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MULTIFOCAL TRANSCRANIAL MAGNETIC STIMULATION IN MIGRAINE AND EPILEPSY

321.05 – CLINICAL NEUROLOGY

Summary of the doctoral thesis in medical sciences

Chișinău, 2025

The thesis was developed at the Department of Neurology No. 1 and the Laboratory of Neurobiology and Medical Genetics, "Nicolae Testemițanu" State University of Medicine and Pharmacy and the Department of Neurology, Epileptology and Internal Diseases of Institute of Emergency Medicine.

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The thesis defense will take place on July 2nd, 2025, at 14:00, in the "Nicolae Testemițanu" State University of Medicine and Pharmacy, 165 Ștefan cel Mare și Sfânt blvd., Chișinău, office 205, in the meeting of the Committee for public defense of the doctoral thesis, approved by the decision of the Scientific Council of the Consortium from 10.04.2025 (protocol no. 59).

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CONTENT

INTRODUCTION

The relevance and importance of the issue addressed.

Neurological disorders remain one of the most prevalent health problems worldwide, representing the leading cause of disability and the second leading cause of death in the general population [1]. Epidemiological studies have found a significant increase in the impact of neurological disorders on health status in recent decades. According to the World Health Organization report, the top five diseases with the greatest contribution to disability-adjusted life years (DALYs) also include neurological disorders with paroxysmal presentation, such as migraine (16.3%) and epilepsy (4.9%) [2]. The paroxysmal specificity of the latter, in terms of time, greatly influences both the therapeutic approach and the actual impact of these diseases on the quality of life of people suffering from migraine or epilepsy [3].

In the Republic of Moldova, according to data presented by the National Center for Health Management of the Republic of Moldova, the prevalence of epilepsy in 2021 was 25.3 with an incidence of 2.1 cases per 10,000 population [4].

Despite the availability of many new antiepileptic drugs (AEDs) with different mechanisms of action, the overall results in the treatment of epilepsy have not improved substantially. An observational study, which included 1795 patients with newly diagnosed epilepsy between 1982 and 2012, highlighted the fact that only 50.5% of patients were seizure-free for ≥ 1 year with the initial AED. However, once the initial AED failed, the chances of not responding to treatment for each subsequent AED became 1.73 times higher [5].

Migraine, in turn, is a recurrent, chronic, progressive pathology in individuals with a genetic and biological predisposition [6]. In the Republic of Moldova, its prevalence has been reported to be 16.5% for episodic migraine and 3.5% for chronic migraine [7].

Similarly to epilepsy, despite the fact that the spectrum of pharmacological interventions in migraine management is currently quite varied, the response rate is frequently suboptimal, occurring in up to 62.2% of patients [8].

Although they appear distinct at first glance, both pathologies, both migraine and epilepsy, present remarkable similarities, common pathophysiological pathways, predisposing genetic and epigenetic substrates, significant overlaps in features such as clinical manifestation or preventive treatment [9].

One of the most obvious links can be observed in patients with familial hemiplegic migraine (FHM). This is a rare form of migraine with aura that is characterized by headache attacks accompanied by hemiparesis and occasionally encephalopathy during the attack, having as substrate mutation of the CACNA1A gene (FHM type 1) encoding voltage-dependent calcium channels of the P/Q type; the ATP1A2 gene encoding transmembrane Na/K-ATPase (FHM type 2); or the SCNA1 gene encoding sodium channels (FHM type 3) [10]. Epilepsy has been reported in all three types of FHM; however, it is more common in MHF type 2 and MHF type 3 due to a higher association of epileptic seizures with mutations in the ATP1A2 and SCNA1 genes. Among patients with epilepsy, 8%–24% also have migraine. The risk of migraine in these patients is several times higher compared to healthy individuals. At the same time, the risk of an epileptic seizure in people suffering from migraine is 3.2 times higher than in those with tension-type headache[11] while presenting a higher incidence of epilepsy (1–17%) than the general population (0.5–1%) [12].

All this has forced over the years to change the perspective of diagnostic and therapeutic approach towards a communication disorder of brain structures [13].

In the last decade, the study of brain connectivity and the analysis of neural networks in patients with epilepsy and migraine has been of increasing interest. Thus, the approach of epilepsy and migraine as a dysfunction of neural networks opens up opportunities for their modulation by neuromodulatory therapies.

Among the emerging treatment methods, transcranial magnetic stimulation (TMS) seems to be an attractive one due to its simple use, relatively low cost, excellent tolerance profile and the possibility of non-invasive quantification of neuronal excitability. TMS allows for non-invasive and focused stimulation of different neuroanatomical circuits by inducing weak electrical currents at the cerebral level [14]. There is evidence that repetitive transcranial magnetic stimulation (rTMS) or theta burst (TBS) can produce effects that last after stimulation, offering potential clinical application in various neurological diseases including migraine and epilepsy [15]. Therefore, TMS could be a non-pharmacological treatment strategy that offers the unique opportunity to avoid adverse effects and drug interactions.

In experimental studies, single-pulse TMS was able to interrupt cortical widespread depression (CSD); an electrophysiological phenomenon predominantly reported in relation to migraine with aura, but also observed in epileptic seizures induced in translational studies At the same time, data in the field of TMS neuromodulation remain contradictory, especially in the field of epilepsy [16].

Thus, research in this area will open new perspectives given the currently limited number of conclusive studies in the field of multifocal TMS use (most studies applying the unifocal paradigm) in the treatment of epilepsy and migraine.

Research aim

To assess the effectiveness of multifocal transcranial magnetic stimulation in the prophylaxis of migraine attacks in patients with episodic migraine and epileptic seizures in patients with generalized epilepsy.

Research objectives

1. Evaluation of the effect of multifocal transcranial magnetic stimulation on migraine days, frequency and intensity of migraine attacks in patients with episodic migraine;
2. Determination of the impact of multifocal TMS on the quality of life in patients with episodic migraine;
3. Assessment of the effect of theta burst stimulation (TBS) on the frequency and severity of epileptic attacks in patients with generalized epilepsy;
4. Analysis of the influence of TBS on the quality of life in patients with generalized epilepsy;
5. Assessment of the safety and tolerability profile of experimental TMS protocols (rTMS and TBS);

Scientific research methodology (general):

The research was organized and conducted at the Department of Neurology no. 1, the Laboratory of Neurobiology and Medical Genetics within the IP "Nicolae Testemițanu" University of Medicine and Pharmacy, the National Center for Epileptology, as well as in the Department of Neurology, Epileptology and Internal Diseases of the IMSP Institute of Emergency Medicine, with the permission of the administration of the respective institution for the collection and processing of primary data, during the period 2017 - 2023. The research project was approved by the Research Ethics Committee of the Nicolae Testemițanu USMF (minutes no. 85 of 19.06.2018).

The novelty and scientific originality of the research

An experimental study was conducted that debuted the multifocal transcranial magnetic stimulation paradigm by examining its therapeutic impact in the preventive treatment of patients with episodic migraine and generalized epilepsy.

Theoretical importance of the research

By implementing a modern method of neuromodulatory treatment of patients with episodic migraine and those with generalized epilepsy from the Republic of Moldova, the research conducted has fundamentalized the contemporary vision in the complex evaluation and treatment algorithm for these patients. In addition, the development and use of a multifocal TMS protocol, innovative not only nationally but also internationally, has allowed the increase of knowledge in the field of neuromodulation methods in the treatment of paroxysmal neurological disorders such as migraine and epilepsy.

The applicative value of the research

The practical value of the research conducted consists in the implementation of an innovative method of preventive treatment of epileptic seizures in patients with generalized epilepsy and migraine in patients with episodic migraine from the Republic of Moldova. The non-invasive nature, the possibility of precise targeting of the elements of interest, as well as the ease of use of the transcranial magnetic stimulation method can provide major advantages in the treatment of these patients, both in terms of therapeutic aspects for the patient and economic aspects for the health system. At the same time, the suboptimal therapeutic response to the indicated pharmacological treatment that occurs in some patients with epilepsy and migraine, dictates the need to increase the spectrum of complementary approaches, and the use of multifocal TMS can serve as a platform for studying biomarkers of cortical excitability in these patients, providing important information in their complex treatment, to the extent that it would subsequently allow the inclusion of TMS in institutional and national protocols as a complementary treatment method.

Acknowledgment of the research results

The scientific results obtained during the research were presented, discussed, published and appreciated in national and international scientific forums: *The 10th Congress of the European Academy of Neurology* (Helsinki, Finlanda, 2024); *Roma Pain Days 2024 Congress* (Roma, Italia, 2024); Congresul Internaţional ”Pregătim viitorul promovând excelenţa”, Ediția a XXXIV-a (Iași, România, 2024); Expoziția Internațională Specializată „INFOINVENT” ediția a XVIII-a (Chișinău, 2023 - **Trophy for "Best Research Project"**); Expoziția Internațională de Inovație și Transfer Tehnologic EXCELLENT IDEA – ediția a II-a (Chișinău, 2023 – **2 Gold Medals**); Conferința Societății Române Împotriva Epilepsiei, Ediția a XXXI-a (București, România, 2023); Congresul Internaţional ”Pregătim viitorul promovând excelenţa”, Ediția a XXXIII-a (Iași, România, 2023); *The 15th edition of EUROINVENT European Exhibition of Creativity and Innovation* (Iași, România, 2023 – **Silver Medal**); *The 15th edition of EUROINVENT European Exhibition of Creativity and Innovation* (Iași, Romania, 2023 – **Carol Davila Award**); *XXIV-я научно-практическая конференция с международным участием «Актуальные проблемы клинической, экспериментальной неврологии, нейрохирургии и нейрофизиологии»* (virtual, Almaty, Kazakhstan, 2023 – **Diploma grad II**); Congresul 37-ea ediție a săptămânii medicale balcanice: „Perspective ale medicinei balcanice în era post COVID-19” (Chișinău, 2023); Conferinta științifico-practică cu participare internațională “Provocări actuale în diagnosticul și tratamentul depresiei” (Chișinău, 2023); Conferința interdisciplinară cu participare internațională

”Academia Durerii” (Chișinău, 2023); Școala de neuroștiințe, ediția I (Republica Moldova, 2023); Congresul Internaţional ”Pregătim viitorul promovând excelenţa”, Ediția a XXXII-a (Iași, România, 2022); Conferința ştiinţifică consacrată aniversării a 77-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu” din Republica Moldova (Chișinău, 2022); Conferința științifică “Performanțe și perspective în urgențele medico-chirurgicale” (Chișinău, 2022); Concursul “Impactul activitatii de cercetare” (Chișinău, 2022 – Laureat); *American Clinical Neurophysiology Society Annual Meeting & Courses* (virtual, SUA, 2021); Congresul VII al Neurologilor din Republica Moldova (Chișinău, 2021); Conferința ştiinţifică consacrată aniversării a 76-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu” din Republica Moldova (Chișinău, 2021); Laureat al concursului pentru Bursa de excelență a Guvernului Republicii Moldova (2020); *The congress dedicated to the 75th anniversary of Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova* (Chișinău, 2020); Congresul Internaţional ”Pregătim viitorul promovând excelenţa”, Ediția a XXX-a (Iași, România, 2020); *The 5th Congress of the European Academy of Neurology* (Oslo, Norway, 2019); Congresul Internațional Pregătim Viitorul, promovând excelența (Iasi, România, 2019); *4th International Conference on Nanotechnologies and Biomedical Engineering. ICNBME* (Chișinău, 2019); Conferința științifică “Performanțe și perspective în urgențele medico-chirurgicale” (Chișinău, 2019); Conferința științifică anuală a cadrelor științifico-didactice, doctoranzilor (Chișinău, 2019); Conferința științifică “Actualități în tratamentul patologiilor sistemului nervos” (Chișinău, 2019); Conferința internațională ”Cefaleea la Copil” (Chișinău, 2018).

Publications on the research topic

The research materials were reflected in 18 scientific publications, including 8 articles, of which 5 articles in journals with impact factor (IF), the author being the first author - **1 article with IF = 8.95;** 6 publications as a single author; presentations and abstracts at 9 national scientific conferences, 6 national ones with international participation, 11 international conferences and congresses and 3 international exhibitions. 5 innovation certificates, 10 implementation acts, 1 copyright were authorized.

Thesis structure

The work is presented on 88 pages of text; includes 45 figures, 6 tables and 16 annexes; is composed of an introduction, 3 chapters, 2 of which contain original material, a synthesis of the results, general conclusions, practical recommendations, annotations in Romanian, Russian and English and a bibliography with 297 references.

Keywords

Transcranial magnetic stimulation, theta burst stimulation, episodic migraine, generalized epilepsy, prevention, neuromodulation.

CONCEPTS IN THE FIELD OF NEUROMODULATION THROUGH TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS is a non-invasive method of modifying cortical excitability by means of the magnetic field emitted by a coil when an alternating current passes through it. The induced magnetic field can reach an intensity of 1 – 2.5 Tesla with a very short duration (≤1 ms). Applied to the scalp, it easily crosses the soft and bony tissues of the skull, reaching the superficial layers of the cerebral cortex, where it induces the local appearance of low-intensity electric currents, known as “Eddy currents” [17].

In vivo, for the first time, transcranial magnetic stimulation was presented in 1985 by Barker and colleagues [18], where with the help of a focused magnetic field it was possible to activate the corticospinal tract with the appearance of compound muscle action potential (CMAP) recorded from the contralateral upper limb.

Despite the fact that the intensity of the magnetic field induced by TMS can be reduced by extracerebral tissues, it is still capable of depolarizing the axon membrane, initiating action potentials and subsequently activating cortical networks [19].

The depth penetration of TMS is limited due to the exponential attenuation of the induced electromagnetic field with increasing distance from the coil. This means that the intensity required for stimulation increases with the distance between the stimulation coil and the cortical target area.

