Neuroendocrinology Letters Volume 45 No. 6 2024
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL PAPER

Effects of high-frequency repetitive transcranial magnetic stimulation of affected hemisphere on motor recovery in patients in the acute stage of ischemic stroke: Preliminary results

Katarína Valovičová[1], Branislav Kollár[1], Stanislava Klobucká[2,3], Zoltán Goldenberg[1], Simona Švaňová[4], Andrea Strečanská[4], Peter Turčáni[1], Pavel Šiarnik[1]

1 1st Department of Neurology, Faculty of Medicine, Comenius University, Bratislava, Slovakia.
2 Rehabilitation Centre Harmony, Bratislava, Slovakia.
3 Department of Physical and Rehabilitation Medicine, Faculty of Medicine, Slovak Medical University, Bratislava, Slovakia.
4 Faculty of Health Sciences, University of Ss. Cyril and Methodius, Trnava, Slovakia.

Correspondence to: Prof. Branislav Kollár, MD, PhD, MPH
1st Department of Neurology, Faculty of Medicine, Comenius University,
Mickiewiczova 13, 813 69, Bratislava, Slovakia
TEL: +421 948 334 417, E-MAIL: branislavkollarmd@gmail.com

Submitted: 2024-08-12 Accepted: 2024-11-05 Published online: 2024-12-12

Key words: **Stroke; high-frequency repetitive transcranial magnetic stimulation; noninvasive brain stimulation; motor recovery; neuroplasticity; interhemispheric inhibition**

Neuroendocrinol Lett 2024; **45**(6):409–417 **PMID:** 39732468 45062408 ©2024 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVES: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neurostimulation technique that uses magnetic field to comprehensively influence events in the brain. Its use in patients after stroke focuses mainly on influencing brain neuroplasticity and therefore has the potential to improve motor functions in these patients. This study investigates the effect of rTMS on motor function recovery in patients in the acute stage of ischemic stroke.
DESIGN: This study was designed as a randomized double-blind placebo-controlled trial.
MATERIALS AND METHODS: A total of 26 patients with motor impairment in the acute stage of ischemic stroke were enrolled. Participants were randomly assigned to receive 5 sessions of 10 Hz ipsilesional rTMS or placebo rTMS, in addition to standard pharmacotherapy and rehabilitation. Clinical evaluations of motor impairment and activity were performed, along with electrophysiological parameters of motor evoked potential (MEP), at baseline (1 –6 days after stroke) and after the completion of the 5 rTMS sessions (10 –14 days after stroke).
RESULTS: The 10 Hz rTMS group demonstrated significantly greater improvements in most clinical motor function assessments compared to the placebo group. However, no significant changes in the electrophysiological parameters of MEPs were observed.
CONCLUSION: The application of 10 Hz rTMS to the ipsilesional hemisphere shows promise in improving motor functions in patients in the acute stage of ischemic stroke. Although the results suggest potential therapeutic benefit, more research with larger sample sizes and comprehensive outcome measures is

required to optimize rTMS protocols and fully understand its effects on motor recovery.

Abbreviations:

AH	- affected hemisphere
BI	- Barthel Index
CMCT	- central motor conduction time
FIM	- Functional Independence Measure
FMA-LE	- Fugl-Meyer Assessment for Lower Extremity
FMA-UE	- Fugl-Meyer Assessment for Upper Extremity
HF-rTMS	- high-frequency repetitive transcranial magnetic stimulation
IHI	- interhemispheric inhibition
LE	- lower extremity
MAS	- Motor Assessment Scale
MAshS	- Modified Ashworth Scale
MEP	- motor evoked potential
NIHSS	- National Institutes of Health Stroke Scale
RMT	- resting motor threshold
rTMS	- repetitive transcranial magnetic stimulation
UE	- upper extremity
UH	- unaffected hemisphere

