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Increased migraine-free intervals with multifocal repetitive transcranial magnetic stimulation

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ABSTRACT

Introduction: Episodic migraine is a debilitating condition associated with vast impairments of health, daily living, and life quality. Several prophylactic treatments exist, having a moderate ratio of action related to side effects and therapy costs. Repetitive transcranial magnetic stimulation (rTMS) is an evidence based therapy in several neuropsychiatric conditions, showing robust efficacy in alleviating specific symptoms. However, its efficacy in migraine disorders is unequivocal and might be tightly linked to the applied rTMS protocol. We hypothesized that multifocal rTMS paradigm could improve clinical outcomes in patients with episodic migraine by reducing the number of migraine days, frequency and intensity of migraine attacks, and improve the quality of life.

Methods: We conducted an experimental, double-blind, randomized controlled study by applying a multifocal rTMS paradigm. Patients with episodic migraine with or without aura were enrolled in two centers from August 2018, to December 2019, and randomized to receive either real (n = 37) or sham (sham coil stimulation, n = 28) multifocal rTMS for six sessions over two weeks. Patients, physicians, and raters were blinded to the applied protocol. The experimental multifocal rTMS protocol included two components; first, swipe stimulation of 13 trains of 140 pulses/train, 67 Hz, 60% of RMT, and 2s intertrain interval and second, spot burst stimulation of 33 trains of 15 pulses/train, 67 Hz, 85% of RMT, and 8s intertrain interval. Reduction >50% from the baseline in migraine days (as primary outcome) and frequency and intensity of migraine attacks (as key secondary outcomes) over a 12-week period were assessed. To balance the baseline variables between the treatment arms, we applied the propensity score matching through the logistic regression.

Results: Among 65 randomized patients, sixty (age 39.7 ± 11.6; 52 females; real rTMS n = 33 and sham rTMS n = 27) completed the trial and five patients dropped out. Over 12 weeks, the responder's rate in the number of migraine days was significantly higher in the real rTMS compared to the sham group (42% vs. 26%, $p < 0.05$). The mean 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 difference with real vs. sham rTMS of −3.2 days ($p < 0.05$). Similarly, over the 12-week period, the responder's rate in the reduction of migraine attacks frequency was higher in the real rTMS compared to the sham group (42% vs 33%, $p < 0.05$). No serious adverse events were observed.

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Conclusion: Our pilot study shows compelling evidence in a double placebo-controlled trial that multifocal rTMS is an effective and well-tolerated preventive treatment in patients with episodic migraine.

1. Introduction

Migraine is one of the most common neurological disorders, having a paroxysmal, progressive and often devastating impact on patient's wellbeing and quality of life. According to the Global Burden of Disease Study, migraine is in the top ten causes of years lived with disability in the general population and is the second cause of disability in both males and females younger than 50 years [1]. As the World Health Organization (WHO) currently reports, migraine affects 15–20% of the population and is three times more prevalent in women (18%) than in men (6%) in the United States and Europe, being ranked among important causes leading to disability [2]. Several studies confirmed the fact that people with migraine had a 2.2 to 4.0 times increased risk of developing depression compared to people without migraine [3–6], thus urging for refined therapeutic approaches for migraine.

In migraine patients, preventive and/or acute pharmacological treatment generally shows an adequate effect in relieving migraine attacks. Usually, acute abortive treatment consists of nonsteroidal anti-inflammatory drugs, 5-hydroxytryptamine receptor agonists or more recently, calcitonin gene-related peptide (CGRP) receptor antagonists [7–10]. Nevertheless, at some point of the migraine course these patients inevitably present a reduced response to acute medication [11], thus creating a pressing need for preventive non-pharmacological remedies [12,13]. Other reasons of treatment failure may include the unfavorable profile of adverse effects or the fact that some medications are contraindicated in individuals with comorbidities such as cardiovascular or renal function impairment, pregnancy or risk of substance overuse [14]. In this sense, non-invasive neuromodulatory techniques such as repetitive transcranial magnetic stimulation (rTMS) have shown promising results in lowering the frequency of migraine attacks as a new therapeutic paradigm for such patients with little to no adverse events [15].

The current vision of the mechanisms underlying migraine attacks is through a scrupulous neurobiological approach, considering migraine as a disorder of sensory neuronal network gain and plasticity [16] and modified cortical excitability [17], thereby making it remediable by neuromodulatory techniques. Although the actual mechanisms of rTMS have not been accepted by a consensus, convincing evidence shows that rTMS is able to induce persistent long-term effects by modulating central and peripheral excitability and sensitization [18] through a neuronal-mediated preconditioning mechanism [18,19].

To date, most published research on rTMS in migraine has approached its employment from a unifocal point of view, utilizing protocols applied over a single cortical region at a certain moment of time [20–23]. In this light, our study propose a new multifocal stimulation paradigm and addresses as main objectives the efficacy, overall safety, and tolerability of the experimental rTMS protocol. We hypothesized that multifocal rTMS compared to placebo stimulation would improve the clinical outcomes in patients with episodic migraine with or without aura by reducing the migraine days, frequency and intensity of headache attacks, and by ameliorating the quality of life.