Another element that limits the propagation of the induced electric field is the impedance of the brain tissue. Because the impedance of gray matter (3.51 Ω*m) is lower than that of white matter (3.91 Ω*m), the electrical currents in subcortical structures are weaker than in superficial layers, so using standard coils, subcortical elements such as the basal ganglia and thalamus are not activated by TMS [20].

TMS-induced action potentials in cortical axons spread trans-synaptically to other neurons, resulting in a propagation of neuronal activation in connected cortical and subcortical areas [21].

Cortical excitability parameters

Based on the phenomenon of electromagnetic induction, TMS has also been applied to measure the excitation and inhibition parameters of the primary motor cortex. Thus, the resting motor threshold (RMT) and the motor evoked potential (MEP) are among the most frequent and accessible biomarkers for assessing cortical excitability. The resting motor threshold represents the minimum value of a TMS stimulus required to produce a defined response (muscle contraction contralateral to the stimulation site), speaking about the membrane excitability of the cortical interneuron [22] while the motor evoked potential (MEP) is defined as a motor response obtained produced to TMS stimuli of the cortex and characterizes the corticospinal projections [23].

The resting motor threshold (RMT) can be modified under the influence of agents that impact electrical conductivity by blocking ion channels, predominantly sodium channels, crucial in regulating membrane excitability [24]; as well as by agents acting on non-N-methyl-D-aspartate (non-NMDA) ionotropic glutamate receptors, such as ketamine [25]. In contrast, other neurotransmitters and neuromodulatory systems such as GABA, dopamine, norepinephrine, serotonin, or acetylcholine have no effect on RMT.

Studies have shown that the motor evoked potential (MEP) can be depressed by agents that inactivate sodium channels, leading to a decrease in the action potential and, in turn, reducing calcium entry into the presynaptic membrane and ultimately impacting synaptic transmission. Furthermore, MEP amplitude has been found to decrease with $GABA_A$ receptor agonists and increase with DOPA and NA agonists [26].

TMS pulse application protocols

In clinical and research protocols there is a diversity of TMS pulse application schemes, in the context of the conducted research, of particular interest are:

Repetitive TMS (rTMS): Most clinical and research protocols use repetitive transcranial magnetic stimulation treatment sessions. In such a sequence, blocks, also called trains, containing multiple pulses are delivered at a predefined frequency. Protocols with frequencies above 5Hz are considered high-frequency protocols. Frequencies of 1Hz and below are considered low-frequency. Frequencies above 1Hz are thought to induce facilitation or potentiation of excitability,

which is comparable to the long-term synaptic potentiation (LTP) observed in animal studies. Frequencies below 1Hz conversely trigger mechanisms of inhibition or depression of cortical excitability, referred to in translational studies as long-term depression (LTD). However, the effects of rTMS can be influenced by a variety of factors, such as stimulation duration, homeostatic plasticity, or drug administration.

Transcranial Theta Burst Magnetic Stimulation (TBS): This sequence is based on the physiological pattern of theta neuronal discharge at a frequency of 50 Hz. In a typical sequence, the application of a block containing three pulses at 50 Hz is repeated every 200 ms (5 Hz, theta frequency). In general, there are two basic models: intermittent theta burst stimulation (iTBS), composed of trains interspersed with pauses, and continuous TBS (cTBS). The importance of these two TBS modalities lies in the induction of opposite effects on neuronal excitability. Thus, iTBS tends to increase excitability, while cTBS decreases it. The induced effects on cortical excitability after TBS appear to be dependent on N-methyl-d-aspartate (NMDA) receptors and Ca^{2+} channels.

Synaptic plasticity induced by rTMS/TBS

Plasticity is the ability of the brain to reorganize itself, allowing for short- and long-term remodeling of neuronal synapses that outlast the influence of a modulatory agent (experimental, behavioral, or training) [27]. Plasticity can occur at different levels of brain organization: from macro (neural networks), meso (nodes within a regional neural network) to micro (molecular, synaptic level). Long-term changes in synaptic strength, such as LTP and LTD, have been and are the focus of a significant amount of human and translational research [28]. LTP is an increase in synaptic strength that could last for days or even weeks and months, which in the neuromodulatory context can be induced under experimental conditions by high-frequency transcranial magnetic stimulation. LTD, in contrast, encompasses the long-term weakening of a neuronal synapse [29]. Changes in synaptic strength induced by LTD and/or LTP have their own special importance, but are not unique in modifying brain plasticity. There are mechanisms that dictate that synaptic activity (or lack thereof) prior to the influence of a magnetic stimulus could also determine the direction of plasticity. This concept is called “Metaplasticity” and involves a wide range of mechanisms, many of which overlap with conventional plasticity mechanisms, and both NMDA and glutamate receptors appear to play a role in it.

Overall safety profile of TMS

The only absolute contraindication for TMS/rTMS/TBS is the presence of a ferromagnetic metallic implant (cochlear implant, internal electrical impulse generator/pacemaker or drug pump) that would come into direct contact with the stimulation coil. The most common side effects of TMS are pain or local discomfort in the stimulation region which according to some authors has been reported in up to 2.7-40%. Another adverse reaction is the occurrence of headache being reported in 6.9-30% [30, 31]. Both adverse reactions, both local discomfort and headache are more frequently associated with deep high-frequency stimulation, stimulation of the trigeminal nerve branches and induction of pericranial muscle contractions. Also, repetitive magnetic stimulation (rTMS and TBS) can produce specific noise that can induce short-term changes in the excitability threshold of the auditory cortex (auditory perception). This can be avoided by using earplugs when necessary [32].

TMS-induced epileptic seizures risk

Seizure induction following TMS is considered the most severe acute adverse effect. These have been reported with TMS protocols using sTMS, ppTMS, and rTMS. Repetitive transcranial

magnetic stimulation could theoretically induce seizures either during or immediately after the stimulation block and at a distance due to modulation of cortical excitability.

In relation to the number of TMS sessions, the overall seizure rate with round or figure-of-eight coils is 0.14 per 1,000 patients, considerably higher than the 5.56 per 1,000 patients with deep rTMS coils (H-coils) [33].

In patients with epilepsy - the overall risk of TMS-induced seizures was 2.9% (95% confidence interval: 1.3 - 4.5) [34].

The general consensus of specialists in the field, given the small number of epileptic seizures compared to the large number of subjects and patients who have undergone rTMS since 1998 (the year it was presented), says that the overall risk of TMS/rTMS inducing epileptic seizures is very low [35].

Safety in pregnancy

For ethical reasons, there are currently no data on TMS studies that have specifically aimed to test safety during pregnancy, but this can be assessed indirectly by quantifying the characteristics of the electric field induced by the stimulation coil in relation to the coil-uterus distance. Application of a single TMS pulse to the occipital region generates a magnetic field that decreases from 0.9 T at 1 cm from the coil surface to approximately $11\times10-6$ T at 46 cm from the coil surface - an approximate point at which the uterus may reach term [35]. While exposure to the electric field is almost absent, the major source of risk to the fetus is a TMS-induced epileptic seizure in the mother.

Regarding possible long-term effects after birth, data are also limited, but there is evidence that children born to mothers treated with high-frequency rTMS for depression during pregnancy did not have an increased risk of perinatal complications and that their motor and neurocognitive development was comparable to that of children born to mothers with untreated depression [36]. Therefore, there is currently no concrete data to indicate the contrary.

MULTIFOCAL TRANSCRANIAL MAGNETIC STIMULATION IN MIGRAINE

2.1 Materials and methods

Study Design

A randomized, double-blind, rTMS-interventional experimental study was conducted in adult subjects with episodic migraine with and without aura. After a 4-week screening period during which the headache agenda was met, all eligible subjects were randomly assigned to either the real rTMS or sham group. Randomization was performed by a separate member of the research team, blinded to any other aspects of the study. All subjects participated in six intervention sessions over a two-week period. They were then followed up for up to three months with visits at predefined intervals at 4, 8, and 12 weeks (figure 1).

Subjects

A total of 807 primary screening questionnaires were analyzed: 265 (37.7%) – without headache; 377 (46.7%) suffered from episodic tension-type headache (TTH), 38 (4.7%) – chronic tension-type headache; 127 (15.7%) – migraine with/without aura.

Of the 127 subjects considered potentially eligible - 36 (4.4%) represented people with chronic migraine, and 19 (2.35%) questionnaires were eliminated due to incomplete completion. After analysis of inclusion and exclusion criteria – 65 eligible subjects were included in the study and randomized to either the real rTMS group (n = 37) or the sham rTMS group (n = 28), of whom

completed the study at 12 weeks in the real rTMS (n = 33) and sham rTMS (n = 27) groups. Each subject was provided with a textile TMS treatment cap that was used to mark the appropriate stimulation sites based on the EEG 10-20 system and ensure optimal coil placement in order to avoid unwanted contractions of the pericranial and facial muscles during the stimulation procedure (figure 3).

Inclusion criteria: Adult patients with episodic migraine, with or without aura, having at least four and up to 14 headache attacks per month were included. The diagnosis of episodic migraine was based on the ICHD-3 criteria [37].

Exclusion criteria: Refusal to sign informed consent; chronic migraine or diagnosis of another type of headache according to ICHD-3; history or signs of metabolic impairment (renal, hepatic); history of oncological pathology; uncontrolled hypertension; history of epileptic seizures; intellectual disability; psychiatric disorders; signs of structural brain injury or focal neurological deficit; drug abuse; use of migraine prevention medication, opioids or muscle relaxants; history of substance abuse; absolute or relative contraindications for TMS (ferromagnetic implants in the head and neck regions, pacemakers and pregnant or breastfeeding women).

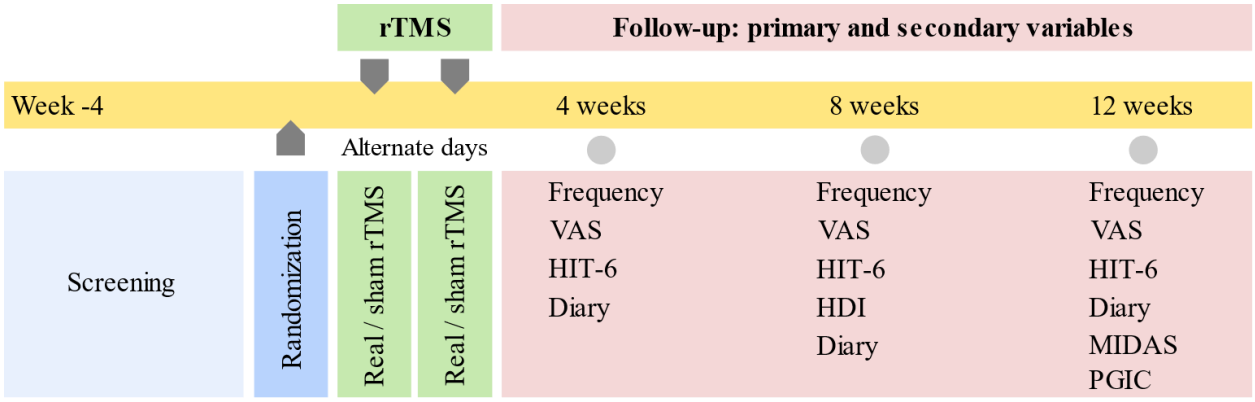

Figure 1. **rTMS-Migraine study design**. Subjects completed a four-week headache diary and the Headache Impact Test (HIT-6), Headache Disability Index (HDI), and Migraine Disability Assessment Score (MIDAS) questionnaires before the first rTMS stimulation session. ≥50% improvement from baseline in migraine days during the 12-week period after rTMS intervention served as the primary outcome variable. ≥50% improvement from baseline in migraine attack frequency and intensity (as measured by the Visual Analogue Scale (VAS)) during the same period served as key secondary outcome variables. Quality of life (HIT-6, MIDAS) and positive global impression of change (PGIC) questionnaires were administered at several follow-up visits and their results were considered as secondary outcome indicators. All questionnaires were completed individually by the subject, and if necessary, assistance was provided to complete the form.

Multifocal rTMS stimulation paradigm

After determining RMT, all subjects underwent either real or sham rTMS using the experimental multifocal stimulation protocol. Blinding was achieved using the MagVenture MMC-140 A/P circular coil, which functions as either an active coil or a placebo coil, depending on the randomization number assigned to the subject.

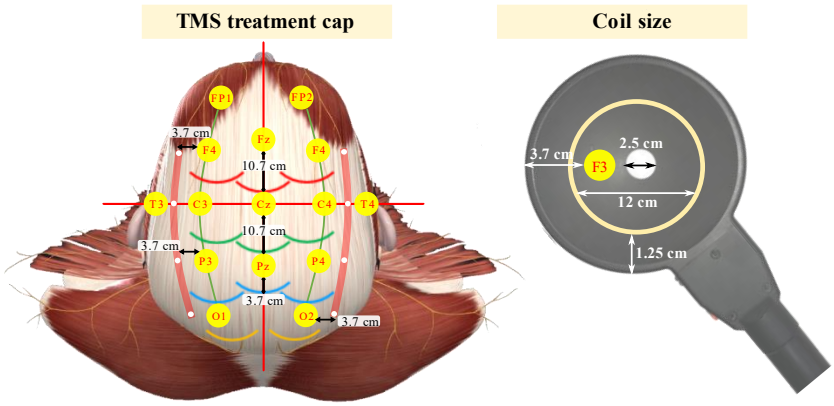

Figure 3. **Boundary marks and spot stimulation areas marked on the TMS treatment cap applied in the experimental stimulation protocol according to the EEG 10-20 system.** Two lateral edge marks (red) indicate the edges of the stimulation to avoid involvement of the pericranial muscles. The eleven horizontal semicircular marks (red, green, blue and yellow) indicate the location of the lower edge of the stimulation coil. The measurements of 3.7 cm and 10.7 cm from the guide lines indicate the distance required for the outer and inner stimulation points, respectively, to be placed below the midpoint of the circuits, given the 14.5 cm diameter of the stimulation coil.