INTRODUCTION

Stroke is one of the leading causes of mortality and long-term disability worldwide (GBD 2019 Stroke Collaborators, 2021; OECD, 2023; World Health Organization, 2024) and in Slovakia alone, 11 383 cases were registered in the national registry in 2022, of which 89.9% were ischemic strokes (National Health Information Centre, 2024). Despite considerable advances in the management of this disease over the past decade and a relatively stable declining incidence of stroke in Europe, stroke remains a devastating disease. Changing demographics in terms of an increase in the elderly population will lead to an increase in the number of patients but with a higher chance of survival due to the implementation of primary prevention strategies, as well as increased access to better quality healthcare in both acute and late stages of the disease (Wafa *et al.* 2020). Despite unquestionable advances in the treatment and care of stroke patients, many remain with some degree of disability after stroke (Katan & Luft, 2018; Wafa *et al.* 2020). Consequently, there is a pressing need to continuously search for and develop new additional therapeutic approaches that could potentially mitigate long-term functional deficits associated with stroke.

Repetitive transcranial magnetic stimulation (rTMS) is one of the noninvasive neurostimulation and neuromodulation techniques, which uses a magnetic field to influence events in the brain (Rossi *et al.* 2009). The overall effect of rTMS is thought to be a combination of several different effects. Changes in gene expression, growth factor production, levels of neurotransmitters and their receptors, ion channel function, and neuroplasticity have been observed in animal models. In humans, changes in growth factor production, neuronal activity, neuroplasticity, levels of some neurotransmitters, cerebral blood flow, and an increase in gray matter volume have been demonstrated (Bates & Rodger, 2015). The use of rTMS in patients after stroke focuses mainly on influencing neuroplastic events in the brain. The primary objective of this study is to investigate the effect of rTMS on facilitating motor recovery in patients during the acute stage of ischemic stroke. By investigating its effects on motor function, this research aims to contribute to the growing body of evidence exploring noninvasive neuromodulation as a therapeutic tool in stroke rehabilitation.

MATERIALS AND METHODS

Materials

This study included patients aged 18 years and older who were diagnosed with acute ischemic stroke (1 – 6 days after onset) involving the dominant or non-dominant hemisphere, and who had motor impairment of the limbs. Participants were recruited from the 1st Department of Neurology, Faculty of Medicine, Comenius University in Bratislava, University Hospital Bratislava between 01/2023 and 06/2024. The diagnosis of ischemic stroke was confirmed by clinical evaluation and neuroimaging – computed tomography or magnetic resonance imaging.

Exclusion criteria were rigorously applied to ensure patient safety and integrity of the study. Patients were explicitly excluded if they met any of the following criteria: phatic and cognitive impairment that would limit cooperation, pre-existing motor impairment of the limbs, presence of a metal implant near the coil site, a history of epilepsy or other seizure disorders, any neurological condition that could affect cognitive or motor abilities, a history of psychiatric disorders, preexisting noise-induced hearing impairment, concomitant use of ototoxic drugs or medications with a known risk of lowering seizure threshold, pregnancy, alcohol and drug abuse, severe heart disease, and the presence of other conditions with a possible lowering of seizure threshold. A detailed list of explicit exclusion criteria, along with conditions that require caution in terms of rTMS application, is provided in our recent publication (Valovičová *et al.* 2022). The project was designed as a randomized double-blind placebo-controlled trial.

Methods

After recruiting eligible patients according to established inclusion and exclusion criteria, informing them about the study protocol, and obtaining informed consent, participants were randomly assigned to one of two groups: the therapeutic rTMS group or the placebo rTMS group. Initial clinical and electrophysiological evaluations were conducted within 1 to 6 days after stroke onset, before the application of either therapeutic or placebo rTMS. The treatment protocol consisted of 5 sessions of rTMS (therapeutic or placebo) administered over 5 consecutive working days. After

Tab. 1. Demographic and clinical characteristics of the study cohort. rTMS – repetitive transcranial magnetic stimulation, NIHSS – National Institutes of Health Stroke Scale. Categorical variables are expressed as numbers and proportions (%), continuous variables as mean ± standard deviation or median, interquartile range, minimum-maximum values.