2. Methods

2.1. Ethics statement

The study protocol was approved by the local institutional review board at the University Medical Center of the Johannes Gutenberg University, Mainz, Germany and the Institute of Emergency Medicine, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova.

2.2. Study design

We conducted an experimental, double-blind, rTMS-interventional study that included adult subjects with episodic migraine with and without aura. Prior to the rTMS stimulation, all subjects were informed about the nature of the study. After signing the informed consent, they were screened for a period of 4 weeks during which a headache diary was kept. The headache diary included the frequency, duration, and intensity of the headache attacks, administered medication (type, quantity, and effectiveness) as well as the individual aspects of the attack such as pain localization and secondary symptoms. At the end of the screening period a diagnosis of episodic migraine with or without aura was confirmed by a trained specialist according to the International Classification of Headache Disorders 3rd edition (ICHD-3) criteria of migraine [24]. All eligible subjects were then randomly assigned to either real or sham rTMS group. The randomization was performed by a separate member of the research team blinded to any other aspects of the study. All subjects attended six intervention sessions within two weeks. Afterwards, they had a follow-up period of up to three months with visits at predefined intervals. The design of the study is summarized in Fig. 1.

2.3. Subjects

Participants were recruited at the Department of Neurology, Institute of Emergency Medicine, Chisinau, Republic of Moldova and at the Department of Neurology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany from August 2018 to December 2019. The enrollment procedure is outlined in Fig. 2. In total, 127 subjects were screened; after analyzing the inclusion criteria, 65 eligible subjects were included into the study and randomized to either the real rTMS group ($n = 37$) or sham rTMS group ($n = 28$).

2.4. Inclusion and exclusion criteria

Adult patients with episodic migraine with or without aura having at least two and up to 14 headache attacks per month were included. The diagnosis of episodic migraine was based on the ICHD-3 criteria [24]. Prior to enrollment, all subjects signed the informed consent.

Conditions that limited subject's participation were considered: refusal to sign the informed consent, chronic migraine or diagnosis of other type of headache according to ICHD-3; history or signs of metabolic impairment (renal, hepatic), neoplasms, uncontrolled

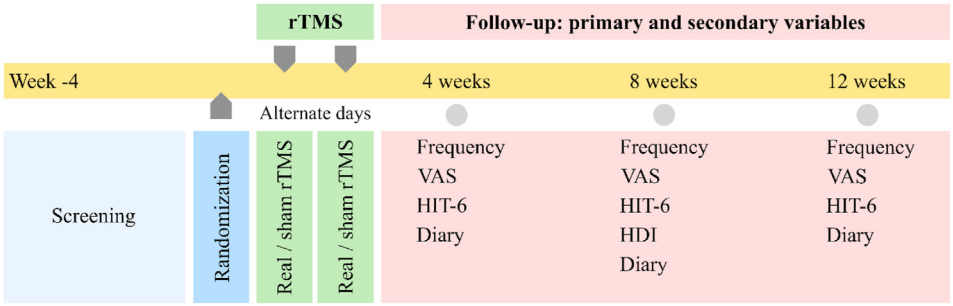

Fig. 1. Study design. Subjects kept a headache diary for four weeks prior to the rTMS intervention and completed the Headache Impact Test (HIT-6) and Headache Disability Index (HDI) questionnaires before the first stimulation session. Improvement >50% from the baseline in migraine days within the 12-week period after the intervention served as primary outcome variable. Improvement >50% from the baseline in frequency and intensity (measured by Visual Analogue Scale (VAS)) of migraine attacks within the same period served as key secondary outcome variables. Quality of life questionnaires were conducted on several follow-up dates.

elevated blood pressure, epileptic seizures, intellectual disability, psychiatric disorders, evidence of structural brain injury or focal neurological deficit. In addition, patients using migraine preventive medication, opioid drugs or muscle relaxants or those with a history of substance abuse were excluded from the study. Patients with absolute or relative contraindications to TMS such as ferromagnetic implants in the head-and-neck regions, cardiac pacemakers and pregnant or lactating females were also excluded.

2.5. Resting motor threshold (RMT) assessment

All subjects were comfortably seated on a chair and asked to be as relaxed as possible. They wore an appropriately sized textile TMS treatment cap (small, medium or large, depending on the head circumference), which was used to mark the corresponding stimulation sites based on the 10–20 EEG system and to ensure optimal coil placement in order to avoid unwanted pericranial and facial muscle contractions during the stimulation procedure. These marks consisted of two lateral margins and 11 spot areas for burst stimulation which were used during the experimental stimulation protocol (Fig. 3). In order to determine the RMT, focal single TMS pulses were delivered using a MagVenture MMC-140-II circular coil connected to the MagVenture MagPro® R30 stimulator, initially over the vertex (Cz) to familiarize the subject with the stimulus and afterwards switched to right hand motor cortex. The stimulating coil was placed over the optimal site for eliciting responses in the contralateral target muscle. Motor evoked potential (MEP) signals were recorded from the left abductor pollicis brevis muscle using Ag–AgCl surface electrodes (0.9 cm diameter) placed 3 cm apart over the belly and tendon of the muscle. The RMT for eliciting responses from the relaxed abductor pollicis brevis muscle was defined as the minimum intensity of stimulation needed to produce responses of 50 μV in at least 50% of 10 trials. Subjects were given visual feedback of muscle activity to help maintain complete muscle relaxation. Stimulation was performed following the IFCN (International Federation of Clinical Neurophysiology) committee safety protocols and recommendations [25].

