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EXPLORING COGNITIVE IMPAIRMENTS IN DRUG-RESISTANT EPILEPSY: INSIGHTS FROM A COMPARATIVE ANALYSIS

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Abstract. This article explores the cognitive impairments in individuals with drug-resistant epilepsy compared to those with well-controlled epilepsy. The research involves 102 subjects (62 with drug-resistant epilepsy and 40 with well-controlled epilepsy), and examines cognitive functions such as verbal and visual memory, attention and language. Subjects were assessed with the MoCA test; the Rey Auditory Verbal Test; the Rey-Osterrieth Complex Figure; the Trail Making Test (parts A and B) and the F-A-S language test. Results show that cognitive deficits are three times more frequent in the drug-resistant epilepsy group, with significant impairments in verbal memory, visual memory, attention and semantic fluency. Additionally, drug-resistant epilepsy individuals, particularly those aged 50-59, with lower education, and more frequent seizures, exhibit more pronounced cognitive issues. These findings align with international research, confirming the strong correlation between seizure frequency and cognitive decline in epilepsy. The study highlights the need for personalized cognitive assessments and interventions for individuals with drug-resistant epilepsy.

Keywords: *cognitive impairments, drug-resistant epilepsy, well-controlled epilepsy.*

Rezumat. Articolul explorează particularitățile cognitive ale pacienților cu epilepsie farmacorezistentă, comparativ cu cei cu epilepsie medicamentos controlată. Cercetarea a inclus 102 subiecți, dintre care 62 au fost diagnosticați cu epilepsie farmacorezistentă și 40 cu epilepsie controlată medicamentos. Procesele cognitive evaluate au inclus memoria verbală, memoria vizuală, atenția și limbajul, utilizând teste standardizate precum MoCA, Test de memorie auditiv-verbală Rey, Figura Complexă Rey-Osterrieth, Testul Trail Making (părțile A și B) și testul de fluență verbală F-A-S. Rezultatele studiului au evidențiat că tulburările cognitive au fost de trei ori mai frecvente în grupul cu epilepsie farmacorezistentă, cu deficite semnificative în domeniile memoriei verbale, memoriei vizuale, atenției și fluenței semantice. Totodată, subiecții cu epilepsie farmacorezistentă, în mod particular cei cu vârste cuprinse între 50 și 59 de ani, cu nivel de educație mediu și cu o frecvență mai mare a crizelor, au prezentat tulburări cognitive mai severe. Studiul a subliniat necesitatea implementării unor evaluări cognitive detaliate și intervenții terapeutice personalizate pentru pacienții cu epilepsie farmacorezistentă, în vederea gestionării eficiente a tulburărilor cognitive asociate.

Cuvinte cheie: *tulburări cognitive, epilepsie farmacorezistentă, epilepsie medicamentos controlată.*

1. Introduction

According to data from the World Health Organization, approximately 50 million people worldwide suffer from epilepsy, with 30% of them being diagnosed with drug-resistant epilepsy [1]. The globally accepted definition, as established by the International League Against Epilepsy (ILAE), is that epilepsy is a brain disorder characterized by a long-standing predisposition to generate epileptic seizures, along with the neurobiological, cognitive, psychological, and social consequences of the condition. ILAE defines drug-resistant epilepsy as "the therapeutic failure of two or more correctly chosen antiepileptic drugs administered at adequate doses with the aim of achieving sustained seizure freedom" [2]. On the other hand, well-controlled epilepsy is defined as a response to treatment where patients are seizure-free or experience fewer than one seizure per year.

Cognitive disorders are the most common comorbidities associated with epilepsy [3, 4]. Recent studies indicate that cognitive deficits are already present at the onset of epilepsy [5-7]. While in cases of well-controlled epilepsy, cognitive impairments are more subtle, in drug-resistant epilepsy, cognitive deficits are observed in 70-80% of individuals [3]. There is growing awareness of the relevance of these comorbidities, as they significantly affect the prognosis of epilepsy, social life, and the overall quality of life of individuals living with epilepsy.

