Doctoral School in Medical Sciences

Manuscript title
UDC: 616.853-072.8-073.7(043.2)

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CLINICAL-NEUROPHYSIOLOGICAL PECULIARITIES OF EPILEPSY WITH MYOCLONIC SEIZURES

321.05 – CLINICAL NEUROLOGY

Summary of Ph.D. Thesis in Medical Sciences

Chisinau, 2024

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CONCEPTUAL FRAMEWORK OF THE RESEARCH

The actuality of the subject and the importance of the studied problem.

Seizures and epileptic syndromes have a high rate of prevalence and incidence, affecting all ages and all races of both sexes. They are an important part of the clinical practice of doctors. People suffering from epilepsy are among the most vulnerable in any society. The stigmatization of these patients is widespread throughout the world and leads to discrimination and people with epilepsy suffer from discriminatory behavior in many domains of life such as limitations in the economic, social and cultural rights. According to the International League Against Epilepsy (ILAE) in 2014 [1], epilepsy is considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy affects approximately 1% (65–70 million) of the global population. About 10% of the population will experience a seizure at some point in their lifetime.

In developed countries, epilepsy occurs most commonly in children and elderly, while in developing countries, epilepsy occurs in adolescents and young adults [2]. ILAE claims that there are 6 million people with epilepsy in Western and Central Europe. The incidence of epilepsy in Germany is 2.9%, in Great Britain varies between 0.3 - 6.49%, and in Sweden 5%. According to other sources, the incidence of epilepsy in developed countries is about 50 per 100.000. The incidence of unprovoked seizures varies across Europe from 33.6 in Sweden to 68.8 per 100.000 in Denmark. According to the National Clinical Protocol "Epilepsy in Adults", the prevalence of epilepsy in the Republic of Moldova in 2015 was 16 cases per 1.000 inhabitants [3]. Statistical data presented by the National Health Management Center of the Republic of Moldova show a total prevalence across the country (excluding the eastern districts) of 16.4 cases per 10.000 inhabitants (5.815 patients) in 2016, and 25.3 cases per 10.000 inhabitants (6.627 patients) in 2021. The incidence presented by the National Center for Health Management for the last years: 2016 – 1.8 per 10.000 population, 2017 – 1.9 per 10.000 population, 2018 – 1.8 per 10.000 population, 2019 – 1.7 per 10.000 population, 2020 – 2.0 per 10.000 population and 2021 – 2.1 per 10.000 population.

People with epilepsy have a higher risk of sudden death, with a reported annual incidence of 1 in 1.000. For those with uncontrolled epilepsy, the incidence is as high as 1 in 200, but the lowest incidence is in children, 0 - 0.2 per 1.000. The risk of sudden death is higher in women - 1.45 per 1.000 compared to men - 0.98 per 1000. The number of people diagnosed with epilepsy worldwide is increasing together with the increase in risk factors: trauma, alcohol consumption, obstetric pathology, etc. Accurate diagnosis is the golden rule in medicine. Epilepsy represents many syndromes and disorders that have a multitude of different causes and manifestations [2]. Epileptic syndromes and epilepsy present a major clinical polymorphism, which frequently induce considerable problems for diagnosis and differential diagnosis. Defining the type of epilepsy should be mandatory, as it provides information on management, disease prognosis and selection of treatment strategies [4]. Myoclonic seizures often remain unrecognized due to their semiologic polymorphism, both from a clinical and neurophysiological point of view. Moreover, myoclonic epilepsies usually remain underdiagnosed. In a study investigating the effect of sleep deprivation on slow-wave spike discharges in patients with idiopathic generalized epilepsy (IGE), the greatest

activation of epileptiform discharges was observed during the light sleep after sleep deprivation [5]. Sleep after sleep deprivation caused an increase in slow-wave spike discharges at all levels of vigilance, including wakefulness. The highest degree of activation was observed in superficial sleep phases (non-REM1 and non-REM2b) [6, 7]. Myoclonic epilepsy is manifested by the presence of involuntary, sudden and short muscle contractions (duration 10-50 ms.), of cortical origin, associated with ictal (poly)spike-and-wave EEG discharges, time-locked with and preceding EMG recording muscle contraction [8]. The prevalence of epilepsy with myoclonic seizures studied in Latin America, Honduras, Medina was 2.2% of all epilepsies, and in Iceland studies showed a 2% rate of generalized myoclonic seizures.

Short-term and long-term management of epilepsy is achieved by the related syndromes and differs significantly between the different syndromes, thus emphasizing the need for an accurate diagnosis. Unspecified diagnosis in epilepsies usually leads to avoidable morbidity and sometimes mortality [9]. Health services need to include information on the accessibility and availability of services, the degree to which evidence-based treatments are provided, and details of possible human rights violations [10].

Involvement of stakeholders in planning and development of the epilepsy healthcare system, epilepsy legislation or in the review and reform of existing legislation that affects the lives of people with epilepsy is crucial to ensure that the health system and legislation meet the different needs of patients as effectively as possible [11]. Each country is unique and has its own needs, cultures and conditions, as well as having legislative conventions that may differ.

In the Republic of Moldova, successes were achieved in the restructuring of the Epileptology service, under the auspices of Academician Stanislav Groppa, where a particular progress was made by the transition of the epileptology service from the psychiatric healthcare system to the neurological one and creation of the National Center of Epileptology (NEC), from December 30, 2011. Following the order of the Ministry of Health (no. 1027), patients with epilepsy were transferred under the NCE management, within the Institute of Emergency Medicine (IEM).

Aim of the study: To study the clinical, neurophysiological and imaging characteristics of myoclonic epileptic seizures in order to identify the pathophysiological aspects and brain networks involved in the epileptogenesis of generalized myoclonic seizures.

Objectives of the study:

1. Studying the clinical features of patients with generalized myoclonic seizures;
2. Studying the neuropsychological profile of patients with generalized myoclonic seizures;
3. Evaluation of electroencephalographic patterns of patients with generalized myoclonic seizures;
4. Morphometric study of brain structures in patients with generalized myoclonic seizures;
5. Identifying the brain network organization abnormalities involved in the epileptogenesis of generalized myoclonic seizures.

Research hypothesis: Patients with generalized myoclonic seizures show distinct clinical, neurophysiological and imaging characteristics, which are conditioned by the particularities of brain network organization.

The general methodology of the research: The research was organized and carried out at the Department of Neurology no. 2 within the State University of Medicine and Pharmacy (SUMPh) „Nicolae Testemitanu", at the National Center of Epileptology and at Epileptology Department of the of the Institute of Emergency Medicine, with the permission of the administration of the respective institution for the collection and processing of primary data, during

the 2015 – 2021 years. The research project was approved by the Research Ethics Committee of the SUMPh „Nicolae Testemitanu" (no. 47/52 from 14.03.2017).

Scientific novelty and originality: a study on cerebral mechanisms of epileptogenesis was carried out with the assessment of the source of epileptiform activity in generalized myoclonic seizures, as well as of neurophysiological, neuroimaging and cerebral connectivity features.

The important scientific problem solved in the thesis: resides on identifying the clinical-neurophysiological polymorphism in association with neuroimaging alterations and modular organization of brain networks in epilepsy with generalized myoclonic seizures.

The theoretical importance of the thesis: Determination of clinical-neurophysiological and neuroimaging correlations to identify the pathophysiology and brain networks involved in the generation of generalized myoclonic seizures.

The applicative value of the work: The usefulness of video-EEG data in correlation with MRI data in detecting the trigger phenomenon during the transition to interictal and ictal states in patients with generalized myoclonic seizures was demonstrated.

Implementation of the results: The results of the study were implemented and utilized in the didactic process at the Department of Neurology no. 2 and in the Laboratory of Neurobiology and Medical Genetics of the SUMPh "Nicolae Testemitanu", as well as in the Department of Epileptology and NCE within the Institute of Emergency Medicine.

Approval of the scientific results: scientific results obtained during the study were presented, discussed and published at different scientific forums:

- International Congress of "Apollonia" University from Iasi "Preparing the future by promoting excellence" XXXIV edition. Iasi, Romania. 29 February – 3 March 2024
- 13th ILAE forum on Pre-Surgical Evaluation for Epilepsy and Epilepsy Surgery (EPODES Advanced II). Brno, Czech Republic. 22-26 January 2024.
- XXXI national conference with international participation of the Romanian Society Against Epilepsy. Bucharest, Romania. November 23-25, 2023.
- International Congress of "Apollonia" University from Iasi "Preparing the future by promoting excellence" XXXIII edition. Iasi, Romania. 2–5 March 2023.
- International Congress of "Apollonia" University from Iasi "Preparing the future by promoting excellence" XXXII edition. Iasi, Romania. February 28 - March 2, 2022.
- SUMPH Days Annual Conference, Research in Biomedicine and Health: Quality, Excellence and Performance. Chisinau, Republic of Moldova, 2022.
- International Congress of "Apollonia" Iasi University "Preparing the future by promoting excellence" edition XXXI. Iasi Romania. March 1-3, 2021.
- SUMPH Days Annual Conference, Research in Biomedicine and Health: Quality, Excellence and Performance. Chisinau, Republic of Moldova. 20–22 October 2021.
- VII Congress of neurologists from the Republic of Moldova. Chisinau, Republic of Moldova. 16–18 September 2021.
- 8th International Medical Congress for Students and Young Doctors MedEspera. Chisinau, Republic of Moldova. 24–26 September 2020.
- International Congress of "Apollonia" University - "We are preparing the future by promoting excellence" XXX edition. Iasi, Romania. February 27 - March 1, 2020.
- XXVII Conference of the Romanian Society Against Epilepsy. Bucharest, Romania. 14–16 November 2019.

- International Conference on Nanotechnology and Biomedical Engineering IV edition. Chisinau, Republic of Moldova. 19–21 September 2019.
- Conference of the Romanian Society against Epilepsy. Sucevita, Romania. 11–13 July 2019.
- International Congress of "Apollonia" University from Iasi "Preparing the future by promoting excellence" XXIX edition. Iasi, Romania. February 28 - March 3, 2019.
- The Annual Scientific Conference of Young Specialists within IEM "Performances and Perspectives in Medical-Surgical Emergencies", dedicated to the International Day of Science for Peace and Development. Chisinau, Republic of Moldova. November 8, 2019.
- Days of the State University of Medicine and Pharmacy "Nicolae Testemițanu" The annual scientific conference of the scientific and teaching staff, doctoral students, master's students, residents and students. Chisinau, Republic of Moldova. 15-18 October 2019.
- The Scientific Conference "News in the treatment of nervous system pathologies" within the Moldmedizin-Molddent International Specialized Exhibition XXV edition. Chisinau, Republic of Moldova. 11–13 September 2019.
- 33rd International Epilepsy Congress. Bangkok, Thailand. June 22-26, 2019.
- International Congress of "Apollonia" University from Iasi "We are preparing the future by promoting excellence" XXIX edition. Iasi, Romania. February 28 - March 3, 2019.
- 9th International Forum of Epileptologists of the CIS countries "Epilepsy and paroxysmal states" Rostov-on-Don, Russia. 26–27 October 2018.
- IVth Eastern European Epilepsy Course. Chernihiv, Ukraine. 13-15 June 2018.
- IVth Congress of Radiologists from the Republic of Moldova with international participation. Chisinau, Republic of Moldova. 31 May – 2 June 2018.
- The annual scientific conference of scientific and didactic staff, doctoral students, master's students, residents and students of SUMPH "Nicolae Testemițanu". Chisinau, Republic of Moldova. 15–19 October 2018.
- The scientific conference of young specialists from IEM "Performances and perspectives in medical-surgical emergencies. Chisinau, Republic of Moldova. May 18, 2018.
- 13th European Congress on Epileptology. Vienna, Austria. August 26-30, 2018.
- The International Congress for Students and Young Doctors - the 7th edition - MedEspera. Chisinau, Republic of Moldova. 3–5 May 2018.
- The National Conference of Neurosciences with international participation, the Reunited Congress of Neurology, the Iasi - Chisinau Symposium 2017, the 15th edition. Iasi Romania. October 19-22, 2017.
- The 3rd Eastern European Epilepsy Course. Borovets, Bulgaria. July 5-8, 2017.
- University Days and the annual scientific conference devoted to the 90th anniversary of the birth of the illustrious doctor and scientist Nicolae Testemițanu. Chisinau, Republic of Moldova. 18–20 October 2017.
- Annual scientific conference of IEM young specialists "Performances and perspectives in medical-surgical emergencies". Chisinau, Republic of Moldova. May 26, 2017.
- The 6th Congress of Neurologists and Neurosurgeons from the Republic of Moldova and the Day of the European Academy of Neurology in the Republic of Moldova. Chisinau, Republic of Moldova. 3–5 October 2017.
- The 24th SRIE National Conference "Treatment in Epilepsy", Bucharest, Romania. 18–19 November 2016.