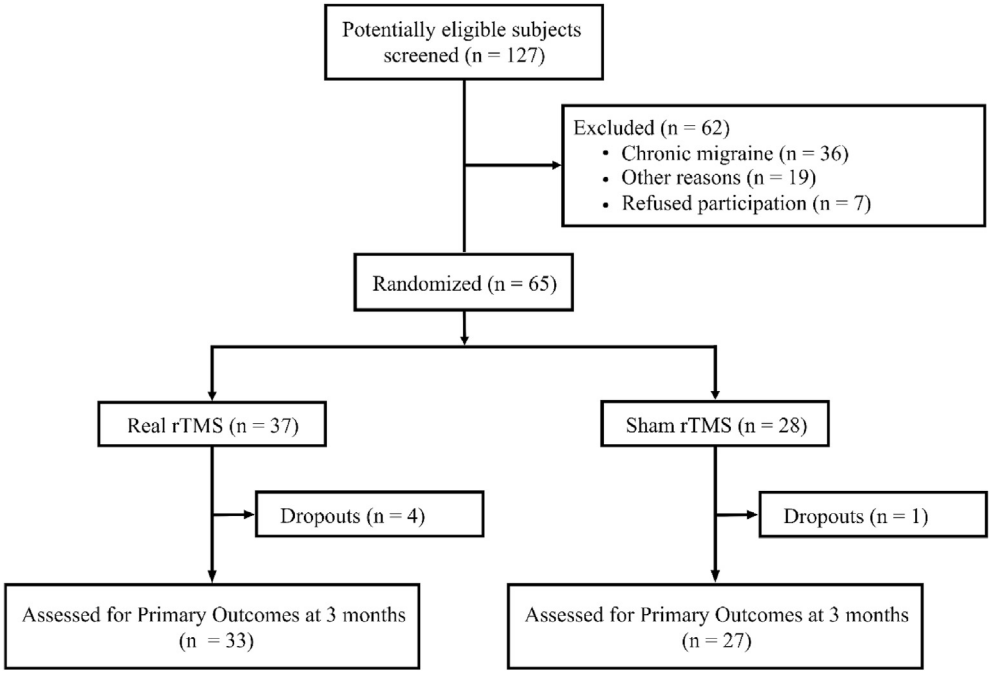

Fig. 2. Flow chart of patient recruitment and randomization.

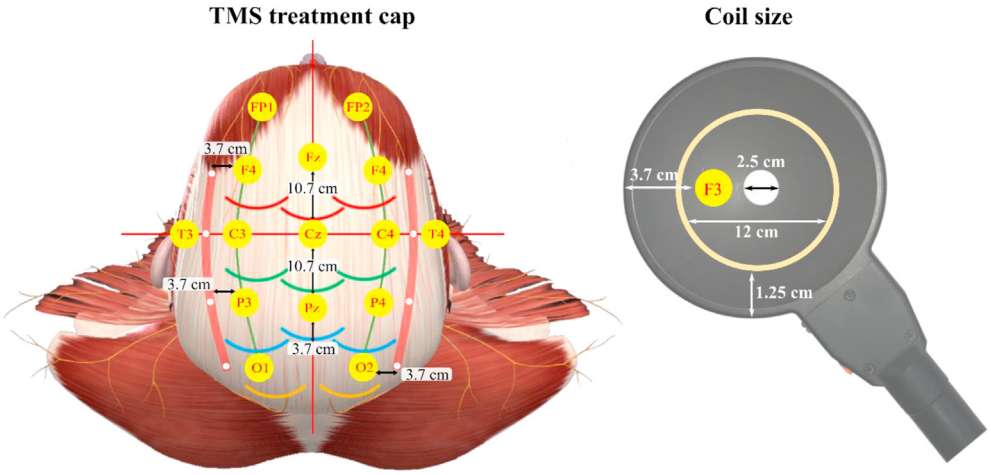

Fig. 3. Borderline tracks and spot stimulation areas marked on the TMS treatment cap applied in the experimental stimulation protocol according to the 10–20 EEG system. Two (red) lateral borderline tracks indicate the margins of the stimulation in order to avoid the involvement of pericranial muscles. The eleven horizontal semicircular lines (red, green, blue, and yellow) indicate the placement of the bottom margin of the stimulation coil. The 3.7 cm and 10.7 cm measurements from the guiding lines indicate the distance required for outer and inner stimulation points, respectively, to be placed under the midpoint of the wiring, considering the 14.5 cm diameter of the stimulation coil. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.6. Experimental rTMS paradigm