Epilepsy varies in terms of etiology, genetic factors, severity, chronicity, and treatment response. The relationship between seizures and cognitive dysfunction is complex and can be influenced by factors such as age, electroencephalographic abnormalities, disease onset and duration, seizure type, and frequency. In some cases, these factors can be more disabling than the seizures themselves [6, 8]. Depending on these variables and with advancing age, the impact on cognitive development differs. Altered cognitive abilities and performance in individuals with epilepsy often occur alongside ongoing seizures, as epilepsy and cognition are closely interconnected. These impairments may emerge simultaneously due to a shared pathological process or could exist in a bidirectional relationship. Recent studies indicate that cognitive deficits frequently precede the onset of epileptic seizures. The cognitive deficits observed at the onset of epilepsy typically include reduced memory, attention, processing speed, visual-spatial abilities, and executive function. Additional risk factors that may trigger or exacerbate cognitive impairment include repetitive brain trauma, episodes of status epilepticus, frequent seizures, and advancing age [6, 9]. Most studies suggest that the earlier the onset of epilepsy, the more pronounced the cognitive deficits [6].

The aim of this study is to investigate the cognitive characteristics of patients with drug-resistant epilepsy.

Objectives of the research: (1) to identify the cognitive characteristics associated with drug-resistant epilepsy, and (2) to compare the cognitive profiles of patients with drug-resistant epilepsy to those of patients with well-controlled epilepsy.

2. Materials and Methods

The research was conducted at the Institute of Emergency Medicine, National Centre of Epileptology. It involved 102 epilepsy patients aged 18-62, including 62 with drug-resistant epilepsy and 40 with well-controlled epilepsy, all diagnosed by an epileptologist. Individuals with dementia or severe cognitive impairment were excluded. The general characteristics of the experimental subjects are reflected in table 1.

Table 1

Presentation of general data of experimental subjects

General dates		**Drug-resistant**		**Well-controlled**	
		Number	*%*	*Number*	*%*
1. Number	Total subjects -102	62	62	40	38
2. Gender	Men	30	48	20	50
	Women	32	52	20	50
3.Age (years)	18-19	2	3	1	3
	20-29	18	29	16	40
	30-39	23	37	13	33
	40-49	15	24	7	18
	50-59	2	3	3	8
	60-69	2	3	0	0
4. Education	Secondary education	29	47	10	25
	Professional technical studies	18	29	6	15
	Higher education	15	24	24	60
5. Professional status	Employed	17	27	32	80
	Unemployed	43	69	6	15
	Pensioner	1	2	0	0
	Student	1	2	2	5
6.Marital status	Married	23	37	14	35
	Single	29	47	24	60
	Divorced	10	16	2	5
7. Living environment	Urban	33	53	21	53
	Rural	29	47	19	48
8. Disease duration (years)	0-9	3	5	15	38
	10-19	24	39	15	38
	20-29	26	42	6	15
	30-39	5	8	3	8
	40-49	3	5	1	3
	50-59	1	2	0	0
9. Etiology of epilepsy	Structural	43	69	25	63
	Unknown	13	21	12	30
	Genetic	6	10	3	8
10. Frequency of seizures	1 – 10/month	43	69	-	-
	11 – 20/month	5	8	-	-
	More than 20/month	14	23	-	-

To achieve the objectives proposed in this research, the methodology applied in the research included:

- *empirical methods*: 1) Montreal Cognitive Assessment Test (MoCA); 2) Rey Auditory Verbal Test (RAVLT); 3) Rey-Osterrieth complex figure (ROCFT); 4) Trail Making Test (TMT); 5) F-A-S language Test (phonemic and semantic fluency).

- *statistical methods*: analysis of frequencies and percentage values, comparison of means by descriptive statistics, difference of means by independent *T-test*.

3. Results and discussions

Results of the MoCA test

The MoCA test results categorize subjects into those with cognitive impaiment and without cognitive impairment. As shown in Figure 1, cognitive impairment was found in 20% of subjects with well-controlled epilepsy and 61% of those with drug-resistant epilepsy. The average MoCA score for subjects with drug-resistant epilepsy (m = 23.40, SD = 4.01) was 3.28 points lower than for those with well-controlled epilepsy (m = 26.68, SD = 2.35). A *t-test* confirmed this difference is statistically significant, indicating that individuals with drug-resistant epilepsy exhibit more cognitive impairment than those with well-controlled epilepsy.