The experimental stimulation protocol consisted of sliding stimulation followed by spot burst stimulation (figure 4).

After the rTMS session, subjects were asked if there were any adverse events during and/or immediately after stimulation, and the results of the responses were recorded on the rTMS adverse reaction monitoring form. This form monitored the occurrence of the following adverse reactions: headache, auditory discomfort, dizziness (vertigo), nausea, single or repeated vomiting, facial muscle contraction, discomfort at the stimulation site, hypertension, loss of consciousness, seizure/convulsive seizure, memory impairment.

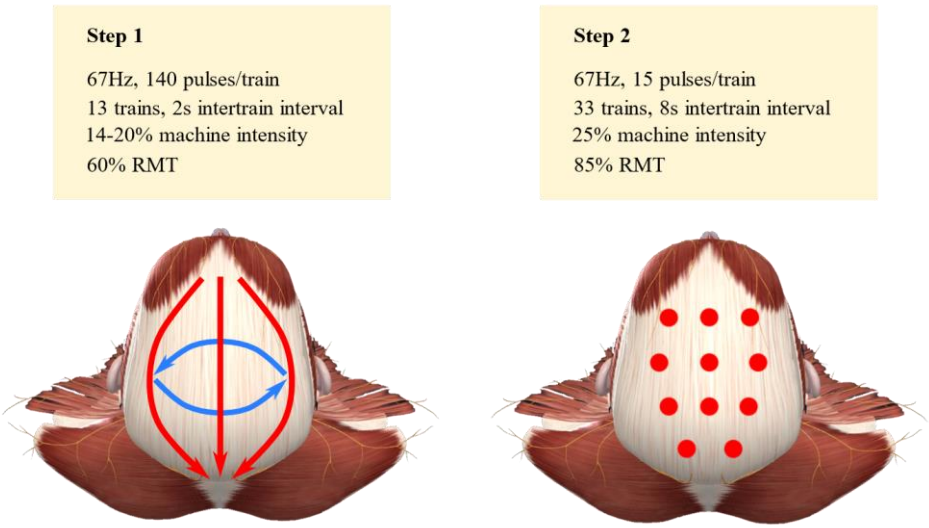

Figure 4. **Multifocal stimulation protocol**. Stage 1 – sliding stimulation, Stage 2 – spot burst stimulation.

All adverse reactions, if present, were categorized by intensity (mild, moderate, severe), duration (minutes, hours) and in relation to the rTMS session (attributed/or not to the rTMS

application). In the case of the occurrence of an adverse reaction in the form of a headache episode, it was also assessed according to the visual analogue scale (VAS) on a scale of 0-10 points. At the same time, immediately after the rTMS sessions, the patient's tolerability towards the applied experimental protocol was also recorded, using the rTMS procedure perception assessment form developed by the researcher. This form included the assessment of three basic components during the rTMS session, namely: "How painful was the procedure?", "How noisy?" and "Did the procedure cause any discomfort?". All three components were quantified scalarly, on a scale from 0-10, where 0 – lack of accusation and 10 – its maximum intensity.

Statistical analysis

Continuous variables are presented as mean values ± standard deviation. Gaussian distribution was verified by histogram analysis and Shapiro-Wilk test. For demographic and clinical characteristics, differences between groups were verified by Student's t-test and Pearson chi-square test. Correlation between parametric variables was assessed by Pearson's (r), with reference values: 1-0.5 strong correlation, 0.3-0.49 moderate, <0.29 weak; and nonparametric variables by Spearman rho (ρ) with reference values 0.20-0.39 weak, 0.40-0.59 moderate, and >0.6 strong. For propensity score matching, we used the Bayesian spatial propensity score matching (BSPM) algorithm, which is an open source toolbox [38] associated with RStudio version 1.1.456. Two-way repeated measures ANOVAs were performed using Matlab R2018, with two factors being GROUP (real vs. sham rTMS) and TIME (baseline, baseline – 4 weeks, baseline – 8 weeks and baseline – 12 weeks) for the primary and secondary outcome variables. Post hoc analyses were performed with paired t-tests at 1.0 to find reliable treatment effects.

For the proportion of rTMS migraine responders (defined as having at least a 50% reduction in the average monthly number of migraine days), the Pearson chi-square test was used. Also, estimates of the number needed to treat (NNT) were calculated based on the primary outcome parameter using the formula: 1/absolute risk reduction. The statistical power of the study was calculated by post hoc Bayesian analysis of the posterior power distribution to verify sample size and effect size.

2.2 Results

Study group

Of the 65 subjects enrolled and randomized, sixty completed the study period and were assessed for the primary outcome at the end of the 12-week follow-up period, and five dropped out. The proportion of subjects who dropped out did not differ between groups (χ^2=2.1; p=0.14). The final study groups consisted of 33 real rTMS subjects (55%) and 27 sham rTMS subjects (45%).

The statistical power of the sample was calculated using Bayesian posterior power analysis [39]. Thus, the posterior distribution of the primary outcome (≥50% reduction in the number of migraine days over the period of 1 to 12 weeks) shows that the 95% high density interval (HDI) is within the effect obtained in our analyzed data (figure 5). This indicates a sufficient sample size for the analysis of the primary outcome in this study.

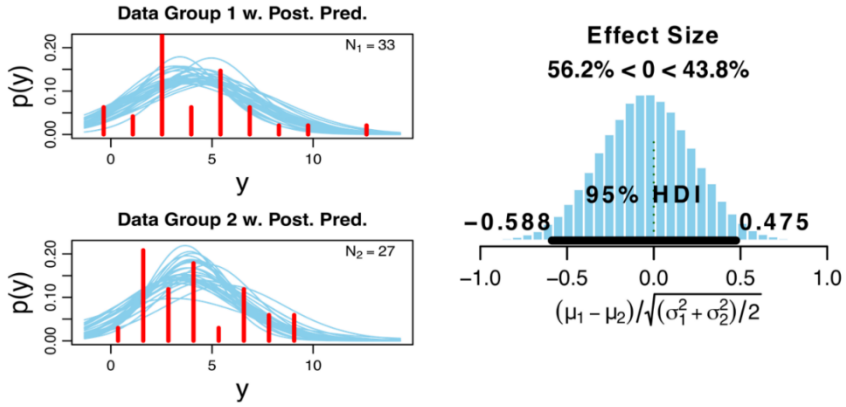

Figure 5. **Posterior distribution of study groups.** Histogram of the effect size distribution displaying the 95% density interval (HDI) of the analyzed data set and indicating a sufficient sample size of subjects included based on the primary outcome (≥50% reduction in the number of migraine days).

According to the distribution by gender, the real rTMS group included 87% (29 subjects) of female gender and 13% (4 subjects) of male gender. In the sham rTMS group – 92% (23 subjects) of female gender and 8% (4 subjects) of male gender. In both groups a prevalence of female gender was attested (p>0.05).

The mean age in the real rTMS group was 39.7 ± 11.53 years and in the sham rTMS group 39.8 ± 11.7 years (figure 6). The onset of the disease in the real rTMS group was in most cases either in Adolescence (10-19 years) 36.3% or in the Adult period (20-50 years) 54.5%, less in Childhood (<10 years) 9%; at the same time in the sham rTMS group it was distributed practically equally for all age groups 18.5% Childhood (<10 years), 22.2% Adolescence (10 - 19 years), 22.2% Adult (20 - 30 years) and 25.9% Adult (30 - 50 years).

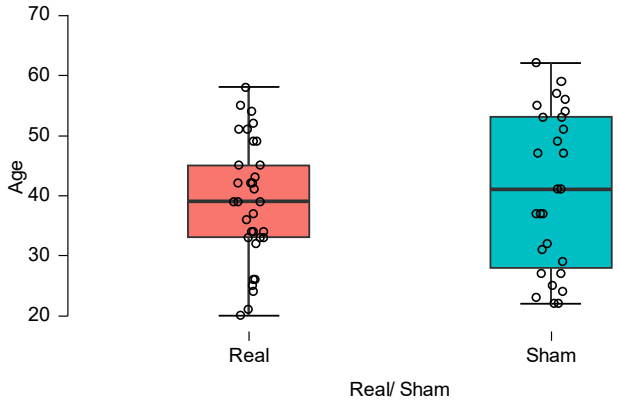

Figure 6. **Age distribution of study groups.**

The analysis of the frequency of migraine attacks in both groups revealed a number of 6.50 ± 3.05 in the real rTMS group and 6.37 ± 2.93 in the sham rTMS group. At the same time, the number of days with migraine in the real vs sham rTMS group was 7.63 ± 3.91 vs 6.22 ± 2.69 (Figure 7). The average duration of the migraine attack reported for the study groups was in most cases up to 24h (69.7%) in the real rTMS group and 81.4% for the sham rTMS group.

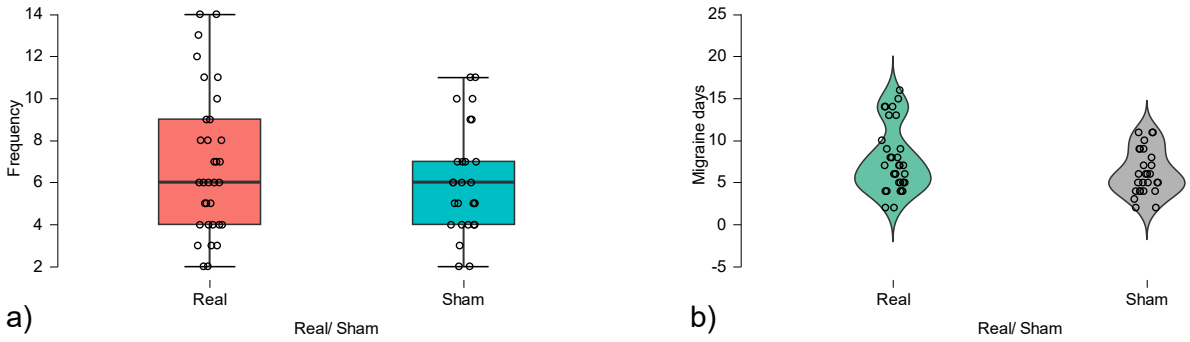

Figure 7. **Distribution of (a) attack frequency and (b) migraine days between real and sham rTMS study groups.**

The clinical presentation in relation to the lateralization of the pain syndrome highlighted the following: unilateral manifestation of pain in 22/33 (66.7%) of the Real rTMS group vs 16/24 (66.7%) Sham rTMS, bilateral 4/33 (12.1%) vs 5/24 (20.8%) and unilateral with evolution to bilateral in 7/33 (21.2%) and correspondingly 3/24 (12.5%).

Determination of the type and ratio of acute antimigraine medication elucidated that 33.3% of the real rTMS group and 55.6% of the sham group, administered NSAIDs as first-line medication in the migraine attack; the use of triptans was reported in 21.2% of the real group vs 18.5% sham rTMS; while the use of combined antimigraine preparations (e.g. paracetamol, caffeine, ergotamine) or the combination of separate components was present in 45.5% of cases in the real rTMS group and 18.5% sham, ($p>0.05$).

Outcome parameters

For migraine days as the primary outcome parameter, the response rate at 12 weeks follow-up was 14/33 (42%) in the real rTMS group and 7/27 (26%) in the sham rTMS group ($p<0.05$), resulting in a number needed to treat (NNT) of 6.0. The mean number of migraine days per month decreased from 7.6 to 4.3 days in the real rTMS group and from 6.2 to 4.3 days in the sham rTMS group, resulting in a between-group difference of -3.2 days ($p<0.05$).

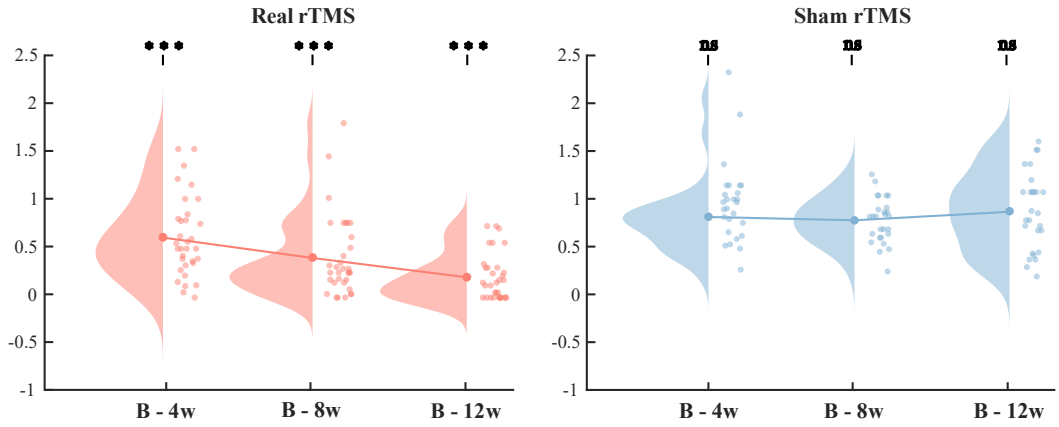

Figure 8. **Primary outcome parameter (migraine days).** Repeated measures ANOVA of migraine days in the real and sham rTMS groups, a significant decrease was observed between all follow-up time points compared to baseline only in the real rTMS group (***$p<0.001$).

