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Executive dysfunction profile in mesial temporal lobe epilepsy

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SUMMARY

Background: The aim of the study was a comprehensive assessment of the profile of executive dysfunctions in patients with MTLE and the search for associations between the results of neuropsychological tests and individual clinical variables.

Material/ Methods: We examined 25 patients with MTLE and 25 healthy controls using the Montreal Cognitive Assessment (MoCA), Color Trails Test (CTT), Tower of London (ToL), Victoria Stroop Test (VLT) and Wisconsin Card Sorting Test (WCST). We considered the possible effects of seizure frequency and lateralization of the epileptogenic zone on various aspects of cognitive functioning.

MTLE group scored significantly lower than controls in MoCA (p = 0.000) and needed significantly more time (p=0.000) in CTT-2. They also had lower scores in several parts of ToL (total correct, p=0.004; additional moves, p=0.038; execution time, p=0.001; problem-solving time, p=0.003) and WCST (error responses, p=0.003; conceptual level responses, p=0.000; completed categories, p=0.007; perseverative responses, p=0.004; perseverative errors, p=0.009). There were no significant differences between the clinical and control group in VST and in other indicators of CTT, ToL and WCST. Neither the laterality of the epileptogenic focus nor the seizure frequency were significantly correlated with the results.

Results: Patients with MTLE exhibit a wide range of executive dysfunctions. Importantly, the disorders were present only in some aspects of functioning, such as: logical reasoning, planning, switching between tasks, cognitive flexibility and problem-solving, while others e.g. inhibition, remained normal. Our results constitute a significant enrichment of knowledge concerning the specificity of functioning of this group of patients which may help clinicians to introduce solutions to improve the functioning of these patients.

Conclusions:

Key words: MTLE, executive functions, cognitive disorders, cognitive functioning

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BACKGROUND

Epilepsy is one of the most common neurological diseases, affecting – around 50 million people worldwide suffer from this disease (Liu et al., 2023). Epilepsy is a chronic neurological disorder characterized by a predisposition to recurrent epileptic seizures, i.e. which are pathological discharges in specific areas of the brain that can affect all spheres of patients'' lives, including their cognitive functioning (Blume et al., 2001).

Mesial temporal lobe epilepsy (MTLE) is the most common type of focal epilepsy, affecting about 40% of all people with epilepsy (Duncan et al., 2006; Kwan and Sander, 2004). It is most often caused by mesial temporal sclerosis and dysplasia (Siemianowski and Królicki, 2005), which particularly affects the memory and language areas (Roger et al., 2020). Because of this, most previous research in patients with epilepsy has focused on deficits in memory and language functions. However, more generalized cognitive impairments are widespread among patients with MTLE. They are not always strictly related to hippocampal atrophy, and frequently involve processing speed, attention and visual perceptual abilities (Hermann et al., 1997; Pachalska et al., 2023). Previous studies showed that in patients with epilepsy abnormal brain volume may also include various cortical and subcortical extratemporal areas (Keller and Roberts, 2008; Pulsipher et al., 2007). Extensive damage beyond the hippocampus might be the reason for a heterogeneous profile of cognitive deficits in patients with MTLE (Hermann et al., 2003; Dow et al., 2004; Seidenberg et al., 2005; Oyegbile et al., 2004; Geary et al., 2009). There is some data showing that patients with MTLE may present impairments in the efficiency of executive functions despite a lack of visible damage to the frontal lobes (Kim et al., 2006; Martin et al., 2000), although visible abnormalities of these areas have also been reported (Dinkelacker et al., 2016; Stretton and Thompson, 2012).

In recent years there has been an increase in the study of executive functions in patients with MTLE, including assessment of particular abilities like initiating of action, inhibiting automatic reactions, monitoring and controlling cognitive processes, correcting and modifying behaviors in fluctuating conditions, planning, prediction, abstract thinking, problem solving (Pąchalska, 2008; Collins and Koechlin, 2012; Lunt et al., 2012). However, most studies investigated selected aspects of the executive functioning of MTLE patients, using limited number of neuropsychological tests, which may lead to the overgeneralization of results and it does not allow for a broader look at the profile of cognitive disorders, taking into account various aspects of executive functions.

The purpose of this study was to determine whether patients with MTLE exhibit executive functions deficits, and if so, exactly which aspects of this broad construct are affected. Moreover, the impact of selected clinical variables on cognitive functioning was also analyzed.

Ethics approval statement

All procedures were in accordance with the Declaration of Helsinki and were approved by the Committee for Ethics of Research at the Faculty of Psychology, University of Warsaw.