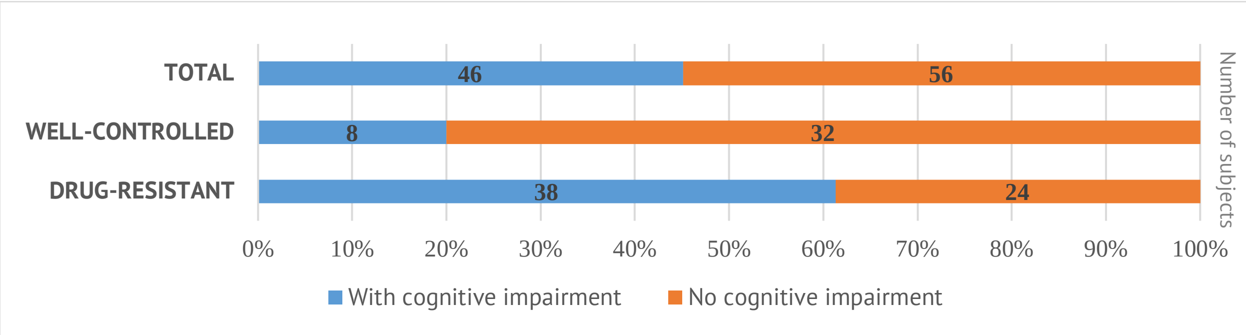

Figure 1. Distribution of subjects according to the MoCA CognitiveTest.

Cognitive impairment by demographic and clinical factors

Cognitive impairment by gender. The analysis reveals that cognitive impairment is more prevalent in women, both in subjects with drug-resistant epilepsy (65% of women vs. 60% of men) and in those with well-controlled epilepsy (25% of women vs. 15% of men).

*Cognitive impairment **by age***: Cognitive impairment is more pronounced in individuals with drug-resistant epilepsy across all age groups, with the highest prevalence (100%) observed in the 50-59-year age group, compared to 33% in well-controlled epilepsy patients of the same age.

*Cognitive impairment **by educational level***: The highest rates of cognitive impairment were found in individuals with secondary education: 79% in drug-resistant epilepsy and 60% in well-controlled epilepsy. Among those with professional-technical education, cognitive impairment was observed in 50% of drug-resistant cases and 40% of higher education subjects. In well-controlled epilepsy, cognitive impairment in these groups was minimal.

*Cognitive impairment **by professional status***: Cognitive impairment was more prevalent in unemployed individuals with drug-resistant epilepsy (70%) compared to employed subjects (47%). Similarly, in well-controlled epilepsy, 50% of unemployed subjects had cognitive disorders, versus 16% of employed subjects. Statistical analysis showed a significant difference (t = 5.77, p = 0.000), with employed subjects scoring higher on cognitive tests (m = 26.54, SD = 2.36) than the unemployed (m = 22.76, SD = 4.06).

*Cognitive impairment **by marital status***: Cognitive impairment was more common in married (59%), single (65%), and divorced (60%) individuals with drug-resistant epilepsy, while only divorced individuals with well-controlled epilepsy (50%) showed significant cognitive impairment. No significant cognitive differences were found between marital statuses (t = 0.82, p = 0.44).

Cognitive impairment ***by living environment***: Cognitive impairment was similarly prevalent in drug-resistant epilepsy subjects from both urban (61%) and rural (62%) areas, compared to well-controlled epilepsy subjects (10% urban, 32% rural).

Cognitive impairment ***by etiology****:* Cognitive impairment was most pronounced in individuals with structural epilepsy: 65% in drug-resistant cases vs. 24% in well-controlled cases. In those with unknown epilepsy, 62% of drug-resistant cases had cognitive deficits, compared to 8% in well-controlled cases. For genetic epilepsy, impairment was equally present in both groups (33%). Statistical analysis showed no significant differences across etiologies ($t = 1.49$, $p = 0.23$).