There was a significant effect of GROUP ($F(1,174)=56.72$, $p<0.001$) and TIME ($F(2,174)=3.37$, $p=0.037$) and a significant GROUP x TIME interaction ($F(2,174)=5.07$, $p=0.007$). Post-hoc tests revealed a significant decrease in migraine days between follow-up points compared

to baseline in the real rTMS group (p<0.001), while no significant reduction in migraine days was detected in the sham rTMS group (figure 8). At 12 weeks of follow-up, the rate of responders regarding migraine attack frequency was higher in the real rTMS group compared to the sham rTMS group (42% vs 33%, p<0.05).

In the repeated measures ANOVA analysis, we found a significant effect of the factors GROUP ($F(1,174) = 92.28$, $p < 0.001$) and TIME ($F(2,174) = 3.75$, $p=0.025$) with a significant GROUP x TIME interaction ($F(1,174) = 11.72$, $p<0.001$). Post hoc tests showed a significant decrease in migraine frequency between follow-up times compared to baseline in the real rTMS group (p<0.001), while the sham rTMS group showed an increase in frequency, which was not statistically significant (figure 9).

When analyzing the VAS parameter, we found a significant effect only for the GROUP factor ($F(1,174) = 25.14$, $p<0.001$), while the TIME factor ($F(2,174) = 1.83$, $p = 0.163$) and the GROUP x TIME interaction ($F(2,174) = 0.49$, $p=0.613$) were not significant (figure 10).

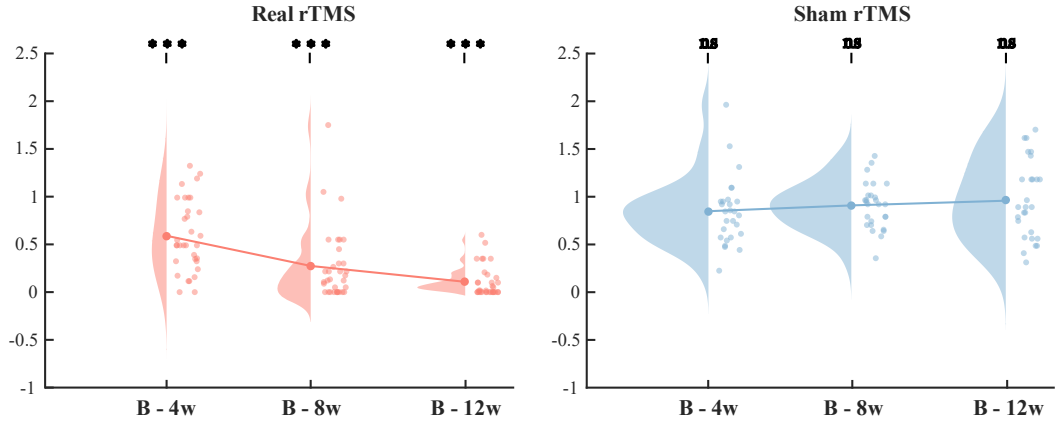

Figure 9. **Secondary outcome parameter (attack frequency).** Repeated measures ANOVA of migraine attack frequency in the real and sham rTMS groups, showing a significant decrease in frequency in the real rTMS group (***p<0.001), while the sham rTMS group showed a slight increase, which was not statistically significant (ns=p>0.05).

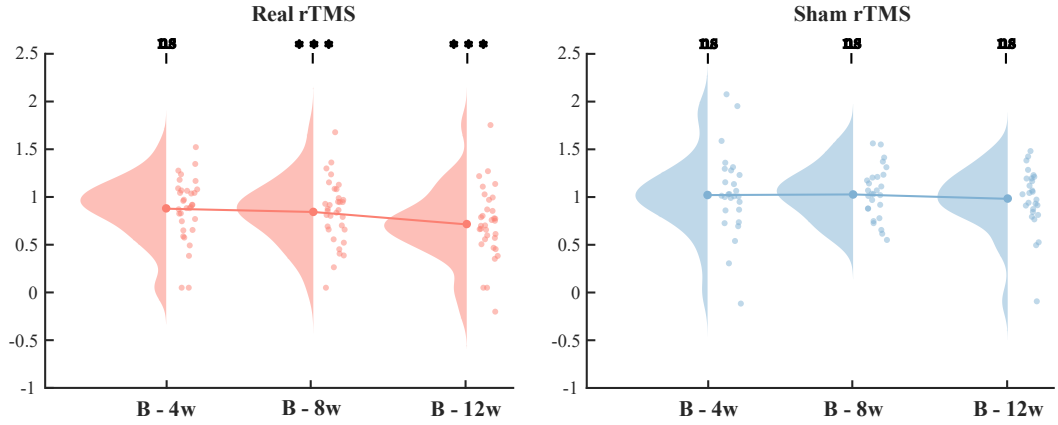

Figure 10. **Secondary outcome parameter (Visual Analogue Scale).** Repeated measures ANOVA of the visual analogue scale (VAS) demonstrated a significant decrease in migraine attack intensity only in the real rTMS group, this being present only for the follow-up periods (8 weeks and 12 weeks) compared to the baseline value (***p<0.001).

As an additional secondary outcome parameter we analyzed HIT-6, which showed a significant effect of the GROUP factor ($F(1,174) = 392.58$, $p < 0.001$) and a clear trend for the TIME factor ($F(2,174) = 2.10$, $p = 0.124$) and for the GROUP x TIME interaction ($F(2,174) = 2.26$, $p = 0.107$) (figure 11).

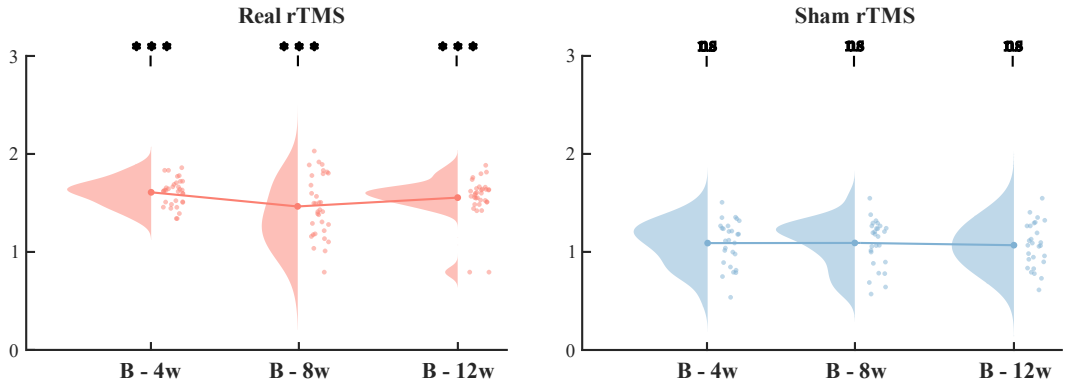

Figure 11. Secondary outcome parameter (HIT-6). Repeated measures ANOVA of HIT-6 score showed a significant difference between groups with reduction in headache impact in the real rTMS group (*p<0.001) and no change in the sham rTMS group.**

In the evaluation of the secondary parameter MIDAS, a significant effect of the factor TIME ($F(1,58) = 19.85$, $p<0.001$) and GROUP ($F(1,58) = 0.53$, $p>0.05$) was observed and for the interaction TIME x GROUP ($F(1,58) = 3.54*10\text{-}4$, $p>0.05$). Thus, although the changes in the MIDAS score were significant for each of the real and sham rTMS groups separately, they were statistically insignificant in the intergroup analysis ($p>0.05$) (figure 12).

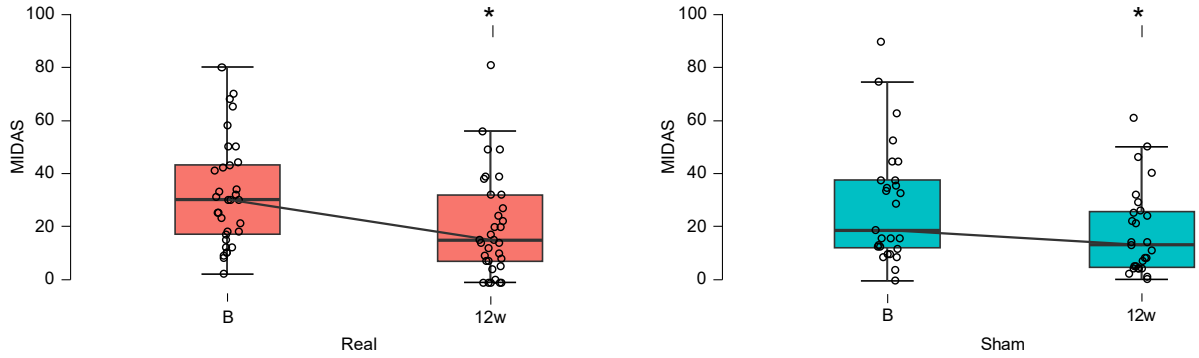

Figure 12. **Secondary outcome parameter (MIDAS).** Repeated measures ANOVA of MIDAS score showed a significant difference between baseline (B) and 12-week (12w) follow-up periods for each group (*p<0.001), however, the real vs sham rTMS inter-group difference was non-significant (p>0.05).

To assess the global impression of change (PGIC) at 12 weeks after the experimental multifocal rTMS protocol, depending on the reported scores, the subjects were assigned to 3 groups: 0-3 (worsening of the condition), 4 (no change), 5-7 (improvement of the condition). At the same time, the assessment of the change in the outcome parameters was performed by calculating the delta (Δ) between the value at 12 weeks and baseline for the frequency of attacks (ΔFR), the number of days with migraine (ΔMIG) and the intensity of migraine attacks (ΔVAS). The correlation analysis between the summary PGIC score and other clinical parameters was performed by Spearman rho (ρ), which revealed a moderate statistically significant correlation

with ΔMIG r(58)=0.44, p<0.001 and ΔFR r(58)=0.40, p=0.002; and for ΔVAS this was statistically insignificant, p>0.05. The difference in reporting PGIC score at 12 weeks in the real vs sham rTMS study groups was insignificant (p>0.05), also the separate correlation analysis of PGIC score for each group with other clinical parameters did not determine significant correlations (p>0.05).

Safety and tolerability

The adverse events recorded were headache, auditory discomfort, dizziness, drowsiness, and local discomfort at the stimulation site. Although the total number of subjects reporting at least one adverse event was slightly lower in the sham group (n=6) than in the real (n=14) rTMS group, this was not statistically significant ($\chi 2 = 2.73$; p>0.05).

No severe adverse events attributed to the experimental rTMS protocol were reported in any of the study groups.

The tolerability of the multifocal rTMS protocol was assessed by evaluating three parameters: the degree of pain created by the rTMS, the intensity of the noise, and the general degree of discomfort. In the real rTMS group: the degree of pain was rated as absent or mild in 87.8% of cases and the intensity of the noise in 84.8%; the general degree of discomfort created by the experimental protocol in 90.9% was reported as absent or mild. In the sham rTMS group, the results were similar (p>0.05).

THETA BURST TRANSCRANIAL MAGNETIC STIMULATION IN EPILEPSY

3.1 Materials and methods

Study design

An experimental, cTBS-interventional, open-label, single-arm study was conducted, which included adult subjects with generalized epilepsy. After a 4-week screening period all eligible subjects were assigned to the theta burst magnetic stimulation (TBS) group for 6 sessions of continuous TBS intervention (cTBS) during 6 consecutive days. This was followed by a follow-up period of up to three months with visits at predefined intervals at 4, 8 and 12 weeks (figure 13).

Statistical power of the sample

To achieve the aim and objectives of the research, the total number of subjects enrolled was calculated taking into account the data on the methodology applied in the TMS/TBS studies [40] and the design of the study in question, these being transposed into the statistical calculation using GPower v.3197. Finally, in order to maintain the statistical power of the study (0.8 – a value frequently used and considered sufficient in experimental biomedical studies [41]), considering that the study includes a single arm, we obtained a value of at least 13 subjects for the real statistical power of 0.8200031.

Subjects

Of the total number of 314 patients with epilepsy analyzed according to the information from the electronic records – 159 (50.6%) patients were excluded in the primary analysis stage (133 (42.3%) patients with focal epilepsy, 17 (5.4%) missing contact data, other causes - 9 patients (2.9%)). At the subsequent stage, of the 155 (49.4%) subjects with generalized epilepsy, 115 (36.6%) people were excluded (72 (23%) patients had a complete therapeutic response on the background of the antiepileptic medication administered and were free of epileptic seizures, 34 (10.8%) patients refused participation, 7 (2.2%) patients – missing secondary telephone contact, 2 (0.6%) – deceased).

In total, subjects with generalized epilepsy potentially eligible for screening – 40 (12.7%) patients, of whom at the end of the screening period – 26 (8.3%) patients were excluded. Finally, 14 (4.45%) subjects with various forms of generalized epilepsy were enrolled in the study for the application of the experimental protocol of "theta burst" magnetic stimulation (TBS).