After determining the RMT, all subjects underwent either real or sham rTMS by applying the experimental stimulation protocol. Blinding was performed by means of the MagVenture MMC-140 A/P circular coil, which functions as either an active or placebo coil depending on the randomization number assigned to the subject. The experimental stimulation protocol comprised the swipe stimulation followed by the spot burst stimulation (Fig. 4). The swipe stimulation consisted of 13 trains of 140 pulses/train delivered with a frequency of 67 Hz and 60% of RMT with a 2 s intertrain interval. Swipe stimulation was performed by pulling the coil across the three anterior-posterior (fronto-occipital) and two lateral-lateral (temporal) tracks. Afterwards, spot burst stimulation was performed, which consisted of 33 trains of 15 pulses/train delivered with a frequency of 67 Hz and 85% of RMT with an 8 s intertrain interval. During spot burst stimulation, each of the 11 marked spot areas were stimulated three times in a row. After the rTMS session, the subjects were asked if any adverse events were experienced during and/or immediately after the stimulation.

2.7. Follow-up

After attending six rTMS intervention sessions within two weeks, all subjects were followed-up for a 3-month period. During this period subjects continued to fill in the headache diary, including the frequency and intensity of the migraine attacks and medication intake. They also completed quality of life questionnaires such as HIT-6 and HDI at given time intervals. If needed, subjects could directly contact the research staff at any time during the follow-up period.

2.8. Primary and secondary outcomes

As primary outcome parameter we considered >50% improvement from the baseline in the number of migraine days over weeks

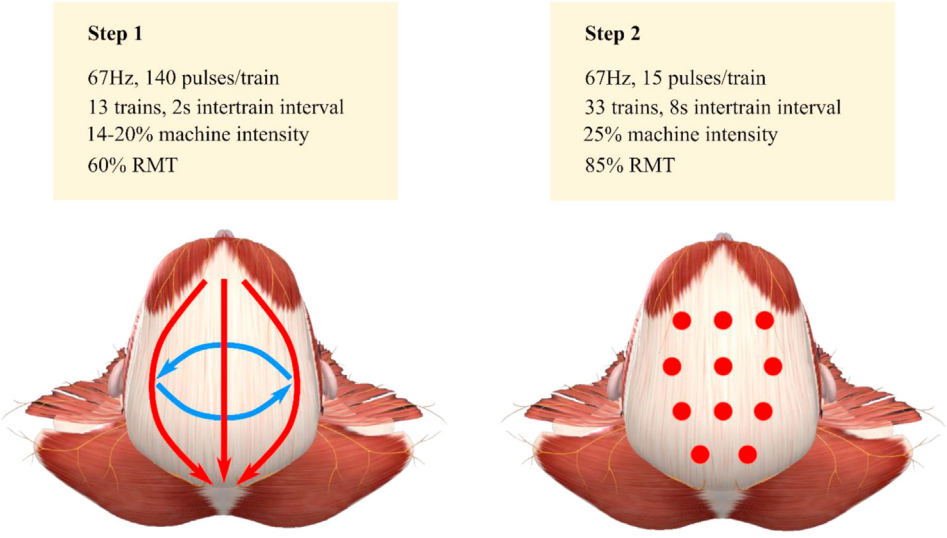

Fig. 4. Experimental stimulation protocol. Step 1 – swipe stimulation, step 2 – spot burst stimulation.

1–12. Improvement >50% from the baseline in migraine attack frequency and visual analogue scale (VAS) over weeks 1–12 were considered key secondary outcome variables. In the first step, we estimated the quotient by taking the follow-up values from the time points − 4 weeks, 8 weeks, and 12 weeks as numerator and the baseline (B) value as denominator. To obtain reliable results only for the treatment effects, we eliminated the potential influence of confounding factors such as age and sex. In the second step, to obtain unbiased results from the two groups (real and sham rTMS) we applied the propensity score matching algorithm through the logistic regression. The steps followed for the computation of propensity scores are described elsewhere [26]. As additional secondary outcome, the quotient of the HIT-6 questionnaire was calculated using the values from the 4-, 8-, and 12-week time points as numerator and the baseline value as denominator.

2.9. Statistical analysis

Continuous variables are presented as mean values ± standard deviation. Gaussian distribution was checked by analyzing the histograms and Shapiro-Wilk test. For demographic and clinical characteristics, between-group differences were checked by Student's t and Pearson's chi-squared tests. For propensity score matching, we used the Bayesian spatial propensity score matching (BSPM) algorithm, which is an open source toolbox [27], along with the RStudio version 1.1.456. Two-way repeated measures ANOVA was performed using the 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 parameters. Post hoc analyses were performed with pairwise t-tests to 1.0 for finding the reliable treatment effects. For the proportion of migraine rTMS responders (defined as having at least a 50% reduction in mean number of monthly migraine days), the Pearson's chi-squared test was used. Also, number needed to treat (NNT) estimates were calculated. The statistical power of the study was calculated by post hoc Bayesian posterior distribution power analysis [28] to verify the sample size and the effect size.