Cognitive impairment ***by duration of disease***: Cognitive impairment was significantly more common in drug-resistant epilepsy subjects (61%) compared to well-controlled subjects (20%). In the 0–9-year range, cognitive impairment was observed in 67% of drug-resistant cases, while only 13% of well-controlled epilepsy subjects showed impairment. The prevalence of cognitive disorders in well-controlled subjects increased with disease duration, reaching 33% in the 30–39-year range, while drug-resistant subjects remained at 67%.

Cognitive impairment ***by seizure frequency***: Higher seizure frequency correlated with more pronounced cognitive deficits. Among drug-resistant subjects, cognitive impairment was found in 56% of those with 1-10 seizures per month, 60% with 11-20 seizures, and 79% with more than 20 seizures per month. Well-controlled subjects had either no seizures or very rare occurrences (1 per 1-2 years).

Table 2 summarizes the MoCA test results for subjects with drug-resistant epilepsy and well-controlled epilepsy, stratified by gender, age, education, professional status, marital status, living environment, disease duration, epilepsy etiology, and seizure frequency.

Table 2

Presentation of MoCA Test results in subjects with drug-resistant epilepsy and subjects with well-controlled epilepsy

MoCA Test		**Drug-resistant epilepsy**		**Well-controlled epilepsy**	
		with cognitive impairment, %	no cognitive impairment, %	with cognitive impairment, %	no cognitive impairment, %
1. Number	Subjects (102)	61	39	20	80
2. Gender	Men	60	40	15	85
	Women	63	37	25	75
3. Age (years)	18-19	50	50	0	100
	20-29	44	56	19	81
	30-39	70	30	23	77
	40-49	67	33	14	86
	50-59	100	0	33	67
	60-69	50	50	0	0
4. Education	Secondary education	79	21	60	40
	Professional technical studies	50	50	0	100
	Higher education	40	60	8	92
5. Professional status	Employed	47	53	16	84
	Unemployed	70	30	50	50

Continuation Table 2

	Pensioner	0	100	0	0
	Student	0	100	0	100
6. Marital status	Married	59	41	17	83
	Single	65	35	21	79
	Divorces	60	40	50	50
7. Living environment	Urban	61	39	9	91
	Rural	62	38	32	68
8. Disease duration (years)	0-9	67	33	13	87
	10-19	54	46	27	73
	20-29	69	31	17	83
	30-39	60	40	33	67
	40-49	67	33	0	100
	50-59	0	100	0	0
9. Etiology of epilepsy	Structural	65	35	24	76
	Unknown	62	38	8	92
	Genetic	33	67	33	67
10. Frequency of seizures	1 – 10 / month	56	44	-	-
	11 – 20 /month	60	40	-	-
	> 20 / month	79	21	-	-

The statistical findings of our research align with the results of several international studies. For example, a study by Gavrilovic et al. (2019) on the impact of drug-resistant epilepsy duration on cognitive processes found significantly lower MoCA scores in individuals with drug-resistant epilepsy compared to those with well-controlled epilepsy. This study also demonstrated a negative correlation between disease duration and cognitive status, while seizure control positively correlated with MoCA performance [10]. Similarly, Wang et al. (2020) identified that higher education levels, seizure control, the use of a single antiepileptic drug, and emotional stability serve as protective factors for cognitive function, whereas low education, high seizure frequency, polytherapy, and depression negatively affect cognitive performance [11]. Furthermore, Montaño-Lozada et al. (2021) also using the MoCA test, concluded that people with epilepsy experience more pronounced cognitive impairments, particularly in memory and attention, compared to a control group without epilepsy [12].