- East European Course of Epilepsy", Cheile Gradistei, Romania. 15–17 June 2016.
- Salzburg Weill Cornell Seminar In Neurology. Austria. 28 February–5 March 2016.

Publications: 35 scientific papers were published on the topic of the thesis, including 13 articles, of which 5 articles in journals with impact factor (IF), article with the highest IF=7.046; 4 publications as a single author, presentations and abstract communications at 9 national scientific conferences and 18 international conferences and congresses. 5 invention patents, 4 implementation documents, 2 national clinical protocols were authorized.

Summary of the thesis sections: the thesis is written on 99 pages of basic text; includes 39 figures, 28 tables and 3 appendices; it is composed of the introduction, 5 chapters of which 3 – contain own material, general conclusions, practical recommendations and bibliography with 318 references. The research was carried out based on the favorable opinion of the Research Ethics Committee of the Nicolae Testemitanu State University of Medicine and Pharmacy (no. 47/52 of 14.03.2017) and of the head of the Institute of Emergency Medicine, where the research was carried out.

Key words: myoclonic epilepsy, clinical polymorphism, neurophysiology, morphological changes, brain network connectivity.

THESIS CONTENT

1. MODERN CONCEPTS IN THE FIELD OF EPILEPSY WITH MYOCLONIC SEIZURES

Juvenile myoclonic epilepsy (JME) has been recognized as a common epileptic syndrome worldwide with an estimated incidence of 1 in 100.000 persons and a prevalence of 0.1 to 0.2 per 100.000. The prevalence of JME in large cohorts has been estimated at 5% to 10% of all epilepsies and is the most common (18%) of all IGE syndromes. Generalized myoclonic seizures are more common on awakening and therefore frequently occur in the morning. Myoclonus is a brief, sudden, involuntary, shock-like muscle contraction. The strongest triggers of generalized myoclonic seizures are sleep deprivation and fatigue. Cognitive and affective disorders are the most common psychiatric comorbidities in epilepsy with a negative impact on individual and professional mental functioning, reducing the quality of life of epilepsy patients [12]. Efficiency of antiepileptic drugs ranges from 60% to 90%. The prognosis of JME is generally considered excellent, as most patients can be successfully treated with antiepileptic drugs but recurrences are frequent. The triad of absence seizures, myoclonic seizures and GTCS shows a characteristic age-related onset in JME [13, 14]. GTCS are usually preceded by a series of myoclonic jerks of increasing severity, and this seizure type is most commonly associated with myoclonic seizures [15]. Other studies demonstrate that the therapeutic outcome in drug-resistant generalized epilepsy is highly dependent on the individual connectivity profile, involving the cerebello-thalamo-cortical circuits [16] and pro-/anticonvulsant neural systems [17], as well as on the correctly selected treatment [18]. Electroencephalography remains the most useful assessment of patients with suspected JME revealing normal background activity and specific interictal spike-slow waves and polyspike waves [19]. Magnetic resonance imaging (MRI) contributes particularly to the etiological diagnosis. Conventional evaluation of MRI usually does not show any pathological changes in JME. However, emergence of high-resolution MRI with a dedicated protocol for epilepsy has significantly increased the value of the application of this technique in the identification of pathological substrates [20]. There are conflicting findings regarding the brain

regions involved in the epileptogenesis of generalized myoclonic seizures. Connectivity measures are increasingly used to investigate the integrity of brain networks in epilepsy [21, 22]. Studies have revealed specific patterns of increase and decrease in connectivity but do not clarify how these complex systems are organized and tell us little about the underlying mechanisms that drive these connectivity alterations.

2. MATERIAL AND RESEARCH METHODS

In order to achieve the purpose and objectives of the research, a descriptive study was conducted that included two groups of patients with epileptic seizures: one with generalized myoclonic seizures that included 40 patients and second with focal clonic seizures, also consisting of 40 patients. Inclusion criteria of the study were: written informed consent, patients with generalized myoclonic and focal clonic seizures, age >18 years. Exclusion criteria were: lack of written informed consent, age <18 years, somatic pathology in the decompensated phase, abuse of alcohol and psychoactive substances. Investigation methods applied in the study were: questionnaire, neurological examination, neuropsychological examination, video-EEG, high density EEG (HD-EEG), MRI, and neural network analysis *(figure 1)*. For quantitative values, mean, median, standard deviation (SD) and interquartile range were calculated. For the qualitative values, 95% confidence intervals for the significance was calculated. The SPSS software (version 21.0; IBM, Armonk, NY, USA) was used to compare the differences between the studied groups. Differences between continuous variables were assessed by Student's T-test in case of normal distribution of data or Mann-Whitney test in case of non-normal distribution. Statistical analysis of neuroimaging data was also performed by using MATLAB 2015a software (Mathworks, Natick, Mass).

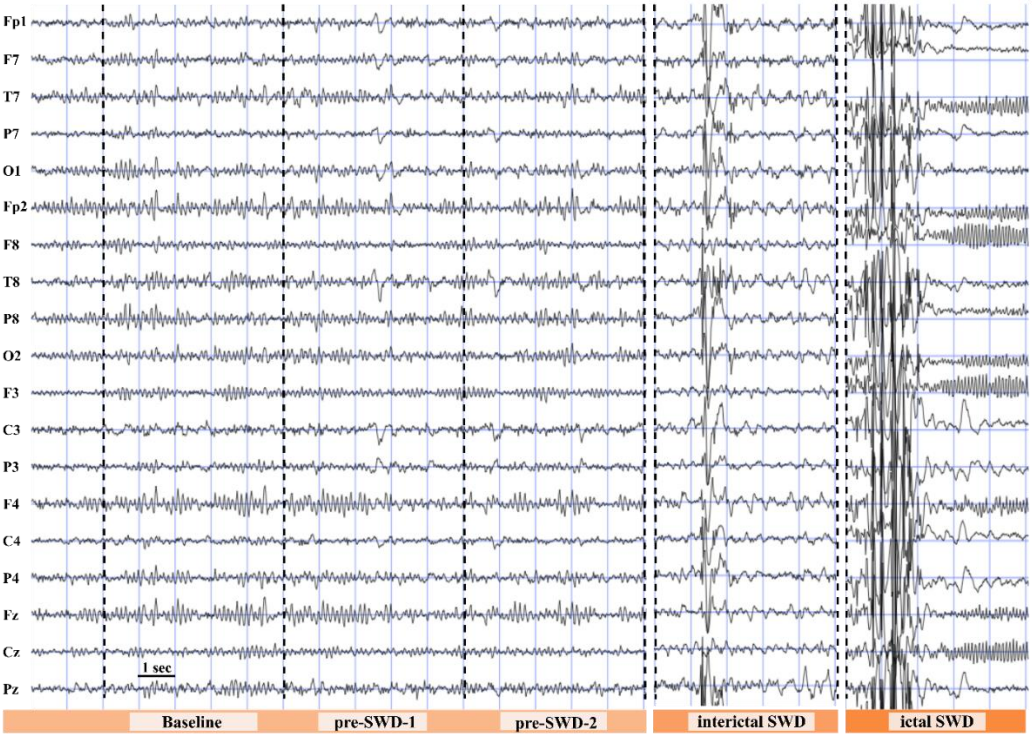

Figure 1. **The analyzed time periods. HD-EEG recordings were epoched into non-overlapping 5-s time windows - two periods before the interictal or ictal spike wave discharges (SWDs), pre-SWD-1 and pre-SWD-2 time windows, and one interictal or ictal time window.**

Distribution of variables was analyzed by the Shapiro-Wilk test. The research design and applied methods allowed the characterization and differentiation of clinical, neurophysiological and imaging features in patients with generalized myoclonic seizures compared to patients with focal clonic seizures, as well as the features of modular organization and dynamic measures of neural networks.

3. NEUROPHYSIOLOGICAL CHARACTERISTICS OF PATIENTS FROM THE STUDIED GROUPS

3.1. General characteristics of the study group

Mean age (± SD) at the time of investigation of the subjects in the study group diagnosed with generalized myoclonic seizures was 24.6 ± 7.3 years (median = 22.0; IIQ = 12; 15 men), being younger compared to the control group with focal clonic seizures (32.6 ± 9.7 years (median = 32.0; IIQ = 13; 15 men), the difference being statistically significant ($p < 0.001$). In order to identify other age characteristics, we analyzed the average age at disease onset, which in the study group was 13.5 ± 6.4 years (median = 14.0; IIQ = 7), and in the control group was 17.2 ± 12.4 years (median = 15.0; IIQ = 19), which did not represent a statistically significant difference ($p = 0.09$). The next age characteristic was the average age of the first seeking of medical help due to these seizures, which in the study group was 14.6 ± 8.1 years (median = 14.0; IIQ =7), and in the control group 17.3 ± 12.4 years (median = 15.5; IIQ = 19) ($p = 0.25$). Evaluating the time elapsed from the moment of disease onset to the request for medical help, the addressability to medical help was delayed in patients from the study group compared to patients from the control group. This fact is probably based on the different initial clinical symptomatology, which in most patients from the study group started with poorly manifesting and underestimated myoclonic seizures, compared to the control group, in which the onset is usually more clinically pronounced. Patients with a minimum age of 18 years were enrolled in both groups, and the maximum age was different: 44 years in the study group and 63 years in the control group, shown in *table 1*.

Table 1. **Distribution of patients according to age and gender**

Groups	Parameters	number		Mean age at disease onset (years)	Mean age at first visit to physician (years)	Mean age at the time of study (years)	Minimum age at the time of study (years)	Maximum age at the time of study (years)
		Absolute	%					
Group I, n = 40	Male	15	37.5	13.5±6.4 (median= 14.0; IIQ=7)	14.6±8,1 (median =14.0; IIQ=7)	24.6±7.3 (median= 22.0; IIQ=12)	18	44
	Female	25	62.5					
Group II, n = 40	Male	15	37.5	17.2 ±12.4 (median= 15.0; IIQ=19)	17.3±12.4 (median =15.5; IIQ=19)	32.6±9.7 (median= 32.0; IIQ=13)	18	63
	Female	25	62.5					
p value				0.09	0.25	0.001		

3.2. Neuropsychological features

Neuropsychological comorbidities are frequently encountered in patients with epilepsy and have a negative impact on individual and professional mental functioning, reducing the quality of life of these patients. Thus, in this study we aimed to evaluate the prevalence of cognitive and affective disorders (depression and anxiety) in patients with generalized myoclonic seizures and to compare these data with the neuropsychological status of patients with focal clonic seizures.