MATERIAL AND METHODS

Participants

The study was approved by the Research Ethics Committee of the Faculty of Psychology, University of Warsaw. All patients provided informed consent prior to inclusion.

Twenty-five right-handed patients diagnosed with drug-resistant MTLE were recruited from the Neurosurgery Department at the Medical University of Warsaw. Exclusion criteria were a history of other neurological or psychiatric disorders, intellectual disability, and prior surgical intervention for epilepsy. For the healthy control group, we recruited 25 participants matched with patients in the MTLE group for age, sex, and education. All participants in the control group were right-handed. Exclusion criteria were a history of neurological or psychiatric disorders or intellectual disability.

Clinical assessment

Video-electroencephalography (vEEG) and magnetic resonance imaging (MRI) were conducted as a part of a standard diagnostic procedure for drug-resistant epilepsy to establish the location of the epileptic focus. All patients were diagnosed with MTLE based on their medical history and clinical, radiological, and EEG findings. All procedures were carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Neuropsychological evaluation

All participants underwent a clinical interview and neuropsychological presurgical examination. The tests described in subsections 2.3.1 to 2.3.5 were used to examine the following aspects of executive functions: response inhibition, working memory, reasoning, cognitive flexibility, planning, problem solving and task switching.

Montreal Cognitive Assessment (MoCA)

The MoCA screening test is widely used for evaluating cognitive function. The test consists of several parts that test language functions, short-term memory, working memory, executive functions (switching, categorizing, searching the semantic memory store, abstraction), attention, visual-spatial ability, and allopsychic orientation. The score recorded is the sum of the scores obtained in each subtest (to a maximum of 30), with a threshold score of 26 points for cognitive impairment.

Color Trails Test (CTT)

This test is used to quickly assess cognitive function and detect mild cognitive disorder. It assesses visual search, attention maintenance, shifting attention, working memory, behavior monitoring, sequential information processing, short-term memory and graphomotor function. The test consists of two parts: CTT-1 and CTT-2. The first part examines psychomotor speed, the ability to effectively search the perceptual field, and short-term memory. The second subtest involves shifting attention and behavior monitoring (Łojek and Stańczak, 2012). In both tasks, 25 dots must be connected. We recorded the time taken to complete both subtests, and the number of errors made.

Tower of London (ToL) test

The ToL test is used to diagnose focal brain lesions. It assesses a person's ability to plan and implement a strategy aimed at solving a problem, and to break down a complex problem into simpler indirect problems, as well as inhibitory control, searching, and working memory.

The participant is asked to recreate on their board with pins the arrangement of balls presented by the researcher. Certain rules must be followed: a single movement of the balls is permitted, and pins of different heights are allowed a maximum number of balls (one on the lowest pin, two on the next pin, three on the highest pin). The test consists of three examples and ten tasks. The maximum execution time for each task is 120 seconds.

The time taken for planning and executing the task (and the total time) is recorded. Also noted are the number of moves made by the participant, the number of patterns arranged with the fewest possible moves, and the frequency of rule-breaking.

Victoria Stroop Test (VST)

The test was performed in 1935 by John Ridley Stroop and since then it has been repeated many times, the following versions are based on the Stroop effect – it is a conflict task, in which the subject is to name the printing color of the presented words denoting the colors, and the color of their printing is not the same the meaning of the written word.

It assesses visual perception, working memory, cognitive flexibility, inhibitory control, executive functions and attention.

In the VST, three cards of 24 items, colored in blue, green, yellow or red and distributed in six rows of four items, are presented to participants who are asked to name as quickly as possible the color of dots (Dot condition—Card 1), the color of the ink in which neutral words are printed (Word condition—Card 2), and the color of the ink in which color names are printed (Interference condition – Card 3). For each condition, the completion time and the number of errors are compiled, and interferences scores are derived by calculating the ratio between the time required to name the color of the ink in the Word and the time required to name the color of dots in the Dot conditions (low interference), and the ratio between the time required to name the colors in the Interference and the Dot conditions (high interference) (Strauss et al., 2006).

The subjects were tested with the Victoria version (Bayard et al., 2011) consisting of three parts of 24 items (colored in blue, green, yellow or red, 4 items in 6 rows). Participants were asked to name as quickly as possible the color of dots (1 part), the color of neutral words (2 part) and in the third part, the color of words denoting colors printed in colors inconsistent with their meaning.

The result of the test is the time to complete each part, the number of errors, as well as the interference score, which is the ratio between the time of the third part and the time of the first part.