3. Results

3.1. Study participants

From 65 randomized subjects, sixty completed the study period and were assessed for primary outcomes at the end of the 12-week follow-up, and five dropped out. From these, four subjects in the real rTMS group (one due to the intensification of headache and four were lost to follow-up) and one (lost to follow-up) in the sham rTMS group. The proportion of dropped out subjects didn't differ between the groups ($\chi^2 = 2.1$, $p = 0.14$). Demographic and clinical characteristics of the included subjects are summarized in Table 1. No significant differences in age, frequency and intensity of migraine attacks, or RMT at baseline were found between the real and sham rTMS groups. Overall, experimental procedures were well tolerated by all subjects and no serious adverse effects were reported.

3.2. Primary outcome

For the primary outcome, i.e., reduction in the number of migraine days, the responder's rate at 12 weeks follow-up consisted of 14/33 (42%) in the real rTMS group and 7/27 (26%) in the sham rTMS group ($p < 0.05$), resulting in 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 ($p < 0.05$).

There was a significant effect of the factors GROUP ($F_{(1,174)} = 56,72$, $p < 0.001$) and TIME ($F_{(2,174)} = 3,37$, $p = 0.037$) and a significant GROUP × TIME interaction ($F_{(2,174)} = 5,07$, $p = 0.007$). The post hoc tests revealed a significant decrease in migraine days between the follow-up time points in comparison to baseline in the real rTMS group ($p < 0.001$), whereas in the sham rTMS group no significant reduction in migraine days was detected (Fig. 5).

3.3. Key secondary outcomes

At 12-week follow-up, the responder's rate in frequency of migraine attacks was higher in the real compared to the sham rTMS group (42% vs 33%, $p < 0.05$).

In repeated measures ANOVA analysis, we found a significant effect of the factors GROUP ($F_{(1,174)} = 92,28$, $p < 0.001$) and TIME ($F_{(2,174)} = 3,75$, $p = 0.025$) and a significant GROUP × TIME interaction ($F_{(1,174)} = 11,72$, $p < 0.001$). The post hoc tests showed a significant decrease in migraine frequency between the follow-up time points and the baseline in the real rTMS group ($p < 0.001$), whereas the sham rTMS group showed an increase in frequency, which was not statistically significant (Fig. 6).

When analyzing the VAS parameter, we found a significant effect only for the factor GROUP ($F_{(1,174)} = 25,14$, $p < 0.001$), whereas the factor TIME ($F_{(2,174)} = 1,83$, $p = 0.163$) and the GROUP × TIME interaction ($F_{(2,174)} = 0,49$, $p = 0.613$) were not significant (Fig. 7).

As additional secondary outcome parameter we analyzed the HIT-6, which showed significant effect of the factor GROUP ($F_{(1,174)} = 392,58$, $p < 0.001$) and a clear trend for the factor TIME ($F_{(2,174)} = 2,10$, $p = 0.124$) and for the GROUP × TIME interaction ($F_{(2,174)} = 2,26$, $p = 0.107$) (Fig. 8).

3.4. Safety and tolerability

The experienced adverse events were headache, auditory discomfort, dizziness, and local discomfort at stimulation site. Although the total number of subjects that reported at least one adverse event was slightly lower in the sham ($n = 6$) than in the real ($n = 10$) rTMS group, this was not statistically significant ($\chi^2 = 0.49$, $p = 0.284$).

4. Discussion

By applying a novel multifocal rTMS paradigm for the treatment of migraine patients, we were able to show its robust effects on primary and secondary outcome variables. Specifically, real stimulation was associated with a significant reduction in migraine days, frequency and intensity of migraine attacks, and HIT-6, while no clinical responses upon sham stimulation could be observed. High responder rates and little to no adverse events led to a significant improvement in quality of life, suggesting that rTMS can induce significant long term clinical outcome changes in patients with episodic migraine.

In our study, we approached the modulation effects of rTMS through a multifocal paradigm relying on the direct stimulation of cortical and peripheral elements engaged in the pathophysiology of migraine [29–31]. Our experimental protocol was designed to include two main aspects of neuromodulation in migraine management: peripheral nerve sensing - consisting of stimulation of the ophthalmic (V1) branch of the trigeminal nerve [2,32] and greater occipital nerve (C2) inputs [33,34], as well as the central mechanisms involving the trigemino-thalamic pathways [16,35,36]. In regard to the peripheral component of modulation,

Table 1
Demographic and clinical characteristics of included subjects.