The Montreal cognitive assessment (MoCA) test was used to assess the cognitive functions. For the assessment of affective domains, the Hamilton anxiety assessment scale (HAM-A), as well as the Beck depression inventory (BDI-II) [23] (*table 2*) were applied.

Table 2. **Demographic and clinical parameters of the groups**

Parameters	Patients with generalized myoclonic seizures	Patients with focal clonic seizures	p value
MoCA, mean ± SD	25.2±4.6 (median=27.0; IIQ=3)	25.7±3.5 (median=27.0; IIQ=3)	0.592
Hamilton, mean + SD	9,9±6,7 (median=8,0; IIQ=8)	11.2±8.7 (median=10.0; IIQ=10)	0.477
Beck, mean + SD	8,7±6,6 (median=7,0; IIQ=5)	9.9±8.4 (median=7.0; IIQ=6)	0.466

The level of depression and anxiety was similar between the groups, probably these comorbidities occur in all patients with epilepsy regardless of epilepsy type – generalized or focal. Cognitive disorders also showed no differences between the groups and the duration of epilepsy did not significantly influence the cognitive and affective state of patients in both research groups.

3.3. Clinical and neurophysiological characterization by video-EEG

In more than half of the patients in the study group, generalized myoclonic seizures with electrographic correlation were recorded, more frequently in the awake state (n=16), mainly in the first minutes after the awakening. Video-EEG ictal polyspike and slow-wave spike discharges had almost the same frequency (n=11) and (n=12), respectively (*table 3*).

Table 3. **Location of generalized myoclonic seizures and their association with video-EEG ictal epileptiform discharges in the study group**

Location of myoclonus	Video-EEG discharges		95% CI
	polyspike-slow wave	spike-slow wave	
Right upper limb	1 (4.4%)	2 (8.6%)	0.05–0.29
Left upper limb	1 (4.4%)	0 (0%)	0.001–0.13
Both upper limbs	6 (26.0%)	7 (30.5%)	0.43–0.75
Right lower limb	1 (4.4%)	0 (0%)	0.001–0.13
Upper + lower limbs	2 (8.6%)	3 (13.1%)	0.05–0.29

Interictal video-EEG discharges were observed both during awake and sleep, more than half of patients (n=24) had discharges both during awake and sleep. In addition to generalized

discharges, during the interictal period focal discharges were also identified in a proportion of 26.3% (95% CI=0.14-0.43) in the awake state and 40% (95% CI=0.24-0.56) during sleep, the most frequent being focal spike-slow wave discharges. The most common frequency of photoparoxysmal response in the study group was at 20 Hz. In 3 (27.3%; 95% CI=0.01-0.20) patients, generalized myoclonic seizures were recorded during the photostimulation test, at 10 Hz in one patient and at 20 Hz in two patients (*figure 2*).

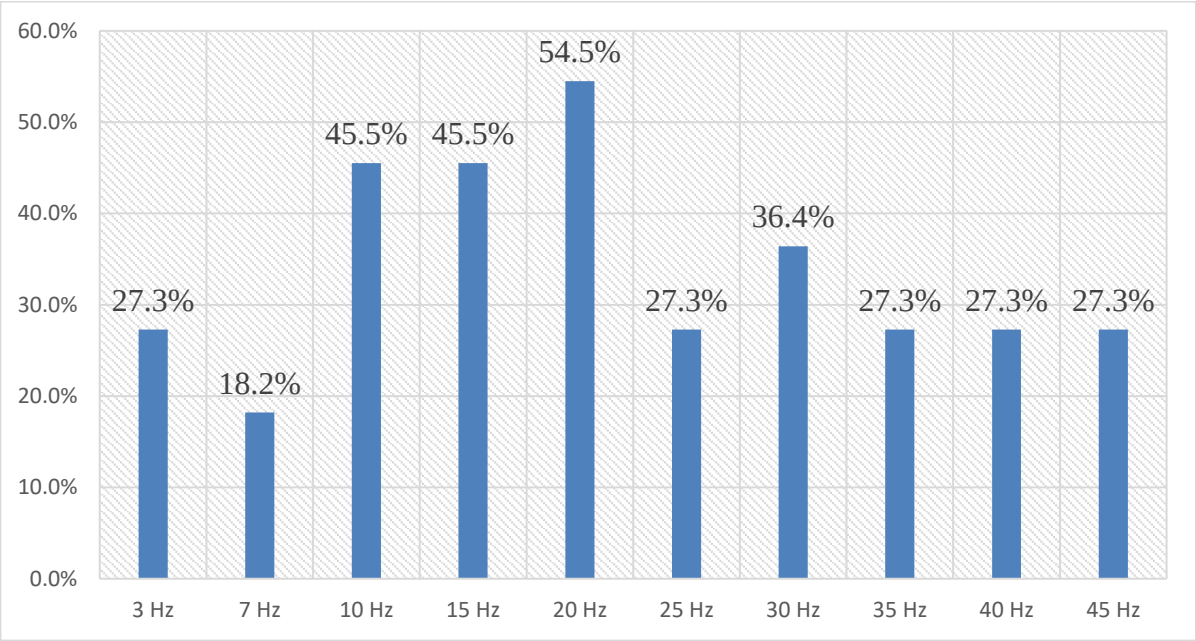

Figure 2. **Photoparoxysmal response in patients of the study group**

The patients in whom no ictal video-EEG recordings was obtained, from the patient history it was identified that most of them presented seizures in both upper limbs. A notable heterogeneity in the clinical-electrophysiological correlation was also identified. Thus, generalized myoclonic seizures occurred at different times of generalized ictal discharges (first, middle, or last third) and at different intervals of the polyspike-slow wave complex (spike and slow wave portions). Most often myoclonus started in the middle of the generalized discharge (39.1%; 95% CI=0.10-0.38) and after analyzing the moment of onset on the polyspike-slow wave complex, a higher frequency was revealed at the beginning of the slow wave of the polyspike-slow wave complex (30.5%; 95% CI=0.07-0.32).

3.4. Neurophysiological characterization by high-density EEG

In all cases, the frontal lobe was identified as the electrical source of epileptiform discharges [24, 25], more frequently in the Brodmann area 6 (33%; 95% CI=0.18-0.49) and 11 (20%; 95% CI=0.09-0.35), which is consistent with the fronto-thalamic hypothesis of discharges in the JME (*figure 3*). In the control group, several electrical sources were identified, mainly in the temporal lobe (*figure 4*).

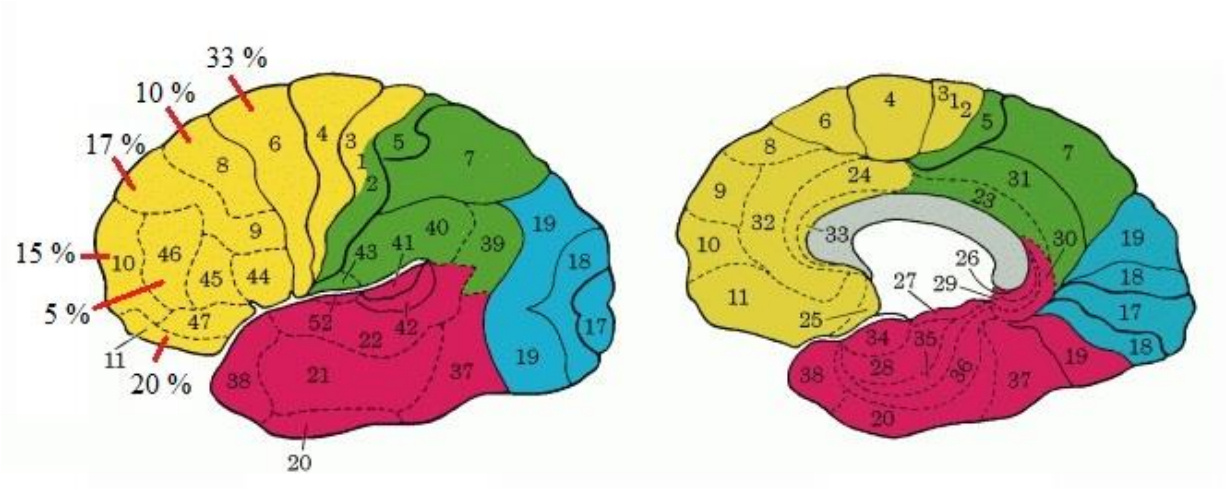

Figure 3. **Localization of electrical sources of generalized interictal discharges according to Brodmann areas in the study group**

Figure 4. **Localization of electrical sources of interictal discharges according to Brodmann areas in the control group.**

Characterizing the particularities of the myoclonic seizures exposed above, we can ascertain the existence of a multidimensional polymorphism, which included the clinical (semiological), electrophysiological, topographical and circadian domains. Thus, the clinical polymorphism of generalized myoclonic seizures was manifested by the differential involvement of the extremities during the ictal period - the involvement of either the upper limbs or the lower limbs or both. The predominant form being the one with the involvement of both upper limbs. Electrophysiological polymorphism was reflected by the variety of both generalized and focal epileptiform discharges and by the variety of frequency (Hz)-dependent photostimulation response. Therefore, ictal/interictal epileptiform discharges ranged from polyspike-slow-wave discharges (the most common) to spike-wave discharges. It is notable that a heterogeneity in the clinical-electrophysiological correlation was also identified. Taking into account the close connection between the generation of epileptiform discharges and the wake-sleep cycle, we can note the presence of a circadian polymorphism, that is, the appearance of epileptiform discharges during wakefulness, during sleep, or in both states.

The topographic polymorphism was expressed by the distinct localization of the electrical sources of generalized discharges - Brodmann areas 6/8/9/10/11/46. This variety of cortical locations as sources of generalized discharges could explain the variety in the extremities involved (i.e., clinical polymorphism), the diversity of epileptiform discharges (i.e., electrophysiological polymorphism), and the correlation between myoclonic generalized seizure onset and generalized discharge interval (i.e., clinical-electrophysiological polymorphism).

4. NEUROIMAGING CHARACTERIZATION OF PATIENTS FROM THE STUDIED GROUPS

4.1. General neuroimaging data

Our aim was to quantify cortical and subcortical volumes as well as to assess cortical thickness in patients with generalized myoclonic seizures. For this purpose, the patients with generalized myoclonic seizures included in the study were examined by 3T MRI, according to a predefined epilepsy protocol, by means of the Siemens Magnetom Skyra scanner [26, 27] The MRI results of these patients were examined in comparison with the standardized model of the healthy adult brain from the Open Access Series of Imaging Studies 3 (OASIS-3) repository (*table 4*) [28]. Technical MRI acquisition parameters in the OASIS-3 repository were similar to MRI parameters in patients with generalized myoclonic seizures.