Wisconsin Card Sorting Test (WCST)

The Polish adaptation of this test was used in the study. The test assesses abstract thinking, cognitive flexibility, inference, and learning from feedback. The participant is asked to assign each card in the deck sequentially to one of four reference cards, based on the researcher's feedback on sorting correctness. The test lasts until six categories are passed or until all 128 cards are used. The time taken to complete the task is not measured, but answers are recorded (in terms of the category they fit). This record enables the following 16 indicators to be calculated later describing various aspects of executive functioning.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 25 for Windows. Results were considered statistically significant when $p \leq 0.05$. The Kolmogorov–Smirnov test was used to check the normality of the distribution of the variables. Relationships between test results and clinical variables (lateralization of the epileptic focus, age of epilepsy onset, epilepsy duration, and seizure frequency) were explored with Spearman's rank correlation coefficient.

RESULTS

Participant characteristics

The group characteristics are presented in Table 1. We summarizes the demographic characteristics for the control and MTLE groups and clinical seizure

Table 1. Demographic and clinical characteristics of patients with MTLE and healthy controls

	Healthy control participants	Patients with MTLE
N	25	25
Age [years]	37.96 (9.3)	37.96 (9.0)
Years of education	13.58 (2.0)	13.24 (2.1)
Gender	14 female 11 male	14 female 11 male
Epilepsy duration [years]	n/a	25.12 (10.5)
Age at epilepsy onset	n/a	12.84 (8.4)
Frequency of seizures (monthly)	n/a	25.25 (58.2)

Note: Data are represented as mean (SD); n/a – not applicable characteristics for the MTLE group. There were no significant differences in age (*t* = 0.000, *p* = 1.000), years of education (*Z* = −0.672, *p* = 0.497) or gender between the groups (14 women, 11 men in each group). Mean age of MTLE onset was 12 years 10 months, mean epilepsy duration was 25 years 1 month, and mean seizure frequency was 25 per month.

Executive functions

Statistically significant differences were found in intergroup comparisons of most indicators of the neuropsychological tests, in both general cognitive functions (MoCA) and executive functions (CTT, TOL, WCST). We found no statistically significant differences in the VST, apart from the Part 1 time (Table 2).

Correlation analyses in the MTLE group performed to determine relationships between neuropsychological test results and clinical variables (age of disease onset, total disease duration, and seizure frequency) revealed that age of onset

Table 2. Results of statistical analysis of neuropsychological indicators

Task	Measure	Control	MTLE patients	p
MoCA	**Mean score**	**27.60 (2.1)**	**22.16 (3.8)**	**0.000**
CTT	CTT-1 time [s]	67.44 (49.5)	67.76 (53.6)	0.915
	CTT-2 time [s]	**74.12 (48.5)**	**135.24 (66.9)**	**0.000**
	CTT-1 errors	0.00 (0.0)	0.04 (0.2)	0.317
	CTT-2 errors	0.40 (1.0)	0.56 (1.0)	0.357
	Disruption rate	1.37 (0.9)	1.50 (1.0)	0.547
TOL	**Total correct**	**4.68 (2.6)**	**2.64 (1.0)**	**0.004**
	Additional moves	**28.28 (17.2)**	**39.00 (18.0)**	**0.038**
	Initiation Time [s]	56.08 (37.7)	50.32 (35.5)	0.655
	Execution time [s]	**205.04 (125.7)**	**356.96 (200.8)**	**0.001**
	Problem-solving time [s]	**260.80 (131.5)**	**408.00 (221.6)**	**0.003**
	Time violations	**0.64 (1.3)**	**1.84 (2.3)**	**0.032**
	Rule violations	0.32 (0.9)	0.64 (1.1)	0.177
VST	**Part 1 time [s]**	**15.88 (3.0)**	**21.01 (10.3)**	**0.032**
	Part 1 errors	0.08 (0.3)	0.44 (1.0)	0.065
	Part 3 time [s]	31.62 (10.5)	38.17 (20.3)	0.322
	Part 3 errors	1.76 (2.1)	1.92 (2.0)	0.756
	Interference score	1.97 (0.5)	1.85 (0.6)	0.218
WCST	**Number of trials**	**92.75 (26.3)**	**118.08 (18,6)**	**0.001**
	Total correct	60.54 (18.3)	64.44 (13.8)	0.465
	Total errors	**30.96 (26.3)**	**53.64 (25.7)**	**0.003**
	% Errors	**28.22 (21.7)**	**43.21 (18.1)**	**0.004**
	Perseverative responses	**16.33 (17.8)**	**31.68 (24.7)**	**0.004**
	% Perseverative responses	**15.09 (12.8)**	**25.44 (18.7)**	**0.006**
	Perseverative errors	**15.42 (16.0)**	**27.16 (18.9)**	**0.009**
	% Perseverative errors	**14.36 (11.3)**	**21.86 (14.2)**	**0.016**
	Non-perseverative errors	**12.33 (11.7)**	**25.32 (20.0)**	**0.007**
	% Non-perseverative errors	**11.26 (8.3)**	**20.81 (14.8)**	**0.013**
	Conceptual level responses	**56.92 (12.2)**	**46.44 (19.6)**	**0.040**
	% Conceptual level responses	**67.46 (23.4)**	**42.27 (23.4)**	**0.000**
	Categories completed	**4.75 (2.0)**	**3.12 (2.2)**	**0.007**
	Trials to complete first category	**19.08 (26.8)**	**36.40 (39.9)**	**0.001**
	Failure to maintain set	0.67 (1.2)	0.72 (0.8)	0.405
	Learning to learn	-2.70 (7.9)	-5.64 (9.6)	0.414