	Entire population	10 Hz rTMS	Placebo	*p*
n	26	13	13	
Age (years)	72.2 ± 12.3	69.9 ± 14.0	74.6 ± 10.4	0.334
Females/males	13/13	6/7	7/6	0.695
NIHSS baseline	5.0, 7.0 (2.0-16.0)	7.0, 9.0 (3.0-16.0)	4.0, 8.0 (2.0-11.0)	0.059
Days to intervention/placebo	3.0, 2.0 (1.0-6.0)	2.0, 2.0 (1.0-6.0)	3.0, 3.0 (2.0-5.0)	0.081
Stroke site (left/right/bilateral)	11/10/5	6/5/2	5/5/3	0.865
Stroke location (cortical/ subcortical/cortico-subcortical)	2/11/13	0/8/5	2/3/8	0.084
Out-patient/in-patient rehabilitation	13/13	8/5	5/8	0.239
Hypertension	23	11	12	0.539
Diabetes mellitus	9	4	5	0.680
Dyslipidemia	24	11	13	0.141
Nicotine abuse	6	3	3	1.0

the completion of the rTMS sessions, a second round of clinical and electrophysiological tests was conducted 10 to 14 days after the onset of the stroke, at the end of the patient's hospitalization. Throughout the study period, all participants received standard pharmacotherapy and participated in conventional rehabilitation protocols tailored to their individual needs during the acute phase of stroke recovery, according to their clinical condition.

Determination of motor cortex and resting motor threshold

Before the application of therapeutic or placebo rTMS, the optimal site and intensity of stimulation were individually determined for each patient. The ipsilesional motor cortex was selected as the target site for stimulation, with the „hot-spot" identified over the motor representation of the contralateral first dorsal interosseous muscle. The site was localized using a combined EMG/EP system (Neuro-MS.NET software) in conjunction with a figure-of-eight coil. The coil handle was positioned at a 45° angle posteriorly from the midline so that the electromagnetic current flowed perpendicular to the central sulcus. The coil was then gradually moved across the scalp over the motor cortex until a motor evoked potential (MEP) was elicited. The site at which the MEP was consistently recorded was identified as the motor „hot-spot". Once the 'hot spot' was located, the resting motor threshold (RMT) was determined. RMT is defined as the minimum stimulus intensity required to generate a MEP with an amplitude ≥ 50 μV in 5 of 10 consecutive trials, at rest during muscle relaxation. The combined EMG/EP system used in our study was able to determine the RMT value automatically. The RMT value was crucial to individualize the parameters during subsequent therapeutic rTMS sessions (Turčanová Koprušáková, 2019; Zohuri & McDaniel, 2022).

rTMS

Following initial clinical and electrophysiological tests (1 – 6 days after stroke), patients underwent a total of 5 rTMS sessions (therapeutic or placebo) administered over 5 consecutive working days, with one session per day. rTMS was applied to the motor cortex – „hot-spot" area corresponding to the first dorsal interosseus muscle of the ipsilesional hemisphere using the Neuro-MS/D magnetic stimulator (Neurosoft LLC, Ivanovo, Russia). If a MEP could not be elicited from the ipsilesional hemisphere, the motor „hot-spot" site and the rTMS intensity were determined by mirroring the contralesional hemisphere. For patients with a bihemispheric ischemic stroke, the hemisphere causing the most significant motor deficit was chosen for stimulation.

The therapeutic rTMS protocol involved the delivery of 1500 pulses – 50 trains of 30 pulses per train, with a 3 second duration for each train and a 27 second interval between trains. The stimulation frequency was set at 10 Hz, with the intensity set to 100% of RMT. Therapeutic rTMS was delivered through a cooled figure-of-eight coil (Cooled angulated figure-of-eight coil "AFEC-02-100-C") attached to a Neuro-MS/D magnetic stimulator held tangentially to the scalp with the junction region approximately perpendicular to the line of the central sulcus. Placebo rTMS was applied to the same ipsilesional area, but the figure-of-eight was coil tilted perpendicular to the scalp surface, delivering

stimulation at 1% RMT amplitude, while all other stimulation parameters were identical to those of the therapeutic rTMS protocol. The parameters for therapeutic rTMS were selected based on current clinical guidelines (Rossi *et al.* 2021); however, we developed our own stimulation protocol based on existing literature (Valovičová *et al.* 2022).