Table 4. **Demographic data in patients with generalized myoclonic seizures compared to the standardized healthy adult brain model examined by MRI**

	Patients	The standardized model of healthy adult brain	p value
Number of subjects	N = 40	N = 40	
Gender (female/male)	25/15	26/14	0,65
Age (years)	24,6 ± 7,3 (median = 22,0; IIQ=12)	23 ± 5,0 (median = 23,0; IIQ=6)	0,17
Handedness (right/left-handed)	37/3	38/2	0,41

4.2. Brain morphometry (cortical thickness and volume, subcortical volume)

a) Cortical thickness analyzed in patients with generalized myoclonic seizures, as epileptiform discharges are mainly generated by the cortex, showed statistically significant regional differences in patients with generalized myoclonic seizures compared to the standardized model of the healthy adult brain in the following clusters of the left hemisphere: the orbital cortex (p max. 4.36), the medio-rostral caudal cortex (p max. -5.30) and the precentral gyrus (p max. -4.18), and in the right hemisphere the supramarginal gyrus (p max. -7.14), after correction for multiple comparisons using Monte Carlo permutation at a statistical threshold of $p < 0.05$ (*table 5 and figure 5*).

Cortical thickness correlated negatively with the age of patients with generalized myoclonic seizures (the older the age, the smaller the cortical thickness) in the following clusters: in the left hemisphere - the opercular part and the superior frontal gyrus, and in the right hemisphere - caudal medio-rostral and superior frontal.

At the same time, the cortical thickness negatively correlated with the duration of epilepsy in patients with generalized myoclonic seizures in the following clusters: in the left hemisphere - the superior frontal gyrus, and in the right hemisphere - the pericalcarine gyrus.

As patients with generalized myoclonic seizures were sensitive to the photostimulation test during video-EEG in a significant proportion (27.5%; 95% CI=0.14–0.43), differences in cortical thickness were analyzed between patients with and without photoparoxysmal response. A statistically significant difference was identified in the cortical thickness of the medial orbitofrontal gyrus of the left hemisphere, and no statistically significant differences were identified in the right hemisphere.

Cortical thickness differences in relation to gender in patients with generalized myoclonic seizures were also analyzed. Thus, a statistically significant difference was identified in the superior frontal gyrus of both hemispheres.

Table 5. **Clusters of statistically significant differences in cortical thickness between patients with generalized myoclonic seizures and the standardized model of the healthy adult brain with maximum p-values (log(10)), surface area (mm^2) and Talairach coordinates (Tal)**

Cluster number	*p*-max	Size (mm^2)	Tal X	Tal Y	Tal Z	Clusters
Left hemisphere						
1.	-5,30	1086,53	-29,90	11,80	44,40	medio-frontal caudal
2.	4,36	2190,69	-36,60	33,50	-10,00	orbital part
3.	-4,18	1118,55	-52,10	-5,60	18,90	precentral gyrus
Right hemisphere						
1.	-7,14	2692,11	59,30	-37,90	26,70	supramarginal gyrus

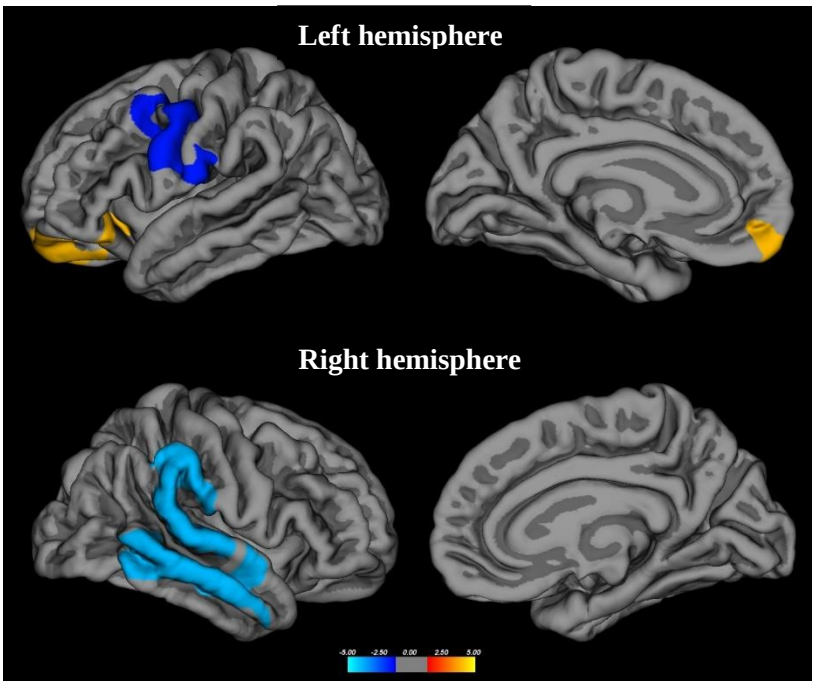

Figure 5. **Clusters of statistically significant differences in cortical thickness between patients with generalized myoclonic seizures and the standardized model of the healthy adult brain (corrected for multiple comparisons by Monte Carlo method, p < 0.05, Z = 1.3)**

b) Cortical volumetry identified that compared to the standardized model of the healthy adult brain, patients with generalized myoclonic seizures presented significantly smaller cortical volumes in the following clusters: superior parietal, postcentral cortex and fusiform cortex of the left hemisphere; the middle temporal cortex of the right hemisphere and the precentral, superior frontal and precuneal cortex of both hemispheres (all $p < 0.05$, corrected by the Monte Carlo method) (*table 6 and figure 6*).

Table 6. **Clusters of statistically significant differences in regional cortical volumes between patients with generalized myoclonic seizures and the standardized model of the healthy adult brain, with maximum p-values (log(10)), surface area (mm^2) and Talairach coordinates (Tal)**

Cluster number	*p*-max	Size (mm^2)	Tal X	Tal Y	Tal Z	Clusters
Left hemisphere						
1.	-6.13	875.23	-29.70	-47.60	49.00	superior parietal
2.	-5.94	6076.56	-50.30	-20.40	32.90	postcentral
3.	-4.45	1064.66	-24.60	-11.00	52.90	precentral
4.	-3.92	737.82	-23.00	17.60	46.30	upper frontal
5.	-3.69	667.55	-35.30	-8.60	-31.20	fusiform
6.	-3.35	681.04	-10.00	-49.90	59.20	precuneus
Right hemisphere						
1.	-8.88	8748.10	60.00	-22.00	-15.30	middle temporal
2.	-5.62	3619.41	52.50	-0.20	40.90	precentral
3.	-5.32	2243.37	8.00	12.30	59.20	upper frontal
4.	-3.77	972.97	5.50	-62.30	36.90	precuneus

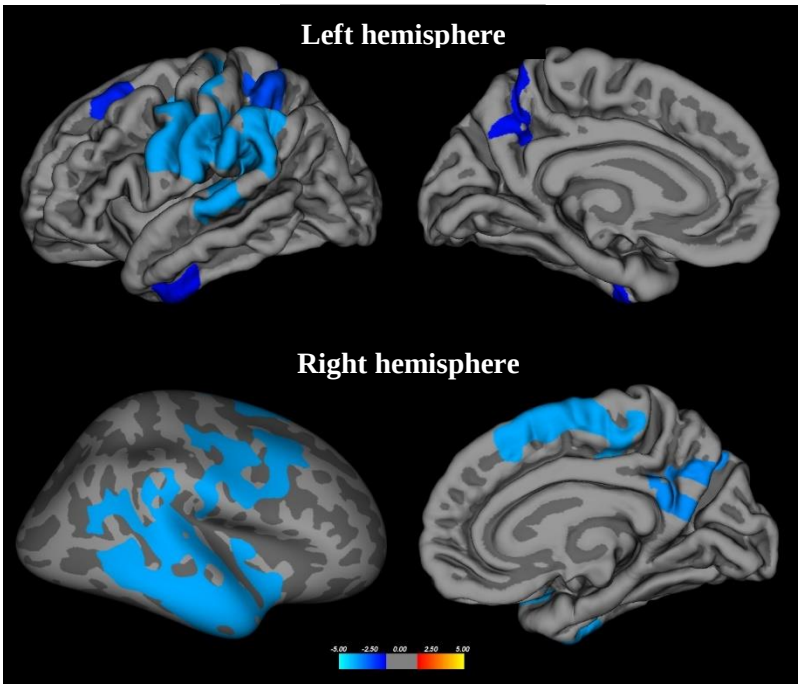

Figure 6. **Clusters of statistically significant differences in cortical volume between patients with generalized myoclonic seizures and the standardized model of the healthy adult brain (corrected for multiple comparisons by Monte Carlo method, $p < 0.05$, $Z = 1.3$).**

Cortical volume correlated negatively with the age of patients with generalized myoclonic seizures in the following clusters: superior frontal in the left hemisphere and medial orbitofrontal in the right hemisphere. Regional cortical volumes also correlated with epilepsy duration in patients with generalized myoclonic seizures in the following clusters: superior frontal gyrus of the left hemisphere and cuneus of the right hemisphere.

The difference in cortical volumes in relation to gender of patients with generalized myoclonic seizures was also investigated. Thus, statistically significant differences were identified in the insular cortex, precentral gyrus, medio-rostral frontal gyrus, superior parietal and superior temporal gyrus of the left hemisphere. In the right hemisphere, differences were determined in the rostral anterior cingulate gyrus, superior frontal gyrus, lateral occipital, insular and precuneal gyrus.

Hemispheric cortical volumes were also analyzed both in patients with generalized myoclonic seizures and in the standardized model of the healthy adult brain. Thus, in patients with generalized myoclonic seizures the average hemispheric volume on the right was 236709.60 mm^3 and on the left was 236723.70 mm^3. In the standardized model of the healthy adult brain, the average hemispheric volume on the right was 245522.21 mm^3 and on the left was 259647.95 mm^3. The reported differences did not reach the threshold of statistical significance ($p > 0.05$).

c) Subcortical volumetry revealed that in patients with generalized myoclonic seizures compared to the standardized model of the healthy adult brain, the volume of the thalamus both in the right hemisphere (7043.8 ± 921.8 mm^3; median = 7043.8; IIQ = 607 vs. 8148.6 ± 720.4 mm^3, median = 7807.0; IIQ = 963, $p < 0.05$), as well as in the left hemisphere (7697.9 ± 1045.5 mm^3, median = 7764.9; IIQ = 469 vs. 9205.4 ± 1151.4 mm^3, median = 95369; IIQ = 2022, $p < 0.05$) was significantly lower (*figure 4.10*). A lower volume of the bilateral caudate nucleus was also identified in patients (right: 3542.9 ± 598.1 mm^3, median = 3542.9; IIQ = 456 / left: 3536.6 ± 575.2 mm^3, median = 3557.8; IIQ = 490), compared to the standardized model of the healthy adult brain (right 3817.4 ± 451.1 mm^3, median =3778.8; IIQ =470 / left 3960.0 ± 438.9 mm^3, median = 3886.3; IIQ = 621, both $p < 0.05$); (*figure 7*).