Data are represented as mean (SD). Statistically significant results are shown in bold.

of epilepsy correlated with the number of errors (rho = 0.44; p = 0.028) and the disruption rate (rho = 0.47; p = 0.017) in CTT2. No other significant relationships were found between the test results and duration of epilepsy, laterality of the epileptogenic zone, or seizure frequency.

DISCUSSION

Due to the complex nature of possible executive disorders, we conducted a comprehensive analysis of the executive functioning of MTLE patients in order to better understand the profile of their deficits.

Results showed, that patients with MTLE performed more poorly than healthy individuals in all neuropsychological tests. The ToL test revealed that patients show poorer-quality planning than healthy individuals. Although the *initiation time* (time spent planning, before the first move) in the ToL test did not differ statistically between the patient and control groups, differences in the level of task performance were noticeable, with the patient group performing statistically worse in all other indicators (*total correct*, *total moves*, *execution time*, *problem-solving time*, and *time violations*). Planning is a key skill in performing the ToL test (Phillips et al., 2001), and a lack of a plan or ability to introduce problem-solving and inhibition of impulsive behavior strategies increases the number of movements needed to achieve the desired ball arrangement, which in turn extends the time to task completion and significantly reduces the probability of completing a given task with the fewest possible moves (*total correct*). The difference in results obtained by the two groups may also be due to poorer searching and working memory in the patient group, which could cause them to take longer to execute the tasks. This result is analogous to those obtained in the CTT.

In the CTT, statistically significant differences were found only in the time to complete CTT-2, suggesting that patients' attention-shifting and behavior-monitoring abilities were reduced. The patient group needed more time to complete this task, but did not make more mistakes than the control group. This suggests that they can perform similarly to healthy people in areas such as visual searching, maintaining attention, sequential information processing, short-term memory and graphomotor function, but that more effort is required, which slows them down.

We did not find any statistically significant differences in the VST, apart from the execution time in Part 1. This is consistent with the TOL test results (*Rule violations* Index). This confirms the observation that patients have no difficulty in inhibiting automatic reactions. They are able to follow the rules and control impulsive behavior on a similar level as healthy people.

In the WCST, patients made more errors and achieved a lower overall score than participants in the control group. However, the percentage improvement in the performance of tasks in subsequent trials was comparable to that of healthy individuals. There was no statistically significant difference in the learning index, which indicates that the effectiveness with which participants formed concepts by going through the successive categories of the test did not differ between groups. In contrast, patients with MTLE scored lower than control participants in *total number of errors*, *percentage of conceptual level responses*, *categories achieved*, *perseverative responses*, and *perseverative errors*, which are all categories that best measure executive functions (Heaton et al., 1993). Furthermore, participants in the MTLE group had great difficulty making conclusions based on feedback, so they needed many more trials to guess the sorting rules and made many more mistakes. They were also characterized by a lack of cognitive flexibility, finding it difficult to switch to a different way of categorizing cards than they previously used, which resulted in perseveration.

We found no correlations between clinical variables and neuropsychological test performance. The lack of correlation between executive functions and number of seizures or duration of epilepsy is particularly surprising, given the findings of previous studies (Lespinet et al., 2002; Motamedi and Meador, 2003; Thompson and Duncan, 2005; Leal et al., 2017). It may be due to patients inaccurately assessing the number of seizures they have or to an insufficient sample size.