Assessment of motor function and electrophysiological parameters

A comprehensive set of clinical and electrophysiological parameters was recorded and analyzed to evaluate the effects of rTMS on motor function recovery. The following assessments were included:

- **Clinical tests for impairment:** Impairment refers to "-a loss or abnormality in body structure or physiological function" (World Health Organization, 2001). The following scales were used to assess impairment:
  - National Institutes of Health Stroke Scale (NIHSS),
  - Fugl-Meyer Assessment for Upper Extremity (FMA-UE),
  - Fugl-Meyer Assessment for Lower Extremity (FMA-LE),
  - Modified Ashworth Scale (MAshS),
  - Motor Assessment Scale (MAS),
- **Clinical tests for activity:** Activity is defined as "-the execution of a task or action by an individual" (World Health Organization, 2001). The following measures were used to assess activity:
  - Barthel Index (BI),
  - Functional Independence Measure (FIM),
- **Electrophysiological testing:** MEPs were recorded, and the following parameters were analyzed:
  - MEP latency,
  - MEP amplitude,
  - Central motor conduction time (CMCT).

Clinical and electrophysiological tests were performed on two occasions: the first session was conducted between 1 and 6 days after the onset of ischemic stroke, prior to the application of rTMS. The second session was performed 10 to 14 days after the stroke, at the end of hospitalization.

These assessments constitute part of a broader testing protocol, which has already been previously published (Valovičová *et al.* 2022). The full protocol includes six testing sessions, where, in addition to clinical and electrophysiological evaluations, secondary outcomes, such as the presence of depressive and anxiety symptoms, are

Tab. 2. Changes in the clinical and neurophysiological parameters tested. HF-rTMS – high-frequency repetitive transcranial magnetic stimulation, NIHSS – National Institute Health Stroke Scale, FMA-UE – Fugl-Meyer Assessment for Upper Extremity, FMA-LE – Fugl-Meyer Assessment for Lower Extremity, FIM – Functional Independence Measure, AH – affected hemisphere, UH – unaffected hemisphere, MEP – motor evoked potential, UE – upper extremity, LE – lower extremity, CMCT – central motor conduction time, Δ – follow-up – baseline values. Categorical variables are expressed as numbers and proportions (%), continuous variables as mean ± standard deviation or median, interquartile range, minimum-maximum values.

	Entire population	HF-rTMS	Placebo	*p*
ΔNIHSS	-1.5, 3.25 (-8.0-3.0)	-3.0, 3.5 (-8.0-0)	0, 1.5 (-2.0-3.0)	<0.001
ΔFMA_UE	8.0, 15.0 (0-31.0)	12.0, 12.5 (2.0-31.0)	3.0, 8.5 (0-17.0)	0.012
ΔFMA_LE	5.0, 4.0 (-2.0-14)	5.0, 7.0 (2.0-14.0)	2.0, 5.0 (-2.0-9.0)	0.082
ΔModified Ashworth Scale	-0.5, 2.0 (-4.0-2.0)	-1.0, 2.0 (-4.0-2.0)	0, 2.0 (-3.0-0)	0.968
ΔMotor Assessment Scale	4.0, 10.0 (-1,0-22.0)	10.0, 15.0 (-1.0-22.0)	4.0, 3.25 (0-17.0)	0.340
ΔBarthel Index	15.0, 17.5 (0-45.0)	25.0, 30.0 (0-45.0)	10.0, 15.0 (0-30.0)	0.017
ΔFIM	13.0, 13.5 (0-38.0)	17.5, 16.25 (5.0-38.0)	6.0, 6.5 (0-15.0)	0.003
ΔAH_MEP_amplitude_UE	0.09, 0.65 (-1.66-2.37)	0.31, 0.63 (-1.14-2.37)	0, 0.83 (-1.66-0.7)	0.199
ΔUH_MEP_amplitude_UE	0.30, 1.21 (-1.44-3.13)	0.33, 1.14 (-1.2-3.13)	-0.09, 1.50 (-1.44-2.25)	0.839
ΔAH_MEP_latency_UE	0, 1.6 (-5.1-27.9)	0, 1.55 (-2.4-27.9)	0, 1.9 (-5.1-27.8)	0.683
ΔUH_MEP_latency_UE	-0.35, 1.28 (-2.8-3.2)	-0.4, 1.2 (-2.6-1.9)	-0.1, 1.8 (-2.8-3.2)	0.468
ΔAH_MEP_CMCT_UE	0, 1.83 (-5.09-12.5)	0, 1.73 (-1.74-9.77)	0, 2.31 (-5.09-12.5)	0.838
ΔUH_MEP_CMCT_UE	-0.125, 1.69 (-2.94-2.9)	-1.2, 1.75 (-2.94-1.05)	-0.13, 1.64 (-2.81-2.9)	0.750
ΔAH_MEP_ampitude_LE	0.16, 0.69 (-0.37-1.32)	0.25, 0.86 (-0.37-1.32)	0.12, 0.69 (-0.36-1.23)	0.562
ΔUH_MEP_ampitude_LE	-0.05, 0.67 (-4.28-1.31)	-0.21, 0.83 (-4.28-1.31)	-0.49, 0.55 (-0.98-0.81)	0.931
ΔAH_MEP_latency_LE	-0.35, 1.25 (-13.3-37.7)	-1.0, 5.5 (-13.3-37.7)	-0.3, 0.5 (-3.4-0.5)	0.295
ΔUH_MEP_latency_LE	0.1, 1.88 (-6.9-4.7)	0.2, 2.1 (-2.1-2.6)	0, 2.6 (-6.9-4.7)	0.562
ΔAH_MEP_CMCT_LE	-0.2, 2.63 (-15.16-11.8)	-1.3, 7.2 (-15.16-11.8)	0, 1.45 (-0.99-2.3)	0.055
ΔUH_MEP_CMCT_LE	0, 2.0 (-5.1-4.6)	-0.4, 2.05 (-3.15-1.9)	0.25, 4.82 (-5.1-4.6)	0.514