Results of the RAVLT Verbal Memory Test

Significant differences were observed between subjects with drug-resistant epilepsy and those with well-controlled epilepsy on the RAVLT verbal memory test. In trials 1 to 6 and proactive interference (List B), the mean scores of subjects with well-controlled epilepsy were consistently higher than those with drug-resistant epilepsy, indicating better verbal memory performance in the former group. However, *t-test* results showed no significant differences for trials 1 (t = -1.4, p = 0.15), 2 (t = -1.5, p = 0.12), and 6 (t = -1.98, p = 0.051). In contrast, significant differences were found in trials 3 (t = -2.1, p = 0.04), 4 (t = -2.16, p = 0.03), 5 (t = -3.36, p = 0.001), and proactive interference (List B) (t = -3.08, p = 0.003). For recall (7), retention (8), and total RAVLT scores, subjects with well-controlled epilepsy again performed better, with significant differences confirmed by *t-test* values for recall (t = -2.6, p = 0.01), retention (t = -2.06, p = 0.042), and total RAVLT (t = -2.14, p = 0.035). The results suggest that verbal memory is more significantly impaired in individuals with drug-resistant epilepsy compared to those with well-controlled epilepsy. This is reflected in lower performance and efficiency in both initial reproduction and subsequent attempts to retain verbal material. Our findings on immediate verbal memory align with international research. For instance, I. Cano-López et al. (2018) identified verbal memory deficits in individuals with drug-resistant epilepsy [13], while M.G. Vaccaro et al. (2018) reported a distinct neurocognitive profile in these individuals, characterized by deficits in immediate verbal memory and recall [14].

Results on visual memory in individuals with epilepsy (ROCFT)

In the first phase of the figure-copying task, 30% of participants from both groups reached the 100th percentile, with 48% from the well-controlled epilepsy group and 19% from the drug-resistant epilepsy group. At the 90th percentile, 32% of subjects scored at this level, with 35% from the drug-resistant epilepsy group and 28% from the well-controlled epilepsy group. At the 80th percentile, only 18% of subjects achieved this level, with 10% from the well-controlled group and 23% from the drug-resistant group. Notably, the lowest performance (10th percentile) was observed in 10% of subjects, all of whom were from the drug-resistant epilepsy group (Figure 2).

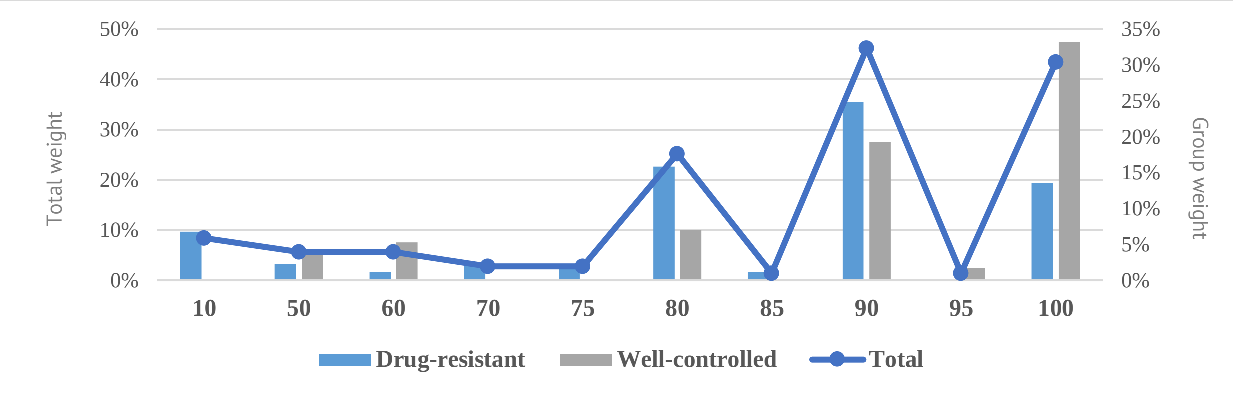

Figure 2. Rey-Osterrieth Complex Figure, phase I - Copying.

The mean score for figure copying in phase I was higher in subjects with well-controlled epilepsy (m = 89.63, SD = 14.52) compared to those with drug-resistant epilepsy (m = 78.95, SD = 25.22), with a difference of 10.68. The *t-test* value (t = -2.43, p = 0.017) indicates a statistically significant difference between the two groups. These results suggest that individuals with drug-resistant epilepsy face greater difficulties in planning, organizing, and accurately copying the figure, likely due to mental slowness, as well as deficits in concentration and attention.