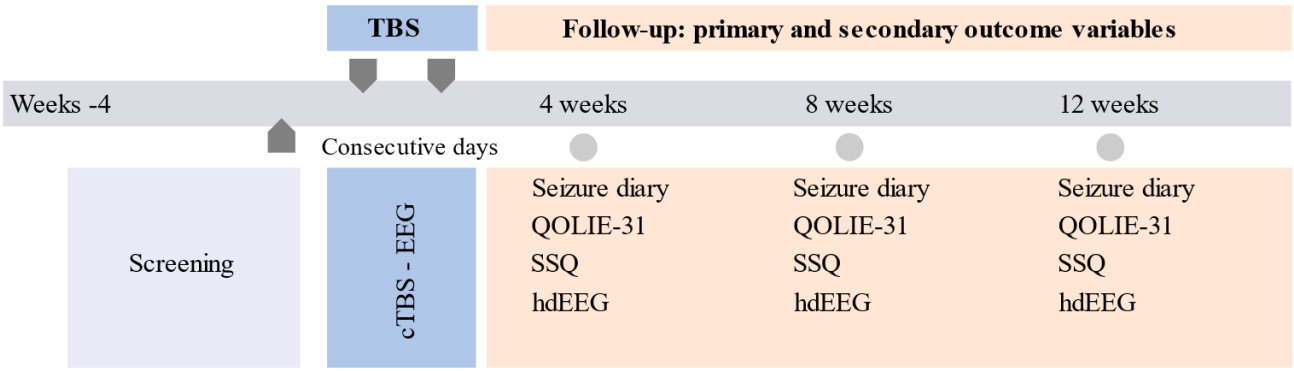

Figure 13. **Design of the cTBS-epilepsy study.** Subjects completed a four-week seizure diary and the Quality Of Life In Epilepsy (QOLIE-31) and Seizure Severity Questionnaire (SSQ) questionnaires before the first cTBS stimulation session. ≥50% improvement from baseline in epilepsy days during the 12-week period after cTBS intervention served as the primary outcome variable. ≥50% improvement from baseline in seizure frequency during the same period served as key secondary outcome variables. Questionnaires on quality of life, seizure severity assessment, and global impression of change were administered at several follow-up visits and their results were considered as secondary outcome indicators. All questionnaires were completed individually by the subject, and assistance was provided as needed to complete the form. During all cTBS sessions (6 in total) as well as at each of the follow-up visits (4, 8 and 12 weeks), hdEEG (high-density EEG) traces were recorded in parallel with cTBS.

Inclusion criteria: Adult patients with generalized epilepsy according to the ILAE 2017 classification were included [42].

Exclusion criteria: Refusal to sign informed consent; focal, combined or unknown epilepsy; drug-resistant form of epilepsy; history or signs of metabolic impairment (renal, hepatic); history of oncological pathology; uncontrolled high blood pressure; intellectual disability; psychiatric disorders; signs of structural brain damage or focal neurological deficit; use of opioid drugs, muscle relaxants; history of substance abuse; ferromagnetic implants in the head and neck regions, pacemakers and pregnant or lactating women.

Resting Motor Threshold (RMT) Assessment

The RMT determination was performed for each patient after placement of the hdEEG electrode mesh to obtain standardized and reliable results considering the additional distance traveled by the electromagnetic pulse emitted by the coil until the motor cortex was stimulated, given that the application of the cTBS experimental protocol will proceed in parallel with high-density EEG recording to monitor cortical electrical changes, including possible induced adverse events. Along with the RMT assessment, the electrophysiological characteristics of the motor evoked potential (MEP) such as its latency and amplitude before and after cTBS were also assessed.

Multifocal cTBS stimulation paradigm

After determining the RMT, all subjects underwent 6 sessions of continuous magnetic stimulation "*theta burst*" (cTBS) according to the research protocol over 6 consecutive days.

The experimental stimulation protocol included 1800 pulses with a frequency of 50Hz, 80% of the RMT divided into 3 trains applied at the vertex level (Cz) with an inter-train interval of 10 min. (figure 14).

After the cTBS session, similar to the previous study (*see rTMS in migraine*) the subjects were evaluated regarding the detection of adverse events during and/or immediately after the stimulation; as well as the perception of the cTBS procedure

Statistical analysis

Continuous variables are presented as mean values ± standard deviation. Gaussian distribution was verified by histogram analysis and Shapiro-Wilk test. Statistical power of the research group was calculated using GPower v.3197. For demographic and clinical characteristics, differences were verified by Student's t-test and Pearson chi-squared tests. Continuous variables with normal distribution were evaluated by Student's t-test or Mann-Whitney test in case of abnormal distribution. Repeated ANOVA analyses were performed using Matlab R2018, RStudio and JASP, assessment intervals consisted of baseline (until cTBS), 4 weeks, 8 weeks and 12 weeks for primary and secondary outcome variables. Post-hoc analyses were performed using RStudio, JASP considering $p<0.05$ statistically significant. For the proportion of cTBS responders (defined as having at least a 50% reduction in the average monthly number of epileptic seizures), the Pearson chi-square test was used.

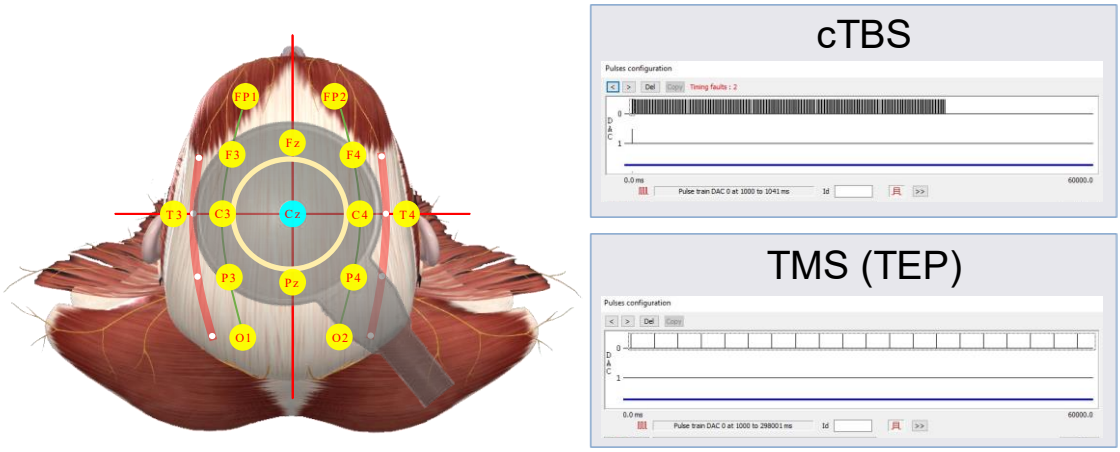

Figure 14. **cTBS stimulation protocol.** Positioning the MMC-140 coil on the vertex (Cz) allows for simultaneous multifocal stimulation of both motor and somatosensory cortical areas. cTBS stimulation protocol (1 cTBS stimulation train containing 600 pulses), TMS stimulation (1 pulse at 3s interval, applied in the evaluation of RMT or Cortical Evoked Potential TEP).

3.2 Results

Study group

To achieve the aim and objectives of the study, considering the necessary statistical power of the group (*see thesis 3.2 Materials and methods*) 14 subjects were enrolled, thirteen completed the study period and were evaluated for primary and secondary outcomes at the end of the 12-week follow-up period, and 1 subject dropped out. The extended presentation of demographic and clinical parameters can be found in table 1.

According to the distribution by gender, the group included 84.6% (11 female subjects) and 15.4% (2 subjects) of male gender. The majority of subjects resided in urban areas 61.5% vs. 38.5% rural; 69.2% of them were actively employed. Interestingly, 76.9% (10 subjects) had a history of episodic tension-type headache and 23.1% (3 subjects) noted migraine-like episodes without aura (possible recall bias), which would correspond to data from the literature regarding the comorbidity between epilepsy and migraine.

At the same time, we see that the average age of the subjects was 32.84 ± 7.34 years, the age at the onset of the disease was 14.76 ± 6.45 years; having an average duration of the disease of 18.07 ± 6.75 years. The characteristic of the initial number of epileptic seizures up to cTBS (baseline) is presented as 6.69 ± 5.58 seizures/month, the quality of life score in epilepsy (QOLIE-31) of 60.29 ± 14.79 and the severity score of epileptic seizures (SSQ) has an average value of 100.69 ± 28.94, being quite high, which signals the significant impact on the quality of life of these patients. The intensity of the stimulus determined in the RMT evaluation was 30.46 ± 7.37%.

Tabelul 1. Demographic description of the study group (continuous variables)

Subjects (n = 13)	Median	Average	SD	Shapiro-Wilk	Shapiro-Wilk (p)	Min	Max
Age	36.00	32.84	7.34	0.913	0.202	19.00	42.00
BMI	24.60	24.97	5.10	0.911	0.190	19.10	37.30
Stim cTBS (%)	28.00	30.46	7.367	0.917	0.229	21.00	48.00
Age at onset	14.00	14.76	6.457	0.942	0.483	1.00	27.00
Disease duration	18.00	18.07	6.751	0.915	0.214	9.00	29.00
Seizure frequency	5.00	6.69	5.588	0.774	0.003*	2.00	22.00
QOLIE-31	59.11	60.29	14.796	0.942	0.488	32.210	86.630
SSQ	108.00	100.69	28.944	0.858	0.037*	39.000	131.000
Seizure duration (s)	5.00	44.111	64.567	0.725	0.003*	2.000	180.000

**p < 0.05. SD – standard deviation, BMI – body mass index, Stim (%) – TBS stimulus intensity, QOLIE-31 - Quality of Life in Epilepsy Score; SSQ - Seizure Severity Score .*

Most subjects had the onset of the disease in adolescence (10-19 years) 61.5%, followed by the period of young adulthood (20-30 years) – 30.8% and only 7.7% in childhood.

The type of seizures encountered in the subjects in the study were represented in 38% of cases by myoclonic-tonic-clonic seizures, 31% by tonic-clonic, 23% by absence type seizures and only in 8% by pure myoclonic.

Analyzing the antiseizure medication (ASM): 38.5% of cases used the combination of Lamotrigine + Valproic Acid, another 23.1% of cases Levetiracetam + Lamotrigine and 7.7% Valproic Acid + Clonazepam. At the same time, monotherapy with ASM consisted of Valproic Acid in 15.4% of cases and equally 7.7% administered Lamotrigine and Levetiracetam respectively.

Outcome parameters

Detailed analysis of the primary and secondary outcome parameters revealed the following changes:

The response rate was 69.2% at 4-week follow-up and 76.9% at 8- and 12-week follow-up, respectively. The mean number of seizures decreased from 6.7 to 2.6 per month ($p<0.05$). A significant decrease in seizure frequency was observed at all follow-up visits (4, 8, and 12 weeks) compared to baseline ($p<0.05$, figure 15).

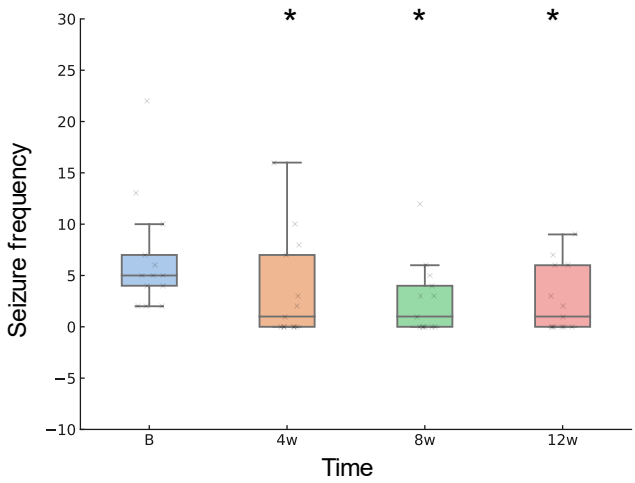

Figure 15. **Primary outcome parameter (seizure frequency).** Repeated measures ANOVA of seizure frequency in the study group, a significant decrease is observed between all follow-up time points compared to baseline (*$p<0.05$).

A mean increase in QOLIE-31 scores of 16.3 points (from 60.3 ± 14.8 to 76.6 ± 12.9, $p<0.001$) was observed between baseline and the 12-week visit (Figure 16). In addition, QOLIE-31 scores increased significantly at all follow-up visits (4, 8, and 12 weeks) compared to baseline ($p<0.001$). The subscores "emotional well-being," "energy/fatigue," "social function," and "cognitive function" improved at all follow-ups (4, 8, 12 weeks) compared to baseline ($p<0.05$). Compared to baseline, the subscore "seizure worry" showed a significant decrease at the 4- and 8-week follow-ups ($p<0.05$), but not at 12 weeks.

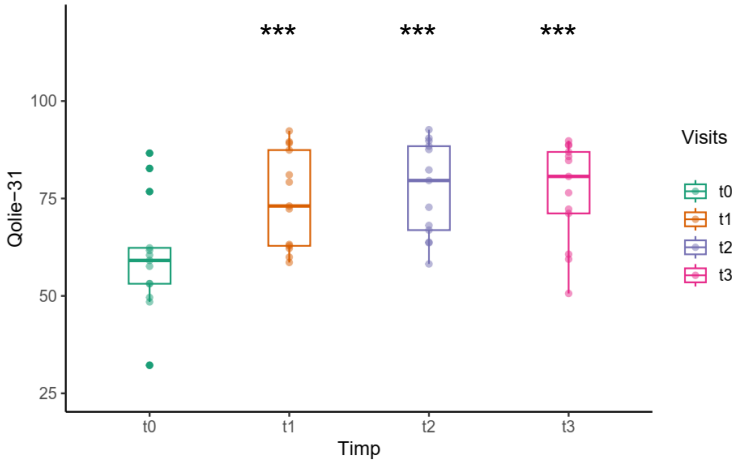

Figure 16. **Secondary outcome parameter (QOLIE-31).** Repeated measures ANOVA of epilepsy quality of life score in the study group, a significant increase is observed between all follow-up time points compared to baseline (***p<0.001).

A significant decrease in seizure severity score (SSQ) was observed at all follow-up visits (4, 8 and 12 weeks) compared to baseline, p<0.001. A mean decrease of 75.3 points (from 100.7 ± 28.9 to 25.4 ± 33.7, p<0.001) was observed between baseline and the 12-week visit (figure 17).