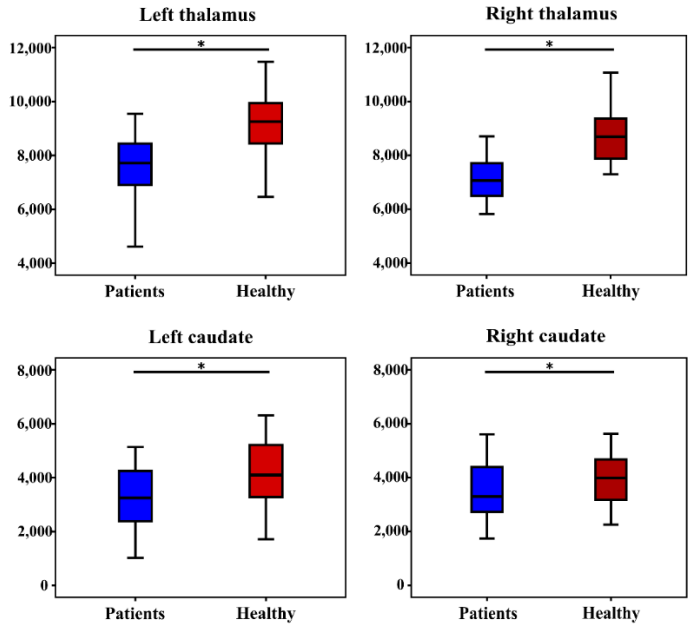

Figure 7. **Differences in the left and right thalamus and caudate nucleus volumes in patients with generalized myoclonic seizures (CM) and the standardized model of the healthy adult brain (p<0.05)**

Alterations of cortical morphometry (thickness, volume) in patients with generalized myoclonic seizures are associated with bilateral reduction of thalamus volume, supporting the hypothesis of the involvement of aberrant cortico-thalamic structures in myoclonic epilepsy. However, the data obtained suggest that structural changes may not be limited to the thalamus and cortex, but may also affect the basal ganglia. These findings highlight clear widespread abnormalities of brain structural integrity related to generalized myoclonic seizures and represent the neuroanatomical fingerprints that may underlie the generation of this type of seizure.

5. MODULAR ORGANIZATION AND DYNAMIC CONTROLLABILITY OF BRAIN NETWORKS

5.1. Intramodular connectivity of brain networks

Using HD-EEG recordings in patients with generalized myoclonic seizures, the organization and dynamic properties of brain network modules (communities) during the transition from the resting state to the interictal and ictal state were investigated. Several modules comprising specific cortical and subcortical regions were identified, depending on the analyzed time periods of the HD-EEG recordings represented in figure 1.

Network communities before and during interictal discharges. Analyzing the interictal discharges in HD-EEG in the beta frequency, six modules were identified in the baseline time period, the same six modules were identified in the pre-SWD-1 time period (*figure 8 A*). In the pre-SWD-2 time period, two additional modules (to the 6 modules identified in the previous time periods) were detected: module 7 and 8 (*figure 8 B*). Two additional modules were identified during the SWD-interictal time period: module 9 and 10 (*figure 8 C*). Respectively, in the beta frequency, in the SWD-interictal time period a total of 10 modules were identified.

Analyzing interictal HD-EEG discharges in the gamma frequency, the same six modules were identified in the baseline and in the pre-SWD-1 time periods (*figure 8 A*), module 7 was identified in the pre-SWD- 2 and module 9 in the interictal SWD time period. Respectively, in the gamma frequency, in the interictal SW- time period a total of 8 modules were identified.

Network communities before and during ictal discharges. Analyzing the ictal discharges in HD-EEG in the beta frequency, it was identified that in the time windows preceding these ictal discharges, namely the pre-SWD-1 and pre-SWD-2 time window had the same modules as those detected before the interictal discharges. During the ictal SWD time window, an additional module comprising basal ganglia (without thalamus) was detected, including the caudate nucleus, putamen, and globus pallidus (*figure 8 D*). The same module was detected in the gamma frequency during the ictal SWD time window. Respectively, in beta and gamma frequencies, a total of 9 modules were identified during the ictal SWD time period.

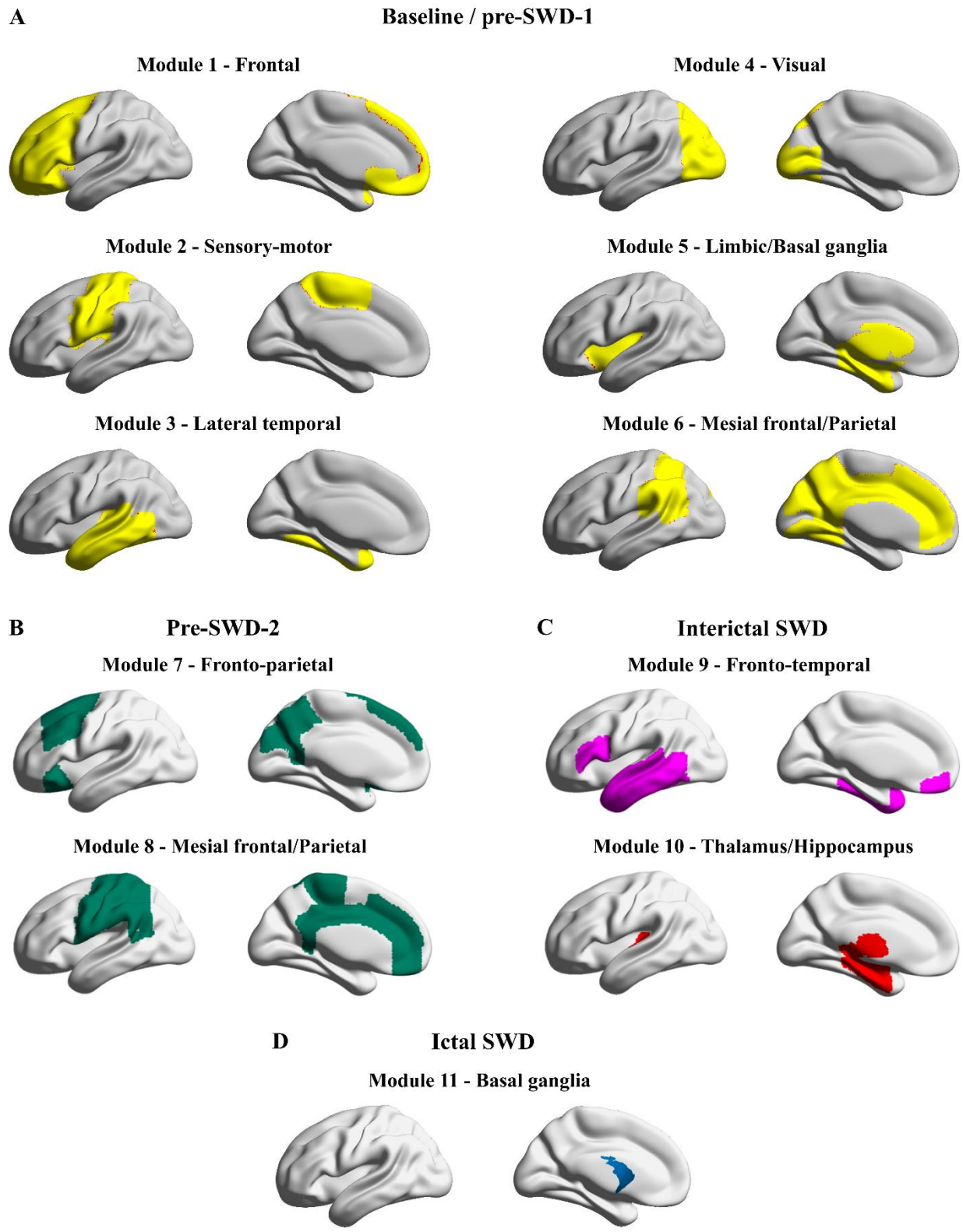

Figure 8. **Network communities identified in the baseline time window and pre-SWD-1, pre-SWD-2, interictal SWD, and ictal SWD time windows.**

5.2. Intermodular connectivity of brain networks

No significant differences were identified in the clustering coefficient between the modules detected in the baseline and the pre-SWD-1 time periods in beta and gamma frequencies of the HD-EEG recordings *(figure 9)*.

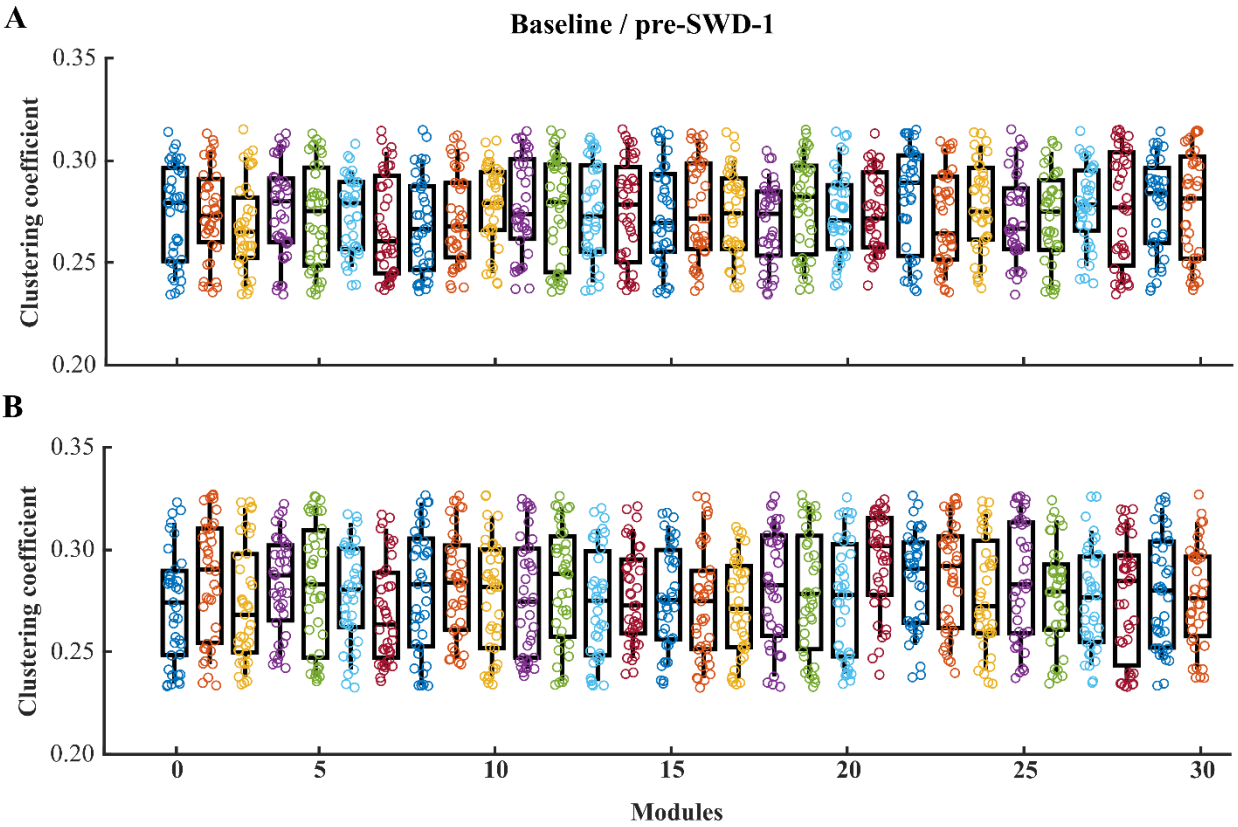

Figure 9. **Clustering coefficient in the baseline and in pre-SWD-1 time periods in the beta (A) and gamma (B) frequency bands; for all comparisons p>0.05.**

An opposite frequency-dependent dynamics of the clustering coefficient between modules was identified in the four time windows. Thus, in the beta frequency the clustering coefficient was lower between the modules identified in the time windows pre-SWD-2 ($F(1, 39) = 3.2$, $p<0.05$), interictal SWD ($F(1, 39) = 8.8$, $p<0.001$) and ictal SWD ($F(1, 14) = 27.2$, $p<0.001$) compared to the preceding time windows *(figure 10)*.