Variables	real rTMS (n = 33)	sham rTMS (n = 27)	t/χ^2
Female, n (%)	29 (87%)	23 (92%)	p = 0.77[a]
Age in years (m ± sd)	39.7 ± 11.53	39.8 ± 11.7	p = 0.97[b]
Range	20–58	22–62	
Age of onset			p = 0.27[a]
Childhood	3 (9%)	5 (18.5%)	
Adolescence (10–19 years)	12 (36.3%)	6 (22.2%)	
20–30 years	11 (33.3%)	6 (22.2%)	
30–50 years	7 (21.2%)	7 (25.9%)	
>50 years	–	–	
N/R	–	3 (11.1%)	
Marital status			p = 0.29[a]
Single	5 (15.1%)	6 (22.2%)	
Married	23 (69.7%)	17 (62.9%)	
Divorced	5 (15.1%)	2 (7.4%)	
N/R	–	2 (7.4%)	
Education			p = 0.71[a]
High school or less	4 (12.1%)	4 (14.8%)	
College	8 (24.2%)	6 (22.2%)	
University	21 (63.7%)	16 (59.3%)	
N/R	–	1 (3.7%)	
Body mass index (m ± sd)	25.2 ± 4.5	24 ± 4.6	p = 0.31[b]
Acute medication			p = 0.12[a]
NSAIDs	11 (33.3%)	15 (55.6%)	
Triptans	7 (21.2%)	5 (18.5%)	
Other (combined)	15 (45.5%)	5 (18.5%)	
No medication	–	1 (3.7%)	
N/R	–	1 (3.7%)	
Duration of migraine attack			p = 0.76[a]
<1h	–	–	
1–4h	8 (24.2%)	5 (18.5%)	
4–12h	9 (27.3%)	8 (29.6%)	
12–24h	6 (18.2%)	9 (33.3%)	
24–48h	7 (21.2%)	3 (11.1%)	
48–72h	3 (9.1%)	2 (7.4%)	
Migraine days per month (m ± sd)	7.63 ± 3.91	6.22 ± 2.69	p = 0.12[b]
Range	2–16	2–11	
Frequency of headache per month (m ± sd)	6.50 ± 3.05	6.37 ± 2.93	p = 0.87[b]
Range	2–14	3–14	
Visual analogue scale (m ± sd)	6.37 ± 1.61	6.32 ± 1.62	p = 0.91[b]

NSAIDs – nonsteroidal anti-inflammatory drugs; N/R – no response.
Variables are presented as means (m) ± standard deviation (sd) and range or absolute numbers (percentage).
[a] P values derived from Pearson's chi-squared test.
[b] P values derived from Student's two-tailed *t*-test.

the stimulation paradigm possibly targeted the nociceptive afferent inputs of trigemino-cervical complex coming both from cervical (muscles, skin) and trigeminal (supratentorial dura, skin) areas, which have been previously shown to have a high level of convergence, sensitization and further facilitation of central nociceptive trigemino-cervical second order neurons [37–41]. Considering the proven efficacy of the V1 trigeminal branch [42,43], the greater and lesser occipital nerves [44], and peripheral magnetic stimulation of pericranial muscle structures [45] in migraine treatment, it may be possible that rTMS stimulation

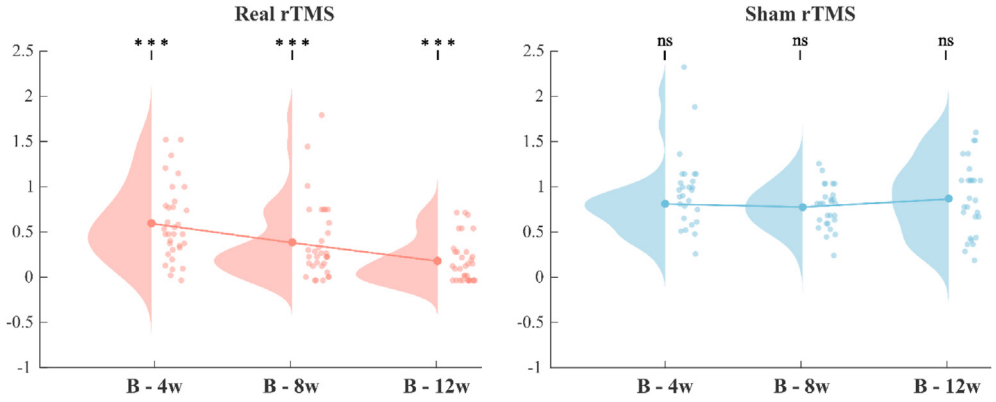

Fig. 5. Primary outcome. Repeated measures ANOVA of migraine days in the real and sham rTMS groups, showing a significant decrease between all follow-up time points in comparison to baseline (B) in the real rTMS group only (***p < 0.001).