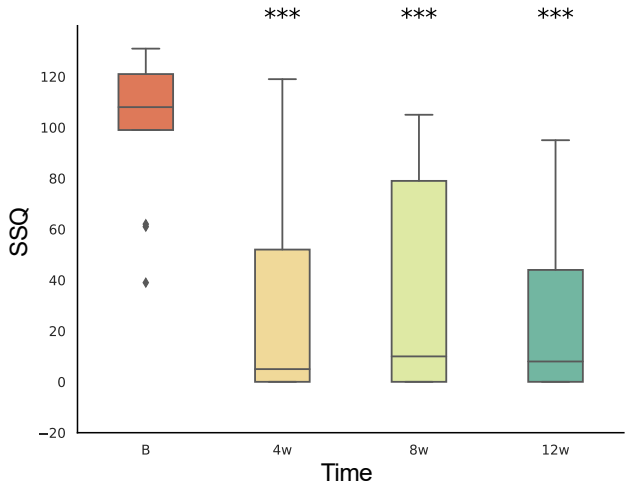

Figure 17. **Secondary outcome parameter (SSQ).** Repeated measures ANOVA of seizure severity score in the study group, a significant decrease is observed between all follow-up time points compared to baseline (***p<0.001).

A decrease in cortical excitability was observed after cTBS by assessing RMT and electrophysiological parameters of MEP. A significantly higher RMT was measured after cTBS (M=43.1±9.4) than RMT before cTBS (M=38.0±9.2, p<0.001), indicating a process of increasing excitatory threshold. Similarly, MEP latency after cTBS (M=21.4±2.8) was significantly higher than MEP latency before cTBS (M=19.9±2.47, p<0.001); while MEP amplitude after cTBS (M=3.1±1.2) was significantly lower compared to pre-cTBS values (M=3.7±1.7, p<0.05, figure 18).

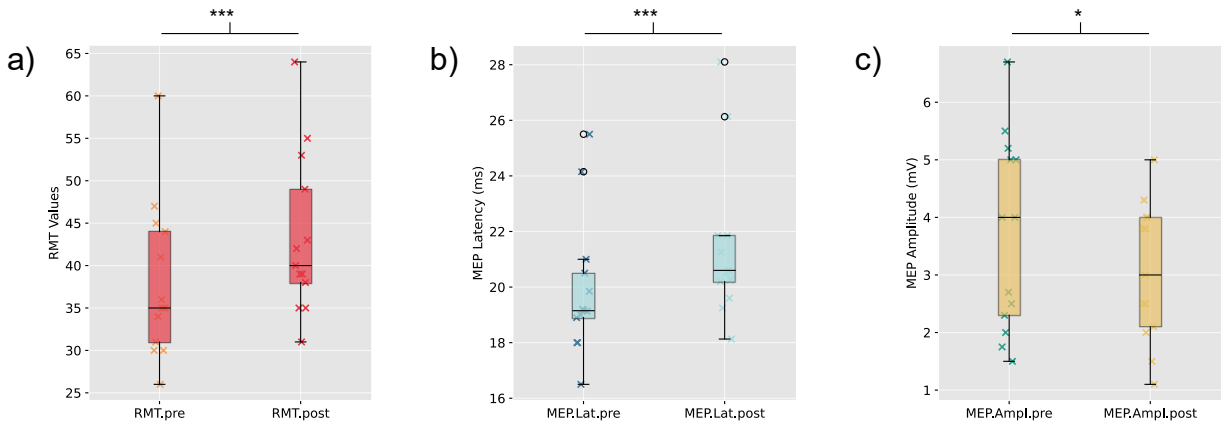

Figure 18. **Changes in cortical excitability parameters pre/post-cTBS**. A statistically significant difference was observed between the parameters (a) resting motor threshold RMT, (b) motor evoked potential latency MEP, (c) motor evoked potential amplitude MEP pre- and post-cTBS. (***p<0.001, *p<0.05).

The results given would suggest the establishment of the LTD effect (long-term synaptic depression) resulting in the diminution of cortical excitability, essentially inducing a mechanism similar to antiepileptic medication.

Adverse events of cTBS in our study were headache in 46.2% of subjects, discomfort at the stimulation site in 7.7% and dizziness in 15.4%. In most cases, the intensity of adverse events was assessed as mild, with a mean duration of 31.5 ± 42.5 minutes (table 2). In 13/13 (100%) cases the adverse event was present after the first cTBS stimulation session, and in 8/9 (89.9%) cases it was attributed to transcranial magnetic stimulation.

Table 2. Description of adverse events in the study group

	Number (abs)	(%)
Intensity		
Mild	7	53.84
Moderate	2	15.38
Severe	-	-
None	4	30.76
N/a	-	-
Duration		
< 15 min	4	30.76
15-30 min	2	15.38
30-60 min	1	7.69
> 60 min	2	15.38
Attributed to cTBS		
Yes	8	61.53
No	1	7.69

The analysis of the perception of the experimental cTBS protocol revealed a strong positive correlation between the intensity of the cTBS pulse stimulus (assessed in dependence on the RMT) and the perception of pain: $r(11)=0.88$, $p<0.001$, 95% CI [0.638, 0.964], $r2 = 77.4\%$. In other words, the intensity of the cTBS stimulus was correlated with 77.4% of the results of the parameter of perception of the degree of pain created by the experimental protocol.

Also, for the intensity of the cTBS stimulus, a weak positive correlation was observed with the perception of discomfort ($r(11)=0.18$, $p>0.05$, 95% CI [-0.416, 0.662]) and a weak negative correlation with the perception of noise ($r(11)= -0.13$, $p>0.05$, 95% CI [-0.637, 0.451]), however, these were statistically insignificant ($p>0.05$).

GENERAL DISCUSSIONS

The importance of researching new treatment methods through the prism of neuromodulation mechanisms is becoming fundamental for modern medicine. The dynamic complexity of the clinical presentation, the ictal involvement of nervous structures, the physical and/or functional disability induced by the spectrum of neurological diseases with paroxysmal presentation makes it difficult to standardize the therapeutic element, while presenting an exciting research horizon. Approaching neurological diseases such as migraine and epilepsy through the vision of disturbances of neuronal networks [43] opens the possibility of influencing their activity

through neuromodulatory therapies. In contrast to the "dispersed" pharmacological treatment, these therapies offer a new perspective: targeting and interrupting the processes of dysfunctional organization of a region or a brain network, based on technological advances and a deepening understanding of the specific mechanisms for each pathology.

Currently, the range of neuromodulatory techniques in the field of epilepsy and migraine includes invasive and non-invasive modulation modalities. In epilepsy, the US Food and Drug Administration (FDA) has approved the use of invasive electrical vagus nerve stimulation (VNS) as an adjunctive therapy in adult and pediatric subjects (age > 4 years) with focal and/or generalized epilepsy that is non-responsive or partially responsive to pharmacological treatment since 1997 [44]. More recently, non-invasive neuromodulatory modalities such as non-invasive/transcutaneous vagus nerve stimulation (n/tVNS) [45], transcranial direct current stimulation (tDCS) or alternating current stimulation (tACS) [46], transcutaneous electrical nerve stimulation (TENS), repetitive transcranial magnetic stimulation (rTMS) or theta burst (TBS) have been increasingly studied in both epilepsy and migraine. Of all these, transcranial magnetic stimulation (TMS) seems to be the most promising, having a number of advantages compared to other neuromodulatory techniques.

And one of the most important advantages of transcranial magnetic stimulation is the high temporal-spatial resolution of the therapeutic act, especially through TMS-EEG coupling that allows selective targeting of the structures of interest and accurate quantification in real time of the induced changes in neuronal excitability. At the same time, transcranial magnetic stimulation protocols in a large part of the studies in the field of migraine and epilepsy apply focal stimulation on brain structures [47].

In this regard, our study was designed and conducted based on the exploration of the multifocal transcranial magnetic stimulation paradigm in the management of patients with neurological disorders with paroxysmal presentation. Based on the increasing number of studies that have highlighted similar pathophysiological mechanisms in migraine attacks and epileptic seizures (the phenomenon of widespread cortical depression (CSD), abnormal neuronal excitability, dysfunction of cortico-subcortical structures [48, 49], convergence of common genetic elements, etc.), we aimed to study the efficacy of multifocal transcranial magnetic stimulation in the prophylaxis of migraine attacks in patients with episodic migraine and of epileptic seizures in patients with generalized epilepsy.

At the same time, the fact that both disorders are separate nosological entities, with individual specificity both in the ictal and inter-ictal periods, determined that the research should include two separate components for each of the diseases, applying, however, the same multifocal neuromodulatory approach through transcranial magnetic stimulation; and the comparative analysis of the research groups (migraine vs. epilepsy) being possible only in the descriptive demographic aspect and the trend of the therapeutic effect of the experimental TMS intervention, taking into account the difference between the number of subjects in both groups.

Thus, the methodology of the study carried out highlighted in the process of questioning the general population (n=807), the rate of migraine patients of 15.7%, which in epidemiological terms confirmed the results of other national studies [7]; this was not possible in the context of patients with epilepsy, due to their enrollment through the analysis of electronic databases. The gender distribution of the research groups highlighted a prevalence of female gender in both studies (90% migraine group vs. 84% epilepsy group), the average age was also similar for both studies (39.7±11.6 years vs. 32.8±7.3 years), by place of residence both summary groups were similar

(81.8% real rTMS/48.1% sham (mimic) rTMS migraine group vs. 61.5% epilepsy group lived in urban areas). There were no significant differences in social status. At the same time, it was observed that the employment rate in the migraine group was on average 76.5% while in the epilepsy group it was 69%, and completed university studies were reported by 61% of the migraine group (63.7% real vs 59.3% sham rTMS) and only 15.4% of the epilepsy group (the majority 53.8% having high school education or lower). So, we can see that the epilepsy group presented a lower level of education and a lower degree of employment, we could admit that this could be correlated with the semiological specificity of epilepsy compared to migraine and/or with the stigmatization of these patients.

In the migraine study, the experimental multifocal rTMS protocol targeted the aberrant pathophysiological mechanisms described in migraine patients, such as central and peripheral sensitization [6]. This results from a complex series of biochemical cascades such as the impact of proinflammatory cytokines such as bradykinin, histamine, serotonin (5-HT), prostaglandin E2 (PGE2); neuropeptides – substance P (SP), calcitonin gene-related peptide (CGRP) that induce the activation of nociceptors capable of influencing the function of voltage-gated ion channels that respond to the electrical excitatory threshold of the cell. The reduction of the latter increases the excitability of the structure (trigemino-cervical complex, thalamus, somatosensory cortex, etc.) and eventually this can be activated by a subthreshold stimulus [50]. Therefore, the experimental protocol included both stimulation of the peripheral element (trigeminal afferents, n. occipitalis major and minor) and direct impact on cortical areas (somatosensory, visual).

The quantification of the therapeutic effect of the experimental protocol was confirmed by its ability to reduce by ≥50% the number of migraine days at 12 weeks post-rTMS exposure, a phenomenon expressed in 42% of the patients in the experimental group, compared to the placebo (sham rTMS) in which it was 26%, and the effect being statistically significant ($p<0.05$). The average number of migraine days per month decreased from 7.6 to 4.3 days in the experimental group and from 6.2 to 4.3 days in the placebo group, resulting in a difference between groups of -3.2 days ($p<0.05$). In addition, a significant decrease in the frequency of migraine attacks by ≥50% was observed in 42% of the experimental group compared to 33% of the placebo group ($p<0.05$). Also, to translate the effectiveness of the studied protocol into clinical experience, we calculated the number needed to treat (NNT), which means the number of patients who need to benefit from the therapeutic intervention to reduce by ≥50% the number of migraine days at 12 weeks, the NNT being 6.0. According to studies assessing the effectiveness of non-invasive neurostimulation techniques, the values obtained in our study not only fall within the reference ranges for preventive treatment (NNT = 1.5-11.1) but are also included in those recommended for acute treatment (NNT = 3.6-6.5) [51], which raises an interest in studying in the future the potential of the multifocal protocol to be used in the acute period of migraine attacks. Another important factor of the analysis was the intensity of migraine attacks. Here we also obtained a promising response in the experimental group compared to the placebo group ($p<0.05$). These results are similar to other studies with high-frequency rTMS [52-54], however, to our knowledge, all described protocols were unifocal, and the experimental protocol in our research was the only multifocal.

In addition, we also analyzed the impact of multifocal rTMS on the quality of life of the enrolled patients, applying the scales recommended in the protocols for evaluating the effectiveness of experimental preventive interventions in episodic migraine developed by the International Headache Society [55]. According to the HIT-6 score (migraine impact assessment score), rTMS with the experimental protocol induced a statistically significant decrease throughout

the study period ($p<0.001$), compared to the sham rTMS group in which there was practically no change. The same trend was highlighted by the decrease in the headache disability index (HDI) at 8 weeks, the results being in favor of the experimental protocol group ($p<0.001$) and in the sham group this being insignificant ($p>0.05$). Another parameter of migraine-induced disability assessment (MIDAS) in contrast showed no differences between the rTMS groups evaluated at 12 weeks, both groups demonstrating a significant improvement ($p<0.001$). This phenomenon could be partially explained by the fact that the HDI and MIDAS scales, due to their specificity, evaluate different periods of time, HDI (2 months) and MIDAS (3 months). Another influencing variable could be the placebo effect of improving the condition, elucidated in the sham rTMS group (26-33%), moreover, well known in non-invasive neuromodulatory research and reported by some authors to be 21-39% [56].

This study is not without limitations. The first limitation may relate to the total number of subjects and the fact that there were only a few subjects with migraine with aura. Several studies have shown important differences between migraine with and without aura at the functional and anatomical levels [13], thus suggesting a potential difference in therapeutic responses. It is important to emphasize that in the general population migraine with aura is much rarer compared to migraine without aura, representing only 1.9–5.2% of migraine patients [57].