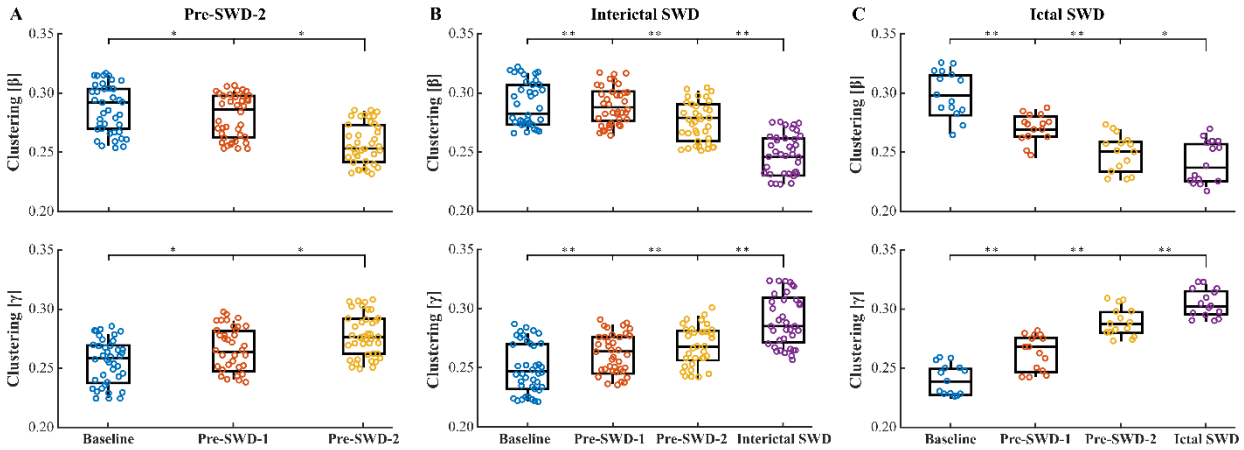

Figure 10. **Intermodular network topology in pre-SWD-2, interictal SWD and ictal SWD time periods (beta and gamma frequencies).** Clustering coefficient between modules identified in the pre-SWD-2 (A), interictal SWD (B) and ictal SWD (C) time windows compared to the preceding time periods; *p<0.05 and **p<0.001.

A higher clustering coefficient was observed in the gamma frequency between the modules identified in the pre-SWD-2 ($F(1, 39) = 7.0$, $p<0.001$), interictal SWD ($F(1, 39)$ time periods) = 12.8, $p<0.001$) and ictal SWD ($F(1, 14) = 76.5$, $p<0.001$) time windows compared to the preceding time periods *(figure 10)*.

5.3. Controllability and flexibility of brain networks

We studied the dynamic properties of network communities, namely flexibility and controllability during the transition from resting to interictal and ictal states using HD-EEG recordings in patients with generalized myoclonic seizures. Controllability is the ability of a network to be switched from its current state to a target state, and flexibility is the frequency with which a functionally defined region of interest changes its assigned community over time.

Analyzing the dynamic properties in beta frequency, no statistically significant differences (all $p>0.05$) were identified in flexibility and controllability measures within the six modules detected in the pre-SWD-1 time period compared to the baseline *(figure 11)*.

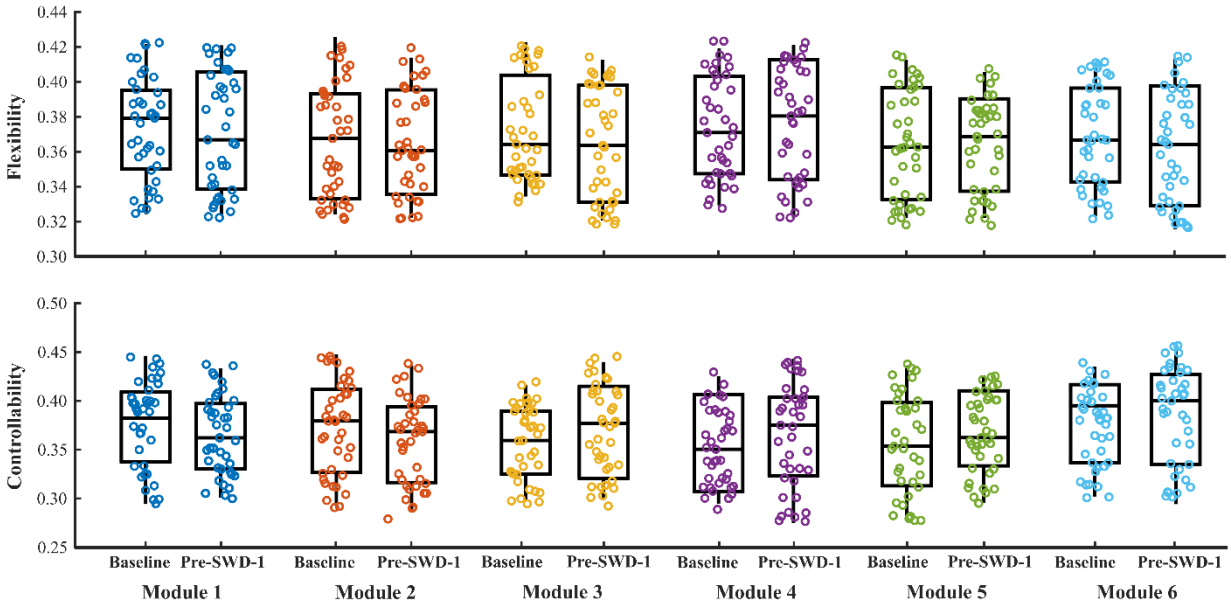

Figure 11. **Flexibility and controllability in the baseline and pre-SWD-1 time periods (beta frequency)**

However, during the pre-SWD-2 time window, flexibility was found to be significantly decreasing ($F(1, 39) = 39.9$, $p<0.001$; $F(1, 39) = 31.3$, $p<0.001$) and controllability increasing ($F(1, 39)$) = 21.7, $p<0.001$; $F(1, 39) = 19.3$, $p<0.001$) in modules 7 and 8 compared to the baseline and pre-SWD-1 time periods (*figure 12 A*). Similarly, during the interictal SWD time window flexibility decreases ($F(1, 39) = 13.6$, $p<0.001$; $F(1, 39) = 27.7$, $p<0.001$) and controllability increases ($F(1, 39) = 17.3$, $p<0.001$; $F(1, 39) = 11.2$, $p<0.001$) in modules 9 and 10 compared to the preceding time periods (*figure 12 B*). Decreased flexibility ($F(1, 14) = 30.6$, $p<0.001$) and increased controllability ($F (1, 14) = 59.8$, $p<0.001$) were again identified in the ictal SWD time window within the module 11 compared to earlier time windows *(figure 12 C)*.

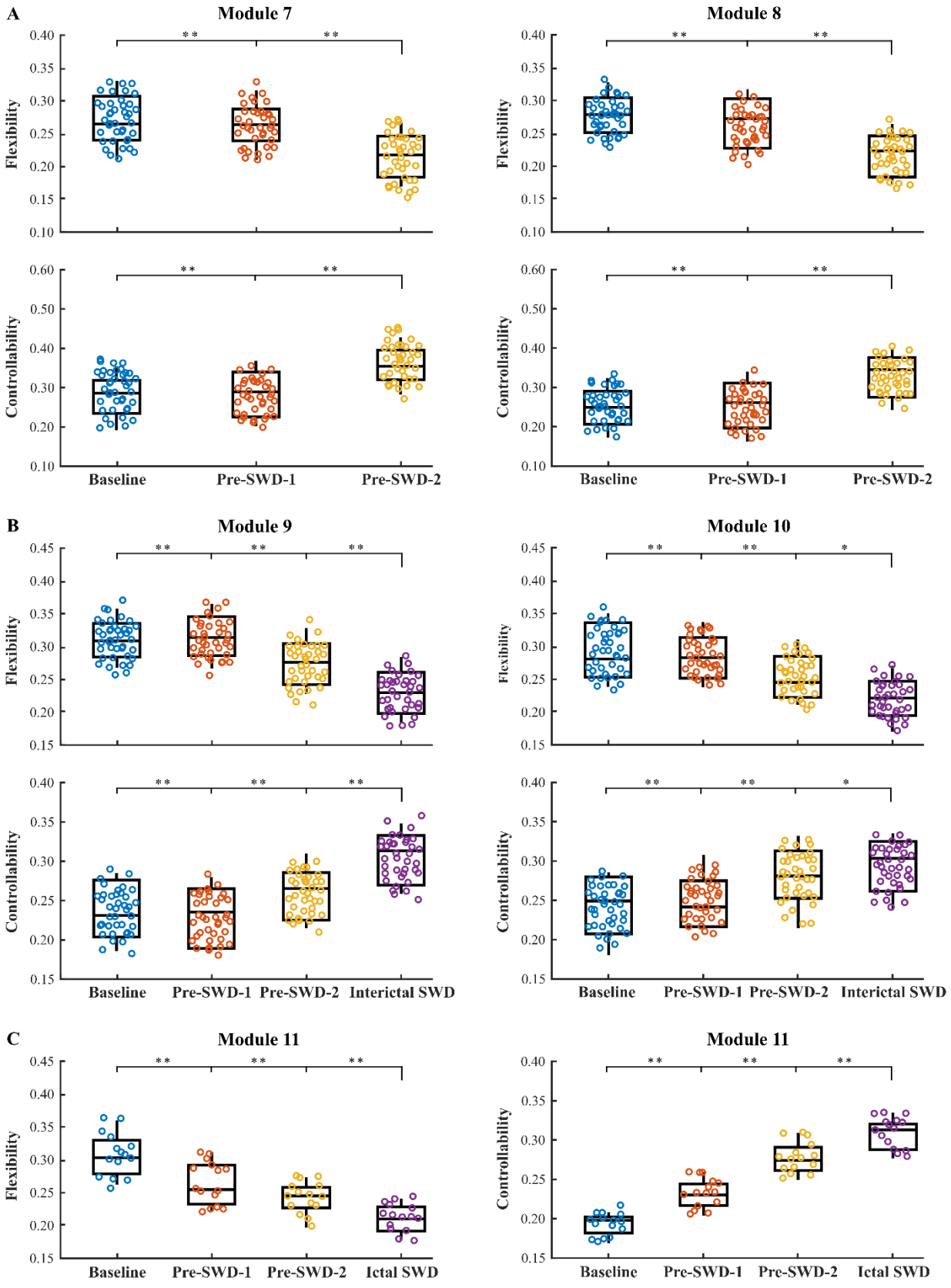

Figure 12. **Flexibility and controllability in the pre-SWD-2, interictal SWD and ictal SWD time windows (beta frequency).** Decreased flexibility and increased controllability in modules 7 and 8 in the pre-SWD-2 time window (A), modules 9 and 10 in the interictal SWD time window (B), and module 11 in the ictal SWD time window (C) ; *p<0.05, **p<0.001.

Analyzing the dynamic properties in the gamma frequency, no statistically significant differences (all $p>0.05$) were identified in the measures of flexibility and controllability (all $p>0.05$) within the six modules detected in the pre-SWD-1 compared to the baseline period of HD-EEG recordings.