In Phase II of the test, the reproduction of the Rey-Osterrieth complex figure from memory, only 2% of participants reached the 100th percentile, with 3% from the well-controlled epilepsy group and 2% from the drug-resistant epilepsy group. The majority (30%) scored at the 10th percentile, with 42% from the drug-resistant group and 13% from the well-controlled group. These findings indicate visual memory difficulties in both groups, with more pronounced deficits in the drug-resistant epilepsy group (Figure 3).

The mean score for figure reproduction in Phase II was significantly higher in subjects with well-controlled epilepsy (m = 56.25, SD = 26.55) compared to those with drug-resistant epilepsy (m = 32.18, SD = 25.44), with a difference of 24.07. The *t-test* value (t = -4.6, p = 0.00) indicates a statistically significant difference between the two groups. These results suggest that reproduction of the Rey-Osterrieth Complex Figure requires greater cognitive effort, involving visual-constructive skills, executive function, planning, abstraction, and sustained attention.

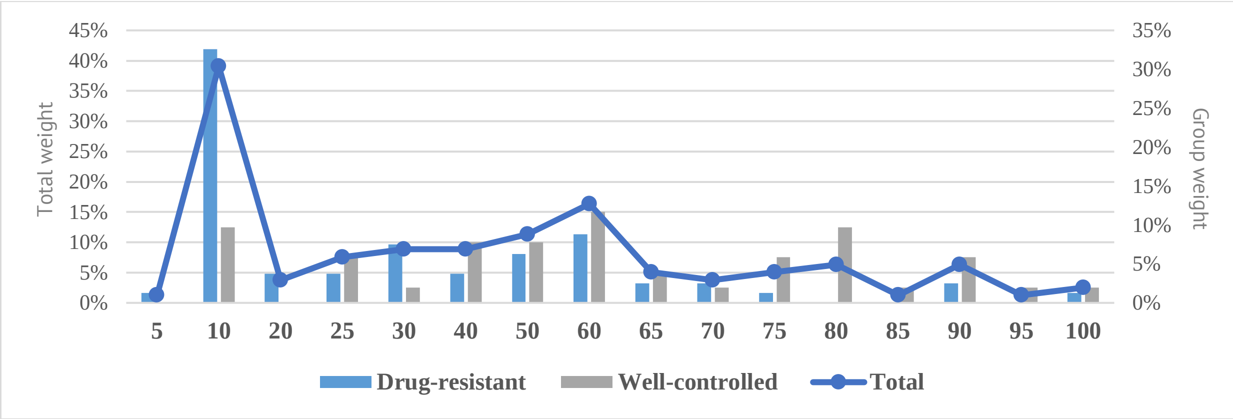

Figure 3. Rey-Osterrieth Complex Figure Test, phase II – Reproduction.

However, in the phase involving reproduction from memory, no significant differences were observed between the groups (t = 2.34, p = 0.102). This indicates that visual memory is similarly impaired in both the drug-resistant and well-controlled epilepsy groups.

The results of our research align with findings from international studies on this topic. For instance, B. Mathon et al. (2020) used the ROCFT to assess visual memory and psychomotor functions in individuals with drug-resistant epilepsy compared to healthy controls. Their study found that individuals with drug-resistant epilepsy performed worse in visuospatial memory, psychomotor functions, sustained concentration, and visual figure scanning. These cognitive deficits were linked to the severity of epilepsy, high seizure frequency, and antiepileptic medication use [15].

Attention results in individuals with epilepsy (Trail Making Test)

In the TMT part A, 45% of all subjects demonstrated a low level of attention, scoring at or below the 10th percentile. This was predominantly observed in the drug-resistant epilepsy group (50%) compared to the well-controlled group (38%). Only 8% of the total subjects reached the 80th percentile, with the majority being from the well-controlled epilepsy group (10%) (Figure 4).

In TMT part B, performance was significantly lower overall, with 74% of subjects scoring at or below the 10th percentile. This was notably higher in the drug-resistant epilepsy group (81%) compared to the well-controlled group (63%). Only 6% of subjects reached the 80th percentile (Figure 4).