Second, despite the methodological precautions regarding sham stimulation, partial unblinding may have occurred, as all subjects received a single real TMS pulse while assessing baseline RMT values, which produces a specific audible and tactile sensation as the pulse passes through the scalp and pericranial tissues. However, this is not unique to our study and is a common problem in TMS research, so we doubt that this fact influenced our conclusions in any way; moreover, a coil specifically designed for double-blind studies was used for rTMS stimulation.

Third, the present study does not have a crossover design, therefore, occasional pericranial muscle contractions in the real rTMS group are unlikely to affect the final results It should also be taken into account that randomization and stimulation were performed by different investigators to maintain a high degree of objectivity of the intervention.

The study of the effects of TMS in patients with generalized epilepsy was based on the paradigm of descending (downstream) cortico-subcortical modulation induced by transcranial magnetic stimulation [58], considering the results of studies in the field that demonstrated the dysfunctions of the thalamo-cortical [59, 60], cortico-basal [61], cortico-cortical [62] neural networks as well as the modification of cortical excitability present in patients with generalized epilepsy. In this regard, the hypothesis was developed and applied that the experimental protocol of continuous multifocal theta burst transcranial magnetic stimulation (cTBS) could reduce the number of epileptic seizures and possibly improve the quality of life in patients with generalized epilepsy. The design of this study was chosen as an open, single-arm one. This was similar to other experimental TBS studies in patients with epilepsy [63, 64]. The multifocal neuromodulatory hypothesis of the experimental protocol was to determine its ability to directly modulate primary/secondary motor and sensory cortical areas.

Confirmation of efficacy was assessed as a ≥50% reduction in the number of epileptic seizures at 12 weeks post-intervention. The results obtained highlighted a response rate of 76.9% ($p<0.05$), which was superior to the results reported by other studies in which the reduction in the number of epileptic seizures was on average 30% (ranging between 17-60%) [63]. The average number of epileptic seizures/month in the study group was determined to decrease from 6.7 to 2.6 ($p<0.05$). Analysis of cortical excitability parameters revealed patterns of increased resting motor

threshold ($p<0.001$), increased latency ($p<0.001$) with decreased amplitude of the evoked motor response ($p<0.05$). Similar effects were also reported by other studies analyzing the impact of unifocal cTBS on cortico-subcortical structures [65]. The probable mechanism underlying this process is the phenomenon of LTD (long-term synaptic depression) which reduces the excitability of target structures, thus decreasing the probability of their depolarization under the influence of a subthreshold or repetitive stimulus. At the same time, a strong negative correlation ($rs(11)= -0.593$, $p<0.05$) was found between the resting motor threshold and the presence of more than 1 type of epileptic seizures in the same patient (*e.g. myoclonic and tonic-clonic seizures*). This phenomenon is probably explained by the dysfunction of the regulation of cortico-subcortical homeostatic activity and could serve as a biomarker of cortical excitability in assessing the pharmacological therapeutic response as well as in the decision to reduce or interrupt antiepileptic medication [66].

Confirming the basic hypothesis, we subsequently evaluated the parameters of epileptic seizure severity (assessed according to the SSQ score) and quality of life in epilepsy (QOLIE-31). A statistically significant decrease in epileptic seizure severity was observed at 12 weeks compared to the baseline period ($p<0.001$), and the analysis of SSQ subscores determined that the strength of the cTBS effect was more expressed in the subscores describing seizure activity and post-ictal recovery, especially the physical and cognitive component ($p<0.001$). At the same time, a strong positive correlation was observed between the summary SSQ ($r(11)=0.61$, $p<0.05$) and the SSQ post-ictal recovery subscore ($r(11)=0.590$, $p<0.05$) with the frequency of epileptic seizures at 12 weeks. The analysis of the quality of life score in epilepsy (QOLIE-31) showed a significant increase between all follow-up visits compared to the initial value ($p < 0.001$).

The appreciation by >80% of subjects of the experimental multifocal protocols (rTMS-migraine, cTBS-epilepsy) as an intervention that causes no or minimal discomfort, speaks in favor of their high degree of tolerability. In tandem, the lack of severe adverse reactions in both studies and the appreciation of those that occurred as mild or moderate (80% of cases) confirm the excellent degree of safety of the applied multifocal protocols.

In relation to the limitations of the study, we could consider that the relatively small number of subjects enrolled in the study as well as the open-label single arm design could be seen as potential limitations. At the same time, it is important to note that the statistical power of the research group was calculated respecting the methodology of biomedical studies [41], as well as the fact that the small number of subjects is a common phenomenon for research in the field of cTBS and epilepsy (*Carrette et al., 2022 - 7 subjects (study period 3 years, open-label single arm design); Koc et al., 2017 - 15 subjects, open-label single arm design; Celebi et al., 2023 - 12 subjects, of which only 5 with generalized epilepsy, cross-over design*) [63, 64, 67]. In this regard, we consider this limitation as a relative one, and increasing the number of subjects as well as the cross-over design could enhance the power and bring additional data to the research of cTBS in patients with epilepsy.

Another element that could have influenced the final results and the reporting of adverse reactions related to the experimental protocol could be the specificity of the neurological disorder, especially the paroxysmal manifestation of epileptic seizures, the patient's increased expectations related to therapeutic results and hesitations related to the probability of failure being strongly expressed in patients with epilepsy.

The methodological complexity of the cTBS-hdEEG sessions could have influenced the reporting of adverse reactions, however, based on the fact that all adverse reactions were reported after the first session, the short duration and the low intensity, we can admit that they were largely

influenced by the degree of anxiety related to cTBS as a stimulation method and less by the experimental protocol.

Also, the 12-week (3-month) follow-up period would not allow for long-term conclusions, however, it represents a time interval that complies with the recommendations for conducting studies in the field of epilepsy and is superior to other published studies of cTBS in epilepsy (4 weeks) [68].

CONCLUSIONS

1. The results of the study demonstrated the ability of the multifocal protocol applied for 6 alternate days to reduce by ≥50% the number of attacks and days with migraine in 42% of patients with episodic migraine over a period of 12 weeks post-stimulation ($p<0.001$). The average number of days with migraine per month, decreased from 7.6 to 4.3 days resulting in a difference between the real rTMS and placebo groups of -3.2 days ($p<0.05$). In addition, multifocal rTMS was shown to be able to reduce the intensity of migraine attacks at 8 and 12 weeks ($p<0.001$) and less at 4 weeks ($p>0.05$) after application.
2. The multifocal rTMS protocol reduced the impact of migraine attacks over a period of 12 weeks ($p<0.001$) and simultaneously improved the degree of migraine-induced disability at 8 weeks ($p<0.001$), an effect that was not maintained at 12 weeks ($p>0.05$).
3. Multifocal continuous theta burst transcranial magnetic stimulation (cTBS) used over a period of 6 consecutive days in patients with generalized epilepsy was able to reduce the frequency of epileptic seizures by at least 50% in 69.2% of cases at 4 weeks and 76.9% at 8 and 12 weeks, respectively. The average number of epileptic seizures decreased from 6.7 to 2.6 ($p<0.05$).
4. Multifocal cTBS induced a significant reduction in the severity of epileptic seizures for a period of 12 weeks, especially by reducing the clinical parameter of activity during epileptic seizures and improving the physical and cognitive parameters of post-ictal recovery ($p<0.001$).
5. The effect of multifocal cTBS on the quality of life in epilepsy induced a significant improvement, sustained over time during the 12-week period, with a more pronounced impact on emotional well-being, energy level, cognitive and social function ($p<0.001$).
6. Both the rTMS protocol and multifocal cTBS demonstrated a favorable safety profile without severe adverse reactions. And the non-invasive nature of TMS favors their implementation in clinical practice with a high degree of certainty in the therapeutic management of generalized epilepsy and episodic migraine.

PRACTICAL RECOMMENDATIONS

1. It is recommended to implement the multifocal rTMS protocol in clinical practice in the management of patients with episodic migraine as a method of non-pharmacological and non-invasive preventive treatment of migraine attacks, especially in cases of therapeutic resistance to standard preventive treatments used.
2. Multifocal continuous theta burst transcranial magnetic stimulation (cTBS) can be used as an element of an adjuvant therapeutic approach for eligible patients with generalized epilepsy; as well as additionally for the purpose of modulating cortical excitability parameters.
3. Transcranial magnetic stimulation (TMS) can be applied as a method of assessing cortical excitability in the context of evaluating the efficacy of antiepileptic medication or in making a decision to modify the dosage or discontinue medication in patients with epilepsy.

4. Transcranial Magnetic Stimulation (rTMS/cTBS) can be considered as a neuromodulatory agent in patients with contraindications to standard pharmacological treatment in generalized epilepsy and episodic migraine.

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LIST OF PUBLICATIONS AND SCIENTIFIC EVENTS

where the results of the PhD thesis in medical sciences on the topic: "Multifocal transcranial magnetic stimulation in migraine and epilepsy", 321.05 - Clinical Neurology, conducted in the Department of neurology No.1, "Nicolae Testemițanu" State University of Medicine and Pharmacy of the Republic of Moldova by Mr. Pavel Leahu were presented.

SCIENTIFIC PUBLICATIONS

✓ **Articles in scientific journals abroad:**

✓ **articles in ISI, SCOPUS journals and other international databases***

1. Vataman A., Ciolac D., Chiosa V., Aftene D., **Leahu P.,** et al. Dynamic flexibility and controllability of network communities in juvenile myoclonic epilepsy. In: *Neurobiology of Disease*. 2023; 179:106055. https://doi.org/10.1016/j.nbd.2023.106055. (**IF 7.046**)
2. **Leahu P.**, Bange M., Ciolac D., Scheiter S, Matei A., et al. Increased migraine-free intervals with multifocal repetitive transcranial magnetic stimulation. In: *Brain stimulation*. 2022; 6(14):1544-1552. ISSN 1935-861X. DOI: https://doi.org/10.1016/j.brs.2021.10.383 **(IF 8.955)**
3. Sacco S., Lampl C., Maassen Van Den Brink A., **Leahu P.**, et al**.** Burden and attitude to resistant and refractory migraine: a survey from the European Headache Federation with the endorsement of the European Migraine & Headache Alliance. In: *J Headache Pain*. 2021; 22(1):39. https://doi.org/10.1186/s10194-021-01252-4 **(IF 7.277)**
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5. **Leahu P.**, Bange M., Ciolac D., Scheiter S, Matei A., Gonzalez-Escamilla G., Chirumamilla VC, Groppa SA, Muthuraman M., Groppa S. Multifocal Repetitive Transcranial Magnetic Stimulation — A Novel Paradigm in Migraine Treatment. In: *Tiginyanu, I., Sontea, V., Railean, S. (eds) 4th International Conference on Nanotechnologies and Biomedical Engineering. ICNBME 2019. IFMBE Proceedings, vol 77*. Springer, Cham. Online ISBN 978-3-030-31866-6. https://doi.org/10.1007/978-3-030-31866-6_87

✓ **Articles in accredited national scientific journals:**

✓ **articles in category B magazines**

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✓ **Summaries/ abstracts/ theses in the proceedings of national and international scientific conferences**

9. **Leahu P**., Groppa S. Theta burst transcranial magnetic stimulation in patients with generalized epilepsy. A TBS-hdEEG paradigm approach. In: *Abstract book. The 10th Congress of the European Academy of Neurology*. Helsinki, Finland, 2024, p.116.
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✓ **Innovator certificates:**

19. ”Implementarea rTMS (stimulare magnetică transcraniană repetitivă) multifocală în tratamentul pacienților cu migrenă”. Autori: **Leahu Pavel**, Groppa Stanislav. Certificat de inovator nr. 5934 din 02.08.2022.
20. ”Protocol de screening și examinare a pacientului cu migrenă”. Autori: **Leahu Pavel**, Matei Alexandru, Groppa Stanislav. Certificat de inovator nr. 5949 din 13.09.2022.
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24. ”Stimularea magnetică transcraniană repetitivă multifocală în tratamentul pacienților cu migrenă”. Autori: Groppa Stanislav, **Leahu Pavel**. Certificat de înregistrare OȘ 7359 din 28.11.2022.

✓ **Participation with communications at scientific forums:**

✓ **International**

25. **Leahu P.,** Groppa S. Exploring multifocal theta burst transcranial magnetic stimulation for generalized epilepsy through a tms/high-density-eeg paradigm. *Congresul Internaţional ”Pregătim viitorul promovând excelenţa”, Ediția a XXXIV-a.* Iași, România, 29 februarie – 3 martie 2024.
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27. **Leahu P**. Эффективность мультифокальной транскраниальной магнитной стимуляции в профилактике эпизодической мигрени. *XXIV-й научно-практической конференции с международным участием «Актуальные проблемы клинической, экспериментальной неврологии, нейрохирургии и нейрофизиологии»*. Almaty, Kazakhstan, 26-27 mai 2023.
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31. **Leahu P**. Neurostimulation possibilities in epilepsy patients. *Congresul Internaţional "Pregătim viitorul promovând excelenţa", Ediția a XXXI-a.* Iași, România, 1-3 martie, 2021.
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✓ **National with international participation**

33. **Leahu P**. Modularea non-invazivă a activității rețelelor neuronale în formele generalizate de epilepsie. *Congresul 37-ea ediție a săptămânii medicale balcanice: "Perspective ale medicinei balcanice în era post COVID-19"*. Chișinău, 07-09 iunie 2023.
34. **Leahu P**. Conceptele neurobiologice moderne ale tulburărilor depresive. *Conferința stiintifico-practică cu participare internațională "Provocări actuale în diagnosticul și tratamentul depresiei"*. Chișinău, 12 mai, 2023.
35. **Leahu P**. Neuromodularea durerii: o abordare moderna a problemei existențiale. *Conferința interdisciplinară cu participare internațională "Academia Durerii"*. Chișinău, 10 martie 2023.
36. **Leahu P**. Rezultatul terapeutic de lungă durată al rTMS multifocale în prevenția migrenei. *Congresul al VII-lea al Neurologilor din Republica Moldova.* Chișinău, 16-18 septembrie 2021.
37. **Leahu P**. Multifocal Repetitive Transcranial Magnetic Stimulation — A Novel Paradigm in Migraine Treatment. *The 4th International Conference on Nanotechnologies and Biomedical Engineering. ICNBME*. Chișinău, 18-21 septembrie 2019.
38. **Leahu P**., Groppa S. Stimularea magnetică transcraniană în practica neurologică. *Conferința internațională "Cefaleea la Copil".* Chișinău, 25 mai 2018.