Within the module 7 identified in the pre-SWD-2 time window, opposite dynamics was detected with significantly increasing flexibility ($F(1, 39) = 34.8$, $p<0.001$) and decreasing controllability ($F(1, 39) = 77.9$, $p<0.001$) compared to the baseline and the pre-SWD-1 time windows *(figure 13 A)*. Similar dynamics of flexibility ($F(1, 39) = 14.5$, $p<0.001$) and controllability ($F(1, 39) = 13.1$, $p<0.001$) were identified within the module 9 from the interictal SWD time window compared to previous time windows *(figure 13 B)*. Also, module 11 network changes during the ictal SWD time window were marked by decreased flexibility ($F(1, 14) = 46.1$, $p<0.001$) and increased controllability ($F(1, 14) = 58.9$, $p<0.001$) compared to previous time windows *(figure 13 C)*.

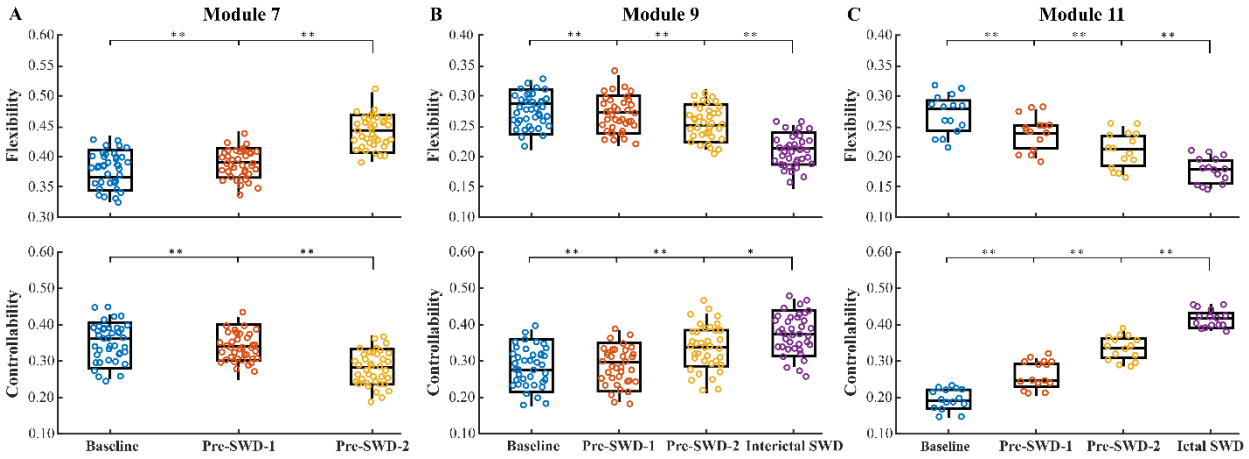

Figure 13. **Flexibility and controllability in the pre-SWD-2, interictal SWD and ictal SWD time window (gamma frequency).** Increased flexibility and decreased controllability within the module 7 of the pre-SWD-2 (A) time window. Opposite dynamics in module 9 of the interictal SWD time window (B) and module 11 of the ictal SWD time window (C); *p<0.05, *p<0.001.

Approaching brain network abnormalities in patients with myoclonic seizures, we demonstrated a modular organization of communities in cortico-subcortical networks during the transition to interictal and ictal states. These changes were accompanied by dynamic changes in the flexibility of the fronto-parietal networks in beta frequency, with evidence of increased controllability immediately before ictal discharges. This indicates that fluctuations in beta frequency could initiate a trigger phenomenon in functional segregation that is further supported by the increased clustering coefficient. The timing of observed changes in brain connectivity could serve as diagnostic and prognostic markers, while also contributing to the development of innovative, targeted, brain state-dependent therapies.

GENERAL CONCLUSIONS AND PRACTICAL RECOMMENDATIONS

GENERAL CONCLUSIONS

1. The results of the study demonstrated that generalized myoclonic seizures present a clinical polymorphism, expressed both by the variety of body distribution of the myoclonus and by the association with other types of seizures, predominantly with generalized tonic-clonic seizures, in 85% of cases. Generalized myoclonic seizures predominantly involved both upper limbs, representing 60% of cases.
2. The level of depression and anxiety was not different between the groups ($p>0.05$), probably these comorbidities occur in all patients with epilepsy regardless of the type of epilepsy – generalized or focal. Cognitive disorders also showed no differences between groups, the duration of epilepsy did not significantly influence the cognitive and affective state of patients in both research groups, but the presence of depression correlated with the presence of cognitive disorders ($p>0.05$).
3. Myoclonic seizures with electrographic correlation were registered in more than half of the patients (57.5%; 95% CI=0.41-0.73) in the basic group, mainly in the first minutes after the awakening. Using HD-EEG, in all cases the frontal lobe was identified as the electrical source of epileptiform discharges, more frequently in the Brodmann area 6 (33%; 95% CI=0.18-0.49) and 11 (20%; 95% CI=0.09-0.35), which is consistent with the fronto-thalamic hypothesis of discharges in myoclonic seizures. In the control group, several electrical sources were identified, mainly in the temporal lobe.
4. Cortical thickness alterations in patients with generalized myoclonic seizures are associated with bilateral thalamic volume reduction ($p<0.05$), supporting the hypothesis of the involvement of aberrant cortico-thalamic structures in myoclonic epilepsy. However, the data obtained suggest that structural changes may not be limited to the thalamus and cortex but may also affect the basal ganglia. These findings highlight clear widespread abnormalities of brain structural integrity related to generalized myoclonic seizures and represent the neuroanatomical fingerprints that may underlie the generation of this type of seizure.
5. Approaching brain network abnormalities in patients with generalized myoclonic seizures, we demonstrated a modular organization of communities in cortico-subcortical networks during the transition to interictal and ictal states. These changes were accompanied by dynamic changes in the flexibility of the fronto-parietal networks in beta frequency, with evidence of increased controllability ($p<0.001$) immediately before ictal discharges. The timing of observed changes in brain connectivity could serve as diagnostic and prognostic markers in patients with myoclonic seizures.

PRACTICAL RECOMMENDATIONS

1. The results of the study argue for the need to inform the population about subtle epilepsy seizures, especially myoclonic ones that are initially underestimated by patients, thus improving the time of addressability to medical services.

2. The interdependence between the cognitive and affective states denotes the importance of evaluating both compartments for the comprehensive assessment of the neurocognitive profile of patients with generalized myoclonic seizures.

3. Patients with generalized myoclonic seizures need to be investigated by video-electroencephalography with long-term monitoring, including recording the first hour after the awakening, with the additional use of electromyographic electrodes

4. In the process of electroencephalographic recording in patients with generalized myoclonic seizures, increased attention is recommended when performing the test with photostimulation at the frequency of 20 Hz.

5. MRI evaluation with automated programs could facilitate the identification of patients with cerebral structural alterations and their correlation with cognitive/affective status.

6. Dynamic parameters of brain networks could support the development of diagnostic and prognostic biomarkers, as well as more targeted neuromodulatory treatment in generalized myoclonic seizures.

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ABBREVIATIONS

BDI-II	- Beck depression inventory
CI	- confidence interval
EMG	- Electromyography
GTCS	- generalized tonic-clonic seizures
HAM-A	- Hamilton anxiety assessment scale
HD-EEG	- high density EEG
IEM	- Institute of Emergency Medicine
IF	- impact factor
IGE	- idiopathic generalized epilepsy
IIQ	- interquartile range
ILAE	- International League Against Epilepsy
JME	- Juvenile myoclonic epilepsy
MoCA	- Montreal cognitive assessment
MRI	- magnetic resonance imaging
NEC	- National Center of Epileptology
OASIS	- Open Access Series of Imaging Studies
SD	- standard deviation
SUMPh	- State University of Medicine and Pharmacy
SWD	- spike wave discharge
Video-EEG	- video-electroencephalography

LIST OF PUBLICATIONS

- **Articles in foreign scientific journals:**

  ✓ **Articles in accredited foreign journals *:**

1. **Vataman A.**, Ciolac D., Chiosa V., et all. Dynamic flexibility and controllability of network communities in juvenile myoclonic epilepsy. In: *Neurobiology of Disease* 2023, 179, 12 p. ISSN 0969-9961 https://doi.org/10.1016/j.nbd.2023.106055

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- **Inovator certificates:**

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41. „Utilizarea înregistrării EEG și EMG la pacienti cu crize mioclonice" Autori: Vataman Anatolie, Chiosa Vitalie, Ciolac Dumitru, Groppa Stanislav. Cerere de inovație nr. 6019 din 07.04.2023.

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69. **Vataman A**., Chiosa V., Ciolac D., Groppa St. „Video-EEG de lungă durată în epilepsia mioconică”. *Conferința Științifică Anuală a Tinerilor Specialiști din cadrul IMSP IMU „Performanțe și Persective în Urgențele Medico-Chirurgicale”*, consacrată zilei internaționale a științei pentru pace și dezvoltare. Chișinău, Republica Moldova. 8 noiembrie 2019.
70. **Vataman A**., Chiosa V., Ciolac D., Groppa St. „De la modificări electroencefalografice la mioclonus”. *Zilele Universității de Stat de Medicină și Farmacie „Nicolae*

Testemițanu" Conferința științifică anuală a cadrelor științifico-didactice, doctoranzilor, masteranzilor, rezidenților și studenților. Chișinău, Republica Moldova. 15 - 18 octombrie 2019.

71. **Vataman A**., Chiosa V., Ciolac D., Groppa St. „Mioclonus epileptic, particularități clinico-neurofiziologice". *Conferința Științifică „Actualități în tratamentul patologiilor sistemului nervos" în cadrul Expoziției Internaționale Specializate Moldmedizin-Molddent ediția a XXV-a*. Chișinău, Republica Moldova. 11 – 13 septembrie 2019.
72. **Vataman A**. „Aspecte clinico-neurofiziologice în epilepsia cu crize mioclonice" *Conferința științifică anuală a cadrelor științifico-didactice, doctoranzilor, masteranzilor, rezidenților și studenților USMF „Nicolae Testemițanu"*. Chișinău, Republica Moldova. 15 – 19 octombrie 2018.
73. **Vataman A**. „Particularităţile clinice şi imagistice la pacienţii cu epilepsie mioclonică". *Conferința științifică anuală a tinerilor specialiști din cadrul IMSP IMU „Performanțe și perspective în urgențele medico-chirurgicale.* Chișinău, Republica Moldova. 18 mai 2018.
74. **Vataman A.**, Chiosa V., Ciolac D., Groppa St. „Particularităţile clinico-neurofiziologice și neuroanatomice ale crizelor epileptice mioclonice". *Zilele Universității și Conferința științifică anuală consacrată aniversării a 90-a de la naşterea ilustrului medic și savant Nicolae Testemițanu.* Chișinău, Republica Moldova. 18 – 20 octombrie 2017.
75. **Vataman A**. „Particularităţile clinico-neurofiziologice ale epilepsiei mioclonice". *Conferinţa ştiinţifică anuală a tinerilor specialiştilor IMSP IMU „Performanţe şi perspective în urgenţele medico-chirurgicale"*. Chișinău, Republica Moldova. 26 mai 2017.