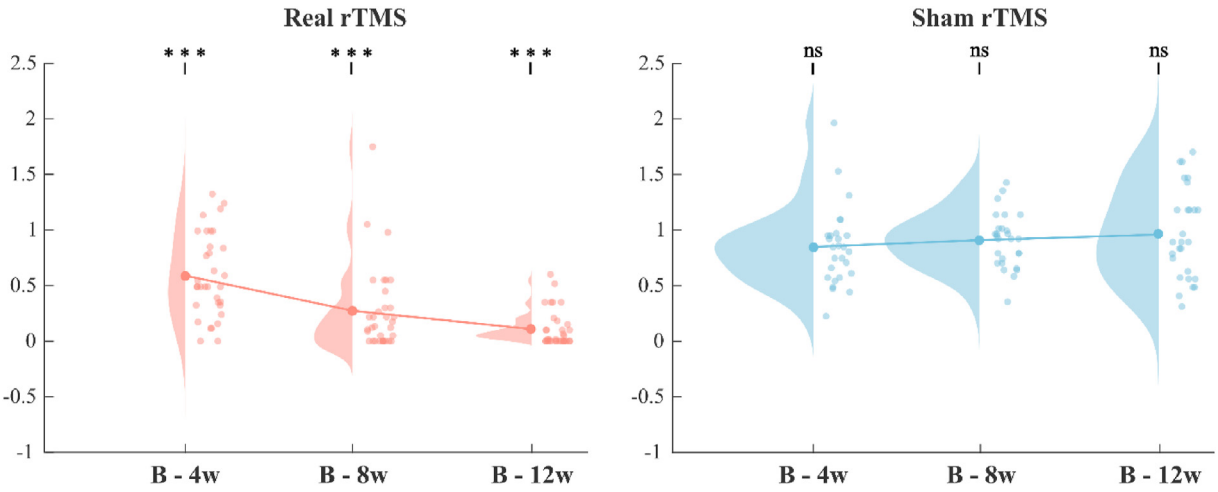

Fig. 6. Key secondary outcomes. Repeated measures ANOVA of frequency of the migraine attacks in the real and sham rTMS groups, showing a significant decrease in frequency in the real rTMS group (***p < 0.001) in comparison to baseline (B), whereas the sham rTMS group presented a slight increase, which was not statistically significant (p > 0.05).

induces similar effects by modulating the diffuse nociceptive control mechanisms of the trigemino-cervical complex. However, we cannot exclude the central component of rTMS action, i.e., direct cortical modulation with further influence on downstream structures such as trigemino-cervical complex. This is supported by rTMS-fMRI studies showing that subthreshold rTMS is able to induce negative cortical BOLD responses [46,47] associated with neuronal suppression [48].

A positive outcome was considered to be >50% improvement from the baseline in migraine days, migraine attack frequency, and headache intensity. The real rTMS group presented a persistently higher degree of improvement in comparison to the sham rTMS group at each follow-up. The decrease in the responders rate in the real rTMS group at 12 weeks follow-up can be partially explained by the fact that in non-invasive neuromodulatory trials, subjects are more exposed to recall bias [49] the longer the post-intervention period is. The overall placebo effect percentage in our study did not differ much from similar studies [22,23,50]. A recent meta-analysis of migraine studies concluded that the pooled estimate of placebo response in migraine prophylaxis was 21%, which was higher in the parallel design as compared to a cross-over design, as well as in European studies compared to North American studies [51]. The placebo response was also higher in non-pharmacological compared to pharmacological migraine treatment studies [51]. In the rTMS studies, the placebo response may be attributed to the finesse and novelty of the treatment and high expectations of the subjects. It is often perceived as a new treatment opportunity for migraine patients, thus, it might have raised the hope and expectations of some subjects.

Improvement in the primary outcome measure indicated that the stimulation using the experimental rTMS paradigm is superior to the sham stimulation in the prevention of migraine attacks, demonstrating a significant improvement in migraine intensity and frequency and migraine days compared to placebo stimulation. These results are similar to other high-rate rTMS studies [15,22,23], however, none of them applied a multifocal stimulation protocol. In our study, the obtained NNT of 6.0 for the >50% reduction in the number of migraine days at 12 weeks is within the range of NNT estimates obtained in studies evaluating the efficacy of non- and invasive neurostimulation techniques for acute (NNT 3.6–6.5) and preventive (NNT 1.5–11.1) migraine treatment [52] and is more beneficial compared to the onabotulinumtoxinA treatment (NNT 8.3) for chronic migraine [53,54].

Subjects recruited in our study presented a mean number of seven migraine attacks per month, which is an important number to cause disability and quality of life reduction, and was similar to previous non-pharmacological or pharmacological preventive studies [32,55]. Nevertheless, they represented the majority of migraine patients in the general population, who required

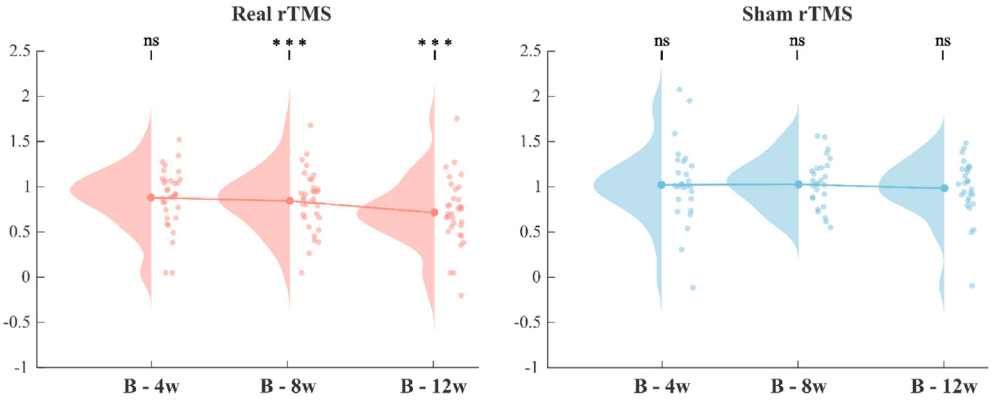

Fig. 7. Key secondary outcomes. Repeated measures ANOVA of the visual analogue scale (VAS) demonstrated a significant decrease only for the follow-up time points (8 weeks and 12 weeks) compared to baseline (B) only in the real rTMS group (***p < 0.001).