✓ **National**

39. **Leahu P**., Groppa SA. Cuplarea stimulării magnetice transcraniene (TMS) cu electroencefalografia de densitate înaltă (hdEEG) în formele generalizate de epilepsie. *Conferința științifică "Performante si perspective in urgentele medico-chirurgicale".* Chișinău, 25 noiembrie 2022.

40. **Leahu P**. Cuplarea stimulării magnetice transcraniene (TMS) cu electroencefalografia de densitate înaltă (hdEEG) în formele generalizate de epilepsie. *Conferința ştiinţifică anuală consacrată aniversării a 77-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu" din Republica Moldova.* Chișinău, 18-21 octombie 2022.
41. **Leahu P**. Progrese în managementul modern al epilepsiei: stimularea cerebrală. *Conferința ştiinţifică anuală consacrată aniversării a 76-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu" din Republica Moldova.* Chișinău, 19-22 octombrie 2021.
42. **Leahu P**. Creșterea perioadei interictale la pacienții cu migrena utilizand stimularea magnetica transcraniană multifocala. *Conferința ştiințifică "Performanțe și perspective în urgențele medico-chirurgicale".* Chișinău, 8 noiembrie 2019.
43. **Leahu P**. Efectul neuromodulator al stimulării magnetice transcraniene multifocale la pacienții cu migrena. *Zilele Universității și Conferința Științifică anuală a cadrelor științifico-didactice, doctoranzilor, masteranzilor, rezidenților și studenților.* Chișinău, 15-18 octombrie 2019.
44. **Leahu P**. Perspective in managementul migrenei. *Conferința ştiințifică "Actualități in tratamentul patologielor sistemului nervos".* Chișinău, 13 septembrie 2019.
45. **Leahu P**. Particularitățile conectivității cerebrale la pacienții cu epilepsie versus migrenă. *Zilele Universităţii şi Conferinţa ştiinţifică anuală, consacrate aniversării a 90-a de la naşterea ilustrului medic şi savant Nicolae Testemiţanu*. Chișinău, 16-20 octombrie 2017.

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

✓ **International**

46. **Leahu P.**, Groppa S. Impact of multifocal repetitive transcranial magnetic stimulation (rTMS) neuromodulation on pain intensity and pain free intervals in episodic migraine patients. *Roma Pain Days 2024 Congress*. Roma, Italy, 13-15 iunie 2024.
47. **Leahu P.**, Groppa S. Theta burst transcranial magnetic stimulation in patients with generalized epilepsy. A TBS-hdEEG paradigm approach (ePresentation). *The 10th Congress of the European Academy of Neurology*. Helsinki, Finland, 29 iunie – 2 iulie 2024.
48. Racila R., Ciolac D., **Leahu P**., Gasnas A., Gorincioi N., et al. Boosting Cortical Inhibition with Theta Burst TMS in a Case of Super-Refractory Status Epilepticus. *American Clinical Neurophysiology Society 2021 ANNUAL MEETING & COURSES.* SUA, 10-14 februarie 2021.
49. **Leahu P.**, Bange M., Ciolac D., Scheiter S, Matei A., et al. Increased migraine-free interval with multifocal repetitive transcranial magnetic stimulation. *The 5th Congress of the European Academy of Neurology.* Oslo, Norway, 29 iunie - 2 iulie 2019.
50. **Leahu P**. Recurrent transcranial magnetic stimulation in the treatment of migraine. *Congresul International Pregatim viitorul, promovind excelenta", sectiunea Repere in medicina avansata - Tribuna practicianului, Universitatea Apollonia din Iasi.* Iasi, România, 28 februarie - 03 martie 2019.

✓ **National**

51. Racila R., Ciolac D., **Leahu P**., Groppa SA. Transcranial magnetic stimulation in the treatment of refractory and superrefractory status epilepticus. *Congresul al VII-lea al Neurologilor din Republica Moldova*. Chișinău, 16-18 septembrie 2021.
52. **Leahu P.,** Groppa S. Neuromodulatory approach in paroxysmal neurological disorders. *The congress dedicated to the 75th anniversary of Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova.* Chișinău, 21-23 octombrie 2020.

ADNOTARE

Leahu Pavel **"Stimularea magnetică transcraniană multifocală în migrenă și epilepsie".** Teza pentru obținerea titlului de doctor în științe medicale, Chișinău, 2025.

Structura tezei. Lucrarea este expusă pe 88 de pagini de text de bază; include 45 figuri, 6 tabele și 16 anexe; este compusă din introducere, 3 capitole dintre care 2 – conțin material propriu, concluzii generale, recomandări practice, adnotare în limbile română, rusă și engleză și bibliografie cu 297 referințe. Rezultatele cercetării au fost publicate în 18 lucrări ştiinţifice

Cuvinte-cheie: Stimulare magnetică transcraniană, stimulare theta burst, migrenă episodică, epilepsie generalizată, prevenție, neuromodulare.

Scopul studiului. Aprecierea eficacității stimulării magnetice transcraniene multifocale în profilaxia atacurilor de migrenă la pacienți cu migrenă episodică și a crizelor epileptice la pacienți cu epilepsie generalizată.

Obiectivele studiului. (1) Evaluarea efectului stimulării magnetice transcraniene multifocale asupra zilelor cu migrenă, frecvenței și intensității crizelor de migrenă la pacienți cu migrenă episodică; (2) Determinarea impactului TMS multifocal asupra calității vieții la pacienți cu migrenă episodică; (3) Aprecierea efectului stimulării theta burst (TBS) asupra frecvenței și severității crizelor epileptice la pacienți cu epilepsie generalizată; (4) Analiza influenței TBS asupra calității vieții la pacienții cu epilepsie generalizată; (5) Aprecierea profilului de siguranță și tolerabilitate a protocoalelor experimentale de TMS (rTMS și TBS);

Originalitatea și noutatea științifică. A fost efectuat un studiu experimental care a debutat paradigma de stimulare magnetică transcraniană multifocală cu examinarea impactului terapeutic al acesteia în tratamentul preventiv al pacienților cu migrenă episodică și epilepsie generalizată.

Problema științifică rezolvată în teză constă în identificarea modalităților noi terapeutice de modulare a activității rețelelor cerebrale cortico-subcorticale prin aplicarea stimulării magnetice transcraniene multifocale, ceea ce va contribui la fundamentalizarea paradigmei multifocale de neuromodulare în cercetările științifice ulterioare.

Semnificația teoretică și valoarea aplicativă. Prin implementarea unei metode moderne de tratament neuromodulator a pacienților cu migrenă episodică și a celor cu epilepsie generalizată din Republica Moldova, cercetarea efectuată a fundamentalizat viziunea contemporană în algoritmul de evaluare și tratament complex la acești pacienți. Pe lângă aceasta, elaborarea și utilizarea unui protocol multifocal de TMS, inovativ nu doar pe plan național dar și internațional,

a permis creșterea cunoștințelor în domeniul metodelor de neuromodulare în tratamentul tulburărilor neurologice paroxismale precum migrena și epilepsia.

Impactul practic al prezentului studiu constă în implementarea în cadrul Laboratorului de neurobiologie și genetică medicală, Universității de Stat de Medicină și Farmacie ”Nicolae Testemițanu” și a departamentului de Neurologie, Epileptologie și Boli interne, IMSP IMU a metodei inovative de neuromodulare a activității cerebrale la pacienți cu migrenă episodică și epilepsie generalizată.

АННОТАЦИЯ

Ляху Павел “**Мультифокальная транскраниальная магнитная стимуляция при мигрени и эпилепсии**”. Диссертация на соискание степени кандидата медицинских наук, Кишинев, 2025.

Структура диссертации. Работа изложена на 88 страницах основного текста; включает 45 фигур, 6 таблиц и 16 приложений; Состоит из введения, 3 глав с общими выводами, практические рекомендации, аннотации на румынском, русском и английском языках и библиографию с 297 ссылками. Результаты исследований опубликованы в 18 научных статьях.

Ключевые слова: транскраниальная магнитная стимуляция, тета-стимуляция, эпизодическая мигрень, генерализованная эпилепсия, профилактика, нейромодуляция.

Цель исследования. Оценка эффективности мультифокальной транскраниальной магнитной стимуляции в профилактики приступов мигрени у больных с эпизодической мигренью и эпилептических припадков у больных с генерализованной эпилепсией.

Задачи исследования: (1) Оценка влияния мультифокальной транскраниальной магнитной стимуляции на количество дней мигрени, частоту и интенсивность приступов мигрени у пациентов с эпизодической мигренью; (2) Определение влияния мультифокальной ТМС на качество жизни пациентов с эпизодической мигренью; (3) Оценка влияния тета-стимуляции (ТБС) на частоту и тяжесть эпилептических припадков у пациентов с генерализованной эпилепсией; (4) Анализ влияния ТБС на качество жизни пациентов с генерализованной эпилепсией; (5) Оценка профиля безопасности и переносимости экспериментальных протоколов ТМС (рТМС и ТБС);

Научная оригинальность и новизна. Проведено экспериментальное исследование, дебютировавшее с парадигмой мультифокальной транскраниальной магнитной стимуляции с изучением ее терапевтического воздействия в профилактическом лечении пациентов с эпизодической мигренью и генерализованной эпилепсией.

Научная проблема, решаемая в диссертации, заключается в выявлении новых терапевтических способов модуляции активности корково-подкорковых сетей головного мозга путем применения мультифокальной транскраниальной магнитной стимуляции, что может способствовать обоснованию парадигмы мультифокальной нейромодуляции в дальнейших научных исследованиях.

Теоретическая значимость и прикладное значение. Внедряя современный метод нейромодулирующего лечения пациентов с эпизодической мигренью и генерализованной эпилепсией в Республики Молдова, проведенное исследование закрепило современное видение алгоритма комплексного обследования и лечения этих пациентов. Помимо этого, разработка и применение мультифокального протокола ТМС, инновационного не только на национальном, но и на международном уровне, позволили расширить знания в области

методов нейромодуляции при лечении пароксизмальных неврологических расстройств, какими являются мигрень и эпилепсия.

Практическая значимость настоящего исследования заключается во внедрении в лаборатории нейробиологии и медицинской генетики Государственного медико-фармацевтического университета им. Николае Тестемицану и Деапартамента неврологии, эпилептологии и внутренних болезней Института Неотложной Медицины, инновационного метода нейромодуляции у больных с эпизодической мигренью и генерализованной эпилепсией.

ANNOTATION

Leahu Pavel "Multifocal transcranial magnetic stimulation in migraine and epilepsy". The thesis for the degree of PhD in medical sciences, Chisinau, 2025.

Structure of the thesis. The thesis is presented on 88 text pages; includes 45 figures, 6 tables and 16 appendices; it is composed of introduction, 3 chapters of which 2 – contain own research data, general conclusions, practical recommendations, annotation in Romanian, Russian and English and 297 bibliographic references. The main results of the research were published in 18 scientific papers.

Keywords: Transcranial magnetic stimulation, theta burst stimulation, episodic migraine, generalized epilepsy, prevention, neuromodulation.

The aim of study. Assesment of multifocal transcranial magnetic stimulation efficacy in prevention of migraine attacks in patients with episodic migraine and epileptic seizures in patients with generalized epilepsy.

Objectives of the study. (1) Assess the effect of multifocal transcranial magnetic stimulation on migraine days, frequency and intensity of migraine attacks in patients with episodic migraine; (2) Determine the impact of multifocal TMS on quality of life in patients with episodic migraine; (3) Assess the effect of theta burst stimulation (TBS) on frequency and severity of epileptic seizures in patients with generalized epilepsy; (4) Analysis of the influence of TBS on quality of life in patients with generalized epilepsy; (5) Safety and tolerability profile assessment of experimental multifocal TMS protocols (rTMS and TBS);

Scientific originality and novelty. An experimental study was conducted that debuted the paradigm of multifocal transcranial magnetic stimulation with the examination of its therapeutic impact in preventive treatment of patients with episodic migraine and generalized epilepsy.

The scientific problem solved in the thesis consists in identifying new therapeutic ways of modulating the activity of cortico-subcortical brain networks by applying multifocal transcranial magnetic stimulation, which will strengthen the foundation of the multifocal neuromodulation paradigm in further scientific research.

Theoretical significance and applicative value. By implementing a modern method of neuromodulatory treatment of patients with episodic migraine and those with generalized epilepsy from the Republic of Moldova, the research conducted has fundamentalized the contemporary vision in the complex evaluation and treatment algorithm for these patients. In addition, the development and use of a multifocal TMS protocol, innovative not only nationally but also

internationally, allowed the increase of knowledge in the field of neuromodulation methods in the treatment of paroxysmal neurological disorders such as migraine and epilepsy.

The practical impact of the present study consists in the implementation within the Laboratory of Neurobiology and Medical Genetics, State University of Medicine and Pharmacy "Nicolae Testemițanu" and the Department of Neurology, Epileptology and Internal Diseases, Emergency Medicine Institute of the innovative method of neuromodulation of brain activity in patients with episodic migraine and generalized epilepsy.