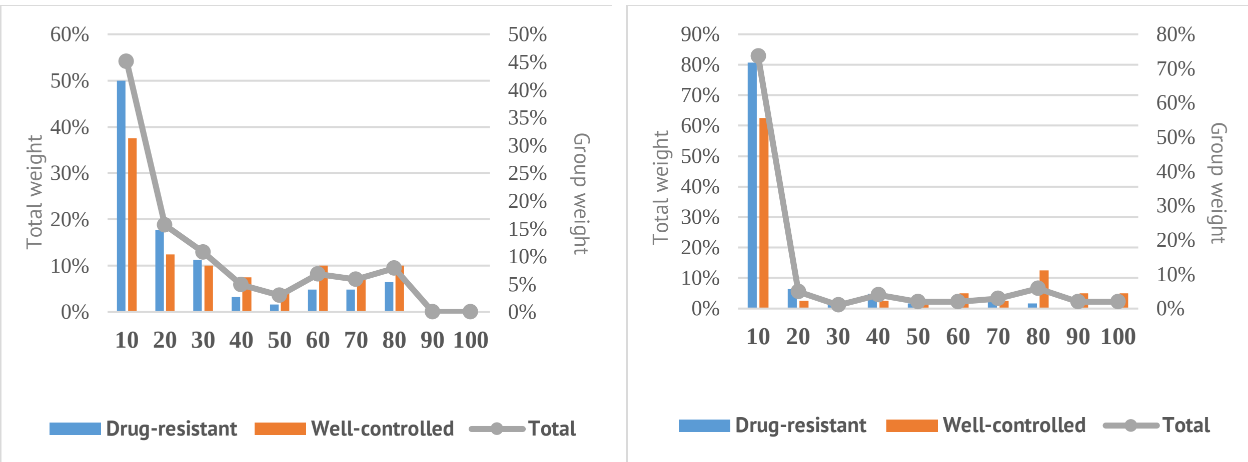

Figure 4. *TMT Test (Part A and B).*

In TMT part A, the mean score for subjects with drug-resistant epilepsy (m = 51.44, SD = 35.39) was 13.16 higher than that of subjects with well-controlled epilepsy (m = 38.28, SD = 18.08). The t-test results (t = 2.4, p = 0.015) indicate a statistically significant difference between the two groups.

In TMT part B, a larger difference of 72.07 was observed between the groups, with subjects with well-controlled epilepsy scoring lower (m = 115.08, SD = 75.00) compared to those with drug-resistant epilepsy (m = 187.15, SD = 116.46). The t-test value (t = 3.8, p = 0.00) confirmed this as a statistically significant difference.

These findings suggest that subjects with drug-resistant epilepsy exhibit poorer attention performance, likely due to uncontrolled seizures, the use of multiple antiepileptic drugs, and the impact of these factors on cognitive processes and reaction speed. Additionally, low attention may correlate with factors such as lack of motivation, sleep disturbances, and depression, which were present in 56% of subjects with drug-resistant epilepsy, as we will further discuss.

Language performance in individuals with epilepsy (F-A-S test)

In the *phonemic fluency test*, 49% of all subjects presented low phonemic fluency, with 50% of drug-resistant epilepsy subjects and 48% of well-controlled epilepsy subjects scoring at this level.

Regarding the *semantic fluency test*, both groups showed low verbal fluency, with 89% of drug-resistant and 88% of well-controlled subjects scoring at or below the 10th percentile. Only 10% of the total subjects reached the 50th percentile, and just 1% reached the 90th percentile (Figure 5).