- **Participation with posters at scientific forums:**

✓ **international**

76. **Vataman A**., Ciolac D., Chiosa V., Doțen N., Groppa St. „Particularități morfologice subcorticale ale epilepsiei cu crize mioclonice" *Congresul Internațional al Universității „Apollonia" din Iași "Pregătim viitorul promovând excelența" ediția XXXIII*. Iași, Romania. 2 – 5 martie 2023.
77. Condrea A., Chiosa V., **Vataman A**., Ciolac D. „A case of temporal lobe epilepsy with hippocampal sclerosis". *8th International Medical Congres For Students and Young Doctors MedEspera*. Chișinău, Republica Moldova. 24 – 26 septembrie 2020.
78. **Vataman A**., Chiosa V., Ciolac D., Doțen N., Groppa St. „Repere electrofiziologice în mioclonusul epileptic". *Congresul Internațional al Universității „Apollonia" din Iași "Pregătim viitorul promovând excelența" ediția XXX*. Iași, Romania. 27 februarie - 1 martie 2020.
79. **Vataman A**., Ciolac D., Chiosa V., Groppa St. „Brain grey matter abnormalities associated with myoclonic seizures". *33rd International Epilepsy Congress*. Bangkok, Thailand. 22-26 iunie 2019.
80. Ciolac D., Chiosa V., Koirala N., **Vataman A**., et all. „*Effective connectivity dynamics within interictal pre-spike networks in focal epilepsy*" 33rd International Epilepsy Congress. Bangkok, Thailand. 22-26 iunie 2019.

81. Ciolac D., Chiosa V., **Vataman A**., Groppa St. „Reorganizarea rețelelor neurale în epilepsie”. *Congresul Internațional al Universității „Apollonia” din Iași "Pregătim viitorul promovând excelența" ediția XXIX*. Iași, Romania. 28 februarie - 3 martie 2019.
82. Groppa St., **Vataman A**., Ciolac D., Chiosa V. „Cortical and subcortical morphological aspects in myoclonic epilepsy”. *13th European Congress on Epileptology.* Vienna, Austria. 26-30 august 2018.
83. Groppa St., Chiosa V., Ciolac D., Muthuraman M., Koirala N., **Vataman A**., et all. „Cortical and subcortical structural alterations mirroring daytime-related seizure occurrence”. *13th European Congress on Epileptology*. Vienna, Austria. 26-30 august 2018.
84. **Vataman A**., Chiosa V., Ciolac D., Groppsa St. „Epilepsy with myoclonic seizures: electrophysiological and neuromorphological peculiarities” *Congresul Internaţional pentru Studenţi şi Medicii tineri – ediţia a 7 –ea MedEspera*. Chișinău, Republica Moldova. 3 – 5 mai 2018.
85. **Vataman A**., Ciocal D., Chiosa V., Groppa St. „Cortical and subcortical morphological aspects in myoclonic epilepsy” *Al 6-lea Congres al Neurologilor și Neurochirurgilor din Republica Moldova și Ziua Academiei Europene de Neurologie în Republica Moldova.* Chișinău, Republica Moldova. 3 – 5 octombrie 2017.

✓ **national**

86. **Vataman A**., Ciocal D., Chiosa V., Groppa St. Alterările substanței cenușii ale creerului asociate cu crize mioclonice. *Conferința anuală Zilelor USMF, Cercetarea În Biomedicină Și Sănătate: Calitate, Excelență Și Performanță*. Chișinău, Republica Moldova. 19 – 21 octombrie 2022.

ANNOTATION

Author of the thesis Vataman Anatolie, for PhD degree in medicine, the thesis title **„Clinical-neurophysiological peculiarities of epilepsy with myoclonic seizures”,** Chisinau, 2023

Structure of the thesis: introduction, 5 chapters, synthesis of results, general conclusions and recommendations, bibliography of 318 titles, 103 pages of basic text, 28 tables, 39 figures. There are published 35 scientific papers, 5 patents and 4 acts of implementation in clinical activity. **Key words:** myoclonic epilepsy, clinical polymorphism, neurophysiology, morphological alterations, brain network connectivity. **Field of study:** clinical neurology. **The aim of the study:** To study the clinical, neurophysiological and imaging characteristics of myoclonic seizures in order to identify the pathophysiological aspects and brain networks involved in the generation of generalized myoclonic seizures. **The objectives of the study:** 1. Studying the clinical features of generalized myoclonic seizures; 2. Study of the neuropsychological profile of patients with myoclonic seizures; 3. Evaluation of electroencephalographic patterns of generalized myoclonic seizures; 4. Morphometric evaluation of brain structures in patients with generalized myoclonic seizures; 5. Identification of pathophysiological aspects and brain networks involved in the generation of generalized myoclonic seizures. **Scientific novelty and originality:** a study of the brain mechanisms of epileptogenesis was carried out with the assessment of the source of epileptiform activity in generalized myoclonic seizures, as well as of neurophysiological, neuroimaging and cerebral connectivity features. **Problem solved in the thesis:** resides on identifying the clinical-neurophysiological polymorphism in association with neuroimaging

alterations and modular organization of brain networks in epilepsy with generalized myoclonic seizures. **Theoretical significance of the study:** Determination of clinical-neurophysiological and neuroimaging correlations to identify the pathophysiology and brain networks involved in the generation of generalized myoclonic seizures. **Practical value of the work:** The usefulness of video-EEG data in correlation with MRI data in detecting a trigger phenomenon during the transition to interictal and ictal states in patients with generalized myoclonic seizures was demonstrated. **Implementation of the results:** The results of the study were implemented and utilized in the didactic process at the Department of Neurology no. 2 and in the Laboratory of Neurobiology and Medical Genetics of the State University of Medicine and Pharmacy "Nicolae Testemitanu", as well as in the Department of Epileptology and National Center of Epileptology of the Institute of Emergency Medicine.

ADNOTARE

Tezei pentru conferirea gradului științific de doctor în medicină D-lui Vataman Anatolie, tema tezei **„Particularităţile clinico-neurofiziologice ale epilepsiei cu crize mioclonice”,** Chișinău, 2023

Structura tezei: introducere, 5 capitole, sinteza rezultatelor, concluzii generale și recomandări, bibliografie din 318 titluri, 103 pagini de text de bază, 28 tabele, 39 figuri. Sunt publicate în 35 lucrări stiinţifice, 5 brevete de invenție și 4 acte de implementare în activitate clinică. **Cuvinte cheie:** epilepsie mioclonică, polimorfism clinic, neurofiziologie, alterări morfologice, conectivitatea rețelelor cerebrale. **Domeniul de studiu:** neurologie clinică. **Scopul studiului:** Studierea particularităţilor clinice, neurofiziologice și imagistice a crizelor epileptice mioclonice pentru a identifica aspectele patofiziologice și rețelele cerebrale implicate în generarea crizelor generalizate mioclonice. **Obiectivele studiului:** 1. Studierea particularităților clinice ale crizelor generlizate mioclonice; 2. Studierea profilului neuropsihologic la pacienți cu crize mioclonice; 3. Aprecierea pattern-elor electroencefalografice ale crizelor generalizate mioclonice; 4. Studierea morfometrică a structurilor cerebrale la pacienti cu crize generalizate mioclonice; 5. Identificarea aspectelor patofiziologice și rețelelor cerebrale implicate în generarea crizelor generalizate mioclonice. **Noutatea și originalitatea stiinţifică:** s-a efectuat un studiu al mecanismelor cerebrale de epileptogeneză cu aprecierea sursei activității epileptiforme în crizele generalizate mioclonice, particularitățile neurofiziologice, neuroimagistice și ale conectivității cerebrale. **Problema soluționată în teză:** rezidă în caracterizarea polimorfismului clinico-neurofiziologic asociat cu alterări neuroimagistice și organizare modulară a rețelelor cerebrale în cadrul epilepsiei cu crize generalizate mioclonice. **Semnificația teoretică:** Determinarea corelațiilor clinico-neurofiziologice și neuroimagistice pentru identificarea patofiziologiei și rețelelor cerebrale implicate în generarea crizelor generalizate mioclonice. **Valoarea aplicativă a lucrării:** A fost demonstrată utilitatea datelor video-EEG în corelare cu datele IRM în detectarea unui fenomen trigger în timpul tranziției la stările interictale și ictale la pacienți cu crize generalizate mioclonice. **Implementarea rezultatelor:** Rezultatele studiului au fost implementate și valorificate în procesul de studiu la Catedra de neurologie nr.2 și la Laboratorul de neurobiologie și genetică medicală ale Universității de Stat de Medicină și Farmacie „N. Testemiţanu”, cât și în secția de epileptologie și Centrul Național de Epileptologie a Institutului de Medicină Urgentă.

АННОТАЦИЯ

Диссертации на соискание научной степени доктора медицинских наук Ватаман Анатолий, тема диссертации **«Клинико-нейрофизиологические особенности эпилепсии с миоклоническими приступами»,** Кишинёв, 2023

Структура диссертации: введение, 5 глав, обобщение результатов, общие выводы и рекомендации, библиография из 318 наименований, 103 стр. основной текст, 28 таблиц, 39 рисунков. Опубликованы 35 научных статьи, пять патентов и четыре акта внедрения в клиническую деятельность. **Ключевые слова:** миоклоническая эпилепсия, клинический полиморфизм, нейрофизиология, морфологические изменения, связность мозговых сетей. **Область исследования:** клиническая неврология. **Цель исследования:** изучить клинические, нейрофизиологические и визуализационные характеристики миоклонических эпилептических приступов с целью выявления патофизиологических аспектов и мозговых сетей, участвующих в генерации генерализованных миоклонических приступов. **Задачи исследования:** 1. Изучение клинических особенностей генерализованных миоклонических судорог; 2. Изучение нейропсихологического профиля у больных с миоклоническими припадками; 3. Оценка электроэнцефалографической картины генерализованных миоклонических приступов; 4. Морфометрическое исследование мозговых структур у больных с генерализованными миоклоническими припадками; 5. Выявление патофизиологических аспектов и мозговых сетей, участвующих в генерации генерализованных миоклонических припадков. **Научная новизна и оригинальность:** проведено изучение церебральных механизмов эпилептогенеза с оценкой источника эпилептиформной активности при генерализованных миоклонических приступах, особенностей нейрофизиологических, нейровизуализационных и церебральных связей. **Проблема, решенная в диссертации:** заключается в выявлении клинико-нейрофизиологического полиморфизма, связанного с нейровизуализирующими изменениями и модульной организацией сетей головного мозга при эпилепсии с генерализованными миоклоническими припадками. **Теоретическое значение исследования:** Определение клинико-нейрофизиологических и нейровизуализационных корреляций для выявления патофизиологии и сетей головного мозга, участвующих в возникновении генерализованных миоклонических судорог. **Практическое значение работы:** Показана полезность данных ЭЭГ в сочетании с данными МРТ при выявлении триггерного феномена при переходе в интериктальные и иктальные состояния у больных с генерализованными миоклоническими судорогами. **Внедрение результатов:** Результаты исследования внедрены в учебном процессе на кафедре Неврологии №2 и в Лаборатории нейробиологии и медицинской генетики ГМФУ «Н. Тестемицану», а также в отделении эпилептологии при Институте скорой медицинской помощи.

VATAMAN Anatolie

CLINICAL-NEUROPHYSIOLOGICAL PECULIARITIES OF EPILEPSY WITH MYOCLONIC SEIZURES

321.05 – CLINICAL NEUROLOGY

Summary of Ph.D. Thesis in Medical Sciences