Interestingly, the affected abilities are not directly related to the temporal lobes. Executive functions are mainly carried out by the frontal lobes (Stuss and Knight, 2013), especially prefrontal cortex (Walsh and Darby, 2008; Stuss, 2011). The importance of the prefrontal cortex in executive functions is mainly related to the numerous connections it creates with other areas of the brain, including the hypothalamus, thalamus, brainstem, amygdala, and cingulate gyrus, as well as the premotor, temporal, and parietal cortices (Sallet et al., 2013).

In recent years, knowledge about MTLE has developed significantly. Previously perceived as a focal pathology, limited to a specific lesion, today it is considered a network disease (Laufs et al., 2012.). Structural neuroimaging has revealed changes in gray and white matter that explain the poorer performance in executive tasks attributed to the frontal lobes (Bonilha et al., 2010; Bernhardt et al., 2011; Besson et al., 2014; Tan et al., 2018; Stretton and Thompson, 2012). In addition to studies showing differences in network dynamics at rest between patients with MTLE and healthy individuals, targeted differences in neural network connectivity and in brain activation during tasks involving executive functions have also been observed (Campo et al., 2009; Stretton et al., 2012; Yang et al., 2018; Zhang et al., 2020). Analysis of functional integration in the brain shows the influence of neurological disorders resulting from the inseparability of diffused neural networks (Buckholtz and Meyer-Lindenberg, 2012; Bassett et al., 2009; Lanillos et al., 2020; Struck et al., 2023).

Studies examining functional and structural brain connections to assess the clinical impact of epilepsy on neural networks (Yang et al., 2018; Bonilha et al., 2012; Doucet et al., 2012; Frings et al., 2009; Liao et al., 2011; Liu et al., 2012; Voets et al., 2012; Zhang et al., 2010) have shown that transmission abnormalities are not confined to a pathologically altered area (often the hippocampus), but may also be observed in other related structures, not only within the same hemisphere but also in the opposite hemisphere. For this reason, mesial TLE has been called the “network disease” for several years (Bonilha et al., 2012).

Atrophy and metabolic changes in the prefrontal cortex (Keller et al., 2009; Tan et al., 2018), as well as thalamic pathologies (Tuchscherer et al., 2010; Hermann et al., 2009; Dinkelacker et al., 2015) have been identified as main causes of the decline in executive functioning in this clinical goup. (Tuchscherer et al., 2010) investigated the role of the thalamus in the executive abilities of patients with MTLE, due to the multisynaptic connections between the hippocampus and the anterior thalamic nuclei via the vault, mastoid bodies, and the thalamo-hippocampal pathway (Herrero et al., 2002). The thalamus, a critical part of the fronto-subcortical junction system, is directly involved in executive functions, and damage to this structure in patients with MTLE has been confirmed in numerous studies (Bonilha et al., 2005; Carrera and Bogousslavsky, 2006; Parrish et al., 2007; Seidenberg et al., 2008; Pulsipher et al., 2009). The existence of extensive systems responsible for language functions and the hippocampal-thalamic pathways, disrupting executive functions, has also been demonstrated (Dinkelacker et al., 2016).

Performance in the tests of executive functions in the present study was similar to that in the studies reported in the cited literature (Hermann et al., 2003; Dow et al., 2004; Seidenberg et al., 2005; Oyegbile et al., 2004; Geary et al., 2009; Kim et al., 2006; Martin et al., 2000).

An interesting direction for further research would be to explore whether and how executive functions improve after surgical treatment, taking into account the extent of resection and the outcome of epilepsy treatment.

A main limitation of the present study, which may have resulted in the lack of statistically significant relationships between neuropsychological indicators and clinico-demographic variables, may be that we were only able to gather information on average seizure frequency, while a more in-depth history of seizures, such as type of seizure, time since last seizure and number of seizures over the past 48 hours, may have given a more detailed picture.

The obtained results regarding various aspects of executive functions may be influenced by, among others, deficits in attention, working memory, verbal memory and even language functions. Furthermore, cognitive functioning in patients with MTLE needs to be extensively investigated taking into account multifactor intercorrelations of individual variables.

CONCLUSIONS

Patients with MTLE showed reduced executive functioning, including planning, attention shifting, behavior monitoring, cognitive flexibility, strategy implementation and reasoning. No significant differences between the groups in response inhibition were detected.

The prevalence of epilepsy makes it important to broaden our knowledge on the profile of cognitive disorders in patients. We expect our findings to raise awareness of executive functions deficits in patients with temporal lobe epilepsy among specialists working with these patients, and to improve the scope and profile of medical and psychological care offered to them in terms of treatment methods, patient contact, and appropriate selection of neuropsychological rehabilitation. It is also worth taking care of such patients not only medically, offering them help in planning activities and expenses by social workers which could improve their everyday living.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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