000
	Controls	84.3	
	TLE	60.9	0.000
Visuo-spatial sketchpad tasks	TLE	52.1	
	FLE	59.0	0.66
	Controls	72.0	
	FLE	59.01	0.000
	Controls	71.26	
	TLE	52.08	0.000
Verbal central executive tasks	TLE	34.1	
	FLE	35.02	0.828
	Controls	51.6	
	FLE	35.0	0.000
	Controls	51.19	
	TLE	34.06	0.000
Nonverbal central executive tasks	TLE	53.00	
	FLE	52.57	0.927
	Controls	73.5	
	FLE	52.6	0.000
	Controls	73.5	
	TLE	53.00	0.000

*Tukey's post hoc analysis was used to detect differences between study groups (control group, FLE and TLE)

Table 4: Multivariate analysis for association between the various medical and social factors and verbal central executive tasks (variables retained in the final model presented).

	Verbal central executive tasks	
	Unstandardised coefficient Beta	**p value**
Phonological loop	0.594	<0.001
Focal seizure frequency	0.014	0.04
Adjusted R squared for whole model	0.551	

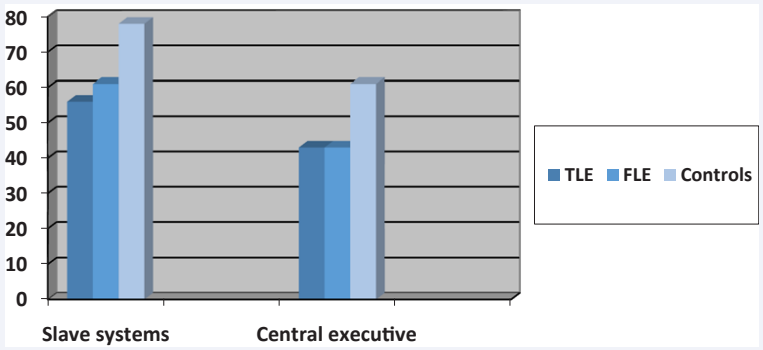

Figure 2 Mean score of slave systems and central executive tasks in control and experimental groups.

seizure frequency and phonological loop were entered into model. *Regression analysis* showed that phonological loop, (β=0.594, p<0.001) and focal seizure frequency (β=0.014, p<0.04) are independent predictors for verbal central executive tasksin TLE group. The R squared value undicates that more than 50% of variqation of dependent variable can be explained by the regression model (Table 4). We did not observe such association in FLE and control groups.

DISCUSSION

Our research results outlined that working memory is impaired in both, TLE and FLE. Moreover, our research

corresponded to the studies that describe working memory decline in TLE patients [3,5-7,18-21,29,30]. As we have already discussed in our study, working memory is impaired in both epileptic syndromes. The given results support the view that working memory is not located in one particular region of the brain, but is regulated by several different systems of the brain [11,29,31]. Some authors explain working memory deficit in TLE explaine by theepisodic buffer, the component of working memory, that provides the temporary maintenance of information fetched from long term and short term memory. Therefore, pathological impact of epileptic syndromes on a single function (in this case, on long-term memory) may affect another function - the working memory, because long-term memory dysfunction will have negative influence on "episodic buffer", and that will on its hand, affect working memory [21].The research of Axmacher and colleagues also reported that hippocampus serves long-term memory encoding processes [32].Studies also indicate that in the process of doing episodic memory and working memory tasks, patterns of brain activation are converged [33].According to "processual-activation" model, working memory and long-term memory are structurally and functionally related [34].

The research revealed, that meaningless slave systems are more impaired in TLE group, than in FLE group. In addition, in FLE, meaningful visuo-spatial sketchpad is more impaired than meaningless visuo-spatial sketchpad. The given result can be explained with neurocognitive model, according to which, maintenance of meaningful information involves long-term memory. Active maintenance of meaningful information requires immediate retrieval of information from long-term memory storage and connecting it to current information, so that past knowladge is activated by meaningful stimuli. According to this neurocognitive model, maintenance of meaningful information is independent and different process from working memory and is more related to the long-term memory [35].

Dissociation between the active maintenance of meaningful and meaningless information is confirmed by some neuropsychological data [36]. In that aspect, our study corresponds to the research, where patients with different types of cortical lesions showed different results in meaningful and meaningless working memory tasks. First patient, who had damaged prefrontal cortex and showed working memory deficit tended to solve meaningless tasks better (though it was still below thenormal range), while the second patient, who had lesions in the left temporal lobe, did meaningful working memory tasks better (but still below the normal range). This dissociation encouraged the authors to propose that maintenance of meaningful and meaningless information is related to different systems of the brain [36].

Research data suggest that deficit of slave system ((visuo-spatial sketchpad) is mostly reported in TLE group, compared to FLE group. Additionally, central executive is impaired on same level in TLE and FLE patients. These findings correspond with the studies that describe visual working memory deficit in patients with temporal lobe disfunction [3,4]. Impaired slave system in TLE patients can be explained by the disfunction of medial temporal structures, that facilitates encoding and temporary maintenance of information [37]. Based on the given results, we may suggest that temporal lobe controls the slave systems of working memory. According some studies executive control and active maintentance are linked with different structures of the brain. Prefrontal cortex is linked with executive control, while temporal lobe and other posterior part are involved in the maintenance of modality-specific information [38,11,29].

Low results of central executive in TLE group can be explained by the deficit of those slave systems that is prevalent in these patients. According to Baddeley, "phonological loop" and "visuo-spatial sketchpad" are those primary stages, that are essential, but not efficient for central executive to function properly because if slave systems do not provide information retention, the task will not be processed properly [2].

CONCLUSION

1. Working memory deficit is evident in TLE and FLE; 2. In patients with TLE verbal and non-verbal working memory are both affected; 3. Visuo-spatial sketchpad is greatly impaired in TLE group compared to FLE group; 4. By means of phonological loop indicator, regardless semantics, verbal central executive can be predicted only in TLE patients. Therefore, if phonological loop is disrupted, than the decline in central executive will also be present.

LIMITATIONS OF THE STUDY

Due to the small number of participants, the amount, dosage and duration of antiepileptic drug treatment that might affect working memory were not controlled. For the same reason seizure frequency and the duration of epilepsy, which could influence working memory were not controlled. For the assessment of control group, EEG and MRI scanning had not been carried out. The information about their health condition was obtained through the interview. The new measurement, used for the assessment of working memory is not a standardized cognitive test.

ACKNOWLEDGEMENTS

We would like to sincerely thank the Faculty of Psychology and Educational Sciences of the Tbilisi State University, within its PhD program was prepared the following article. We would like to express special gratitude toward the Institute of Neurology and Neuropsychology.

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Cite this article

Mosiashvili Z, Kasradze S, Gagoshidze T (2017) Working Memory Deficit in Patients with Temporal and Frontal Lobe Epilepsy. JSM Brain Sci 2(2): 1015.