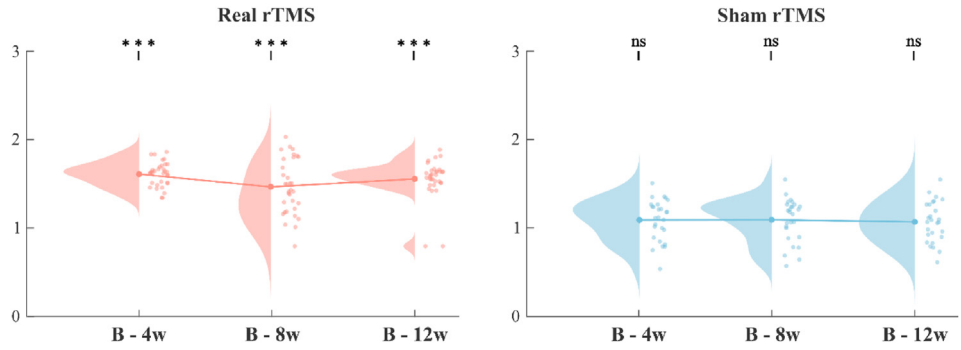

Fig. 8. Additional secondary outcomes. Repeated measures ANOVA of the HIT-6 showed a significant between-group difference with reduction in the real rTMS group (***p < 0.001) and no significant change in the sham rTMS group as compared to baseline (B).

preventive treatment according to the international board recommendations [56].

The percentage of adverse events in our study was also comparable to similar studies, which suggested that adverse events occur in almost 30% of subjects in the placebo group, being significantly higher in the North American studies than in those conducted in Europe [51].

This study is not without limitations. The first might relate to the total number of subjects and the fact that there were only a few subjects with migraine with aura. Several studies showed important differences between migraine with and without aura on functional and anatomical levels [57,58], thereby suggesting a potential difference in therapeutic responses [59]. It is important to highlight that in the general population migraine with aura is much more uncommon compared to migraine without aura, and represents only 1.9–5.2% of migraine patients [60–62]. Second, despite methodological precautions concerning the sham stimulation, partial un-blinding may have occurred as all subjects received a real single TMS pulse while assessing the baseline RMT levels, which produces a specific audible and tactile sensation as the pulse passes through the scalp and pericranial tissues [63,64]. However, this is not unique to our study and this is a common issue in TMS research, thus we doubt that this fact influenced our findings in any way; we also used a specifically designed coil for double-blinded studies. Third, the present study does not have a cross-over design, thus, occasional pericranial muscle contractions in the real rTMS group are unlikely to impact the final outcome results [22]. Also, it should be taken into account that randomization and stimulation were performed by different investigators. Non-invasive neurostimulation has been repeatedly delivering stable results in the field of primary headache management [65], being more accessible and less demanding compared to invasive neurostimulation [66]. This could empower its application in patients with resistant migraine, while long term data and longer follow-up in distinct group of patients, i.e., resistant to CGRP monoclonal antibodies should be gathered [67]. In our study, the 3-months follow-up is limiting us for drawing conclusions on the long term. However, this period is well in range within the suggested minimal 4-week follow-up period recommended by methodological guidelines in the field of headache preventive therapies [68].

5. Conclusions

Our study showed compelling evidence that the experimental multifocal rTMS paradigm reduces the number and intensity of migraine attacks compared to placebo treatment. It is a safe and well tolerated protocol. We suggest that multifocal rTMS could be considered a novel and effective preventive measure in adult patients with episodic migraine. Future studies are needed to further evaluate the efficacy of multifocal rTMS in different types of migraines and to assess the optimal stimulation parameters for prevention of migraine attacks.

CRediT authorship contribution statement

Pavel Leahu: Investigation, Resources, Writing – original draft, Formal analysis. **Manuel Bange:** Investigation, Resources, Writing – original draft. **Dumitru Ciolac:** Investigation, Resources, Writing – original draft, Formal analysis, Writing – review & editing. **Stefanie Scheiter:** Investigation, Resources. **Alexandru Matei:** Investigation, Resources. **Gabriel Gonzalez-Escamilla:** Investigation, Resources, Formal analysis, Writing – review & editing. **Venkata C. Chirumamilla:** Investigation, Resources. **Stanislav A. Groppa:** Investigation, Resources. **Muthuraman Muthuraman:** Formal analysis, Writing – review & editing. **Sergiu Groppa:** Conceptualization, Writing – original draft, Formal analysis, Writing – review & editing.

Declaration of competing interest

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

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