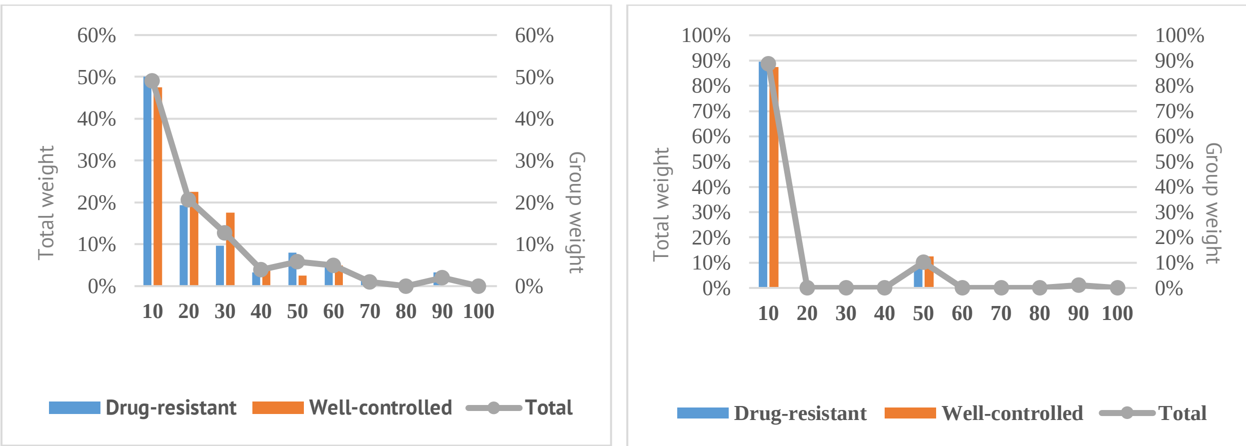

Figure 5. *Phonemic and semantic fluency (F-A-S test).*

In subjects with well-controlled epilepsy, mean scores for both phonemic fluency and semantic fluency were higher by 1.35 and 2.37 points, respectively, compared to subjects with drug-resistant epilepsy. The *t-test* for phonemic fluency revealed no significant difference between the groups (t = -0.64, p = 0.5). However, the *t-test* for semantic fluency indicated a significant difference, with subjects with well-controlled epilepsy performing better (t = -2.87, p = 0.005).

Recent studies on cognitive impairment in epilepsy provide valuable insights. A. B. Bjorke et al. (2021) examined cognitive deficits in adults with temporal lobe epilepsy without structural brain lesions, finding impairments in visual memory and executive function (TMT and verbal fluency tests) at the onset of the disease. However, no significant differences were observed in verbal memory, attention, or processing speed [5].

C. Helmstaedter (2017) analyzed three studies involving 500 adults with drug-resistant epilepsy, revealing that over 70% exhibited cognitive deficits, particularly in memory, attention, and executive function. Key predictors of cognitive impairment included education level, epilepsy etiology, and the presence of generalized tonic-clonic seizures [3].

F. Tabibian et al. (2023) investigated the impact of structural brain lesions on cognitive performance in drug-resistant epilepsy. Their findings indicated that subjects with hippocampal sclerosis performed better on cognitive tests (including ROCFT, Verbal Fluency, RAVLT and TMT) than those with atrophic lesions or cortical dysplasia [16]. Additionally, retrospective studies indicate that prolonged epilepsy duration is associated with more pronounced cognitive decline [3,18].

A recent study by N. Doțen *et al.* (2021) at the National Centre for Epileptology in Chisinau identified several predictive factors for cognitive impairment in drug-resistant epilepsy, including low education level, polytherapy with more than four antiepileptic drugs, depression, and the absence of structural brain lesions [19]. Similarly, Novak et al. (2022) found that cognitive impairment in drug-resistant epilepsy is influenced by factors such as early onset of epilepsy, high seizure frequency, frequent interictal discharges, low education level, and polytherapy with antiepileptic drugs [9].

4. Conclusions

The results of our study highlight significant cognitive impairments in individuals with drug-resistant epilepsy, with these deficits occurring three times more frequently compared to those with well-controlled epilepsy. Statistically significant differences were found in verbal memory, visual memory, semantic fluency, attention, and executive function, whereas phonemic fluency did not show significant differences. Cognitive impairments were more pronounced in individuals with drug-resistant epilepsy who were aged 50-59 years, female, had secondary education, were unemployed, single, and had epilepsy of unknown or structural etiology. Additionally, most individuals with drug-resistant epilepsy with cognitive impairment experienced more than 20 seizures per month. Cognitive deficits were evident early in the disease course, although no significant differences were observed based on gender or living environment.

Conflict of interest: The author declares no conflict of interest.

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