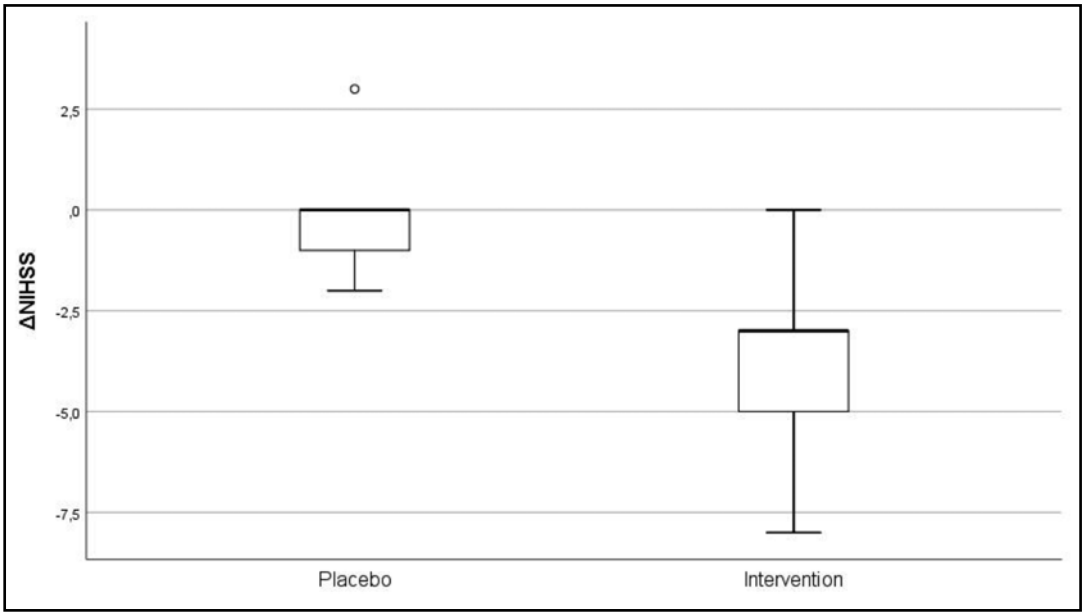

Fig. 1. Comparison of changes in clinical testing scores (National Institutes of Health Stroke Scale; NIHSS) in the therapeutic rTMS group versus the placebo group of patients.

assessed using standardized questionnaires. This multidimensional approach ensures a thorough evaluation of the impact of rTMS on motor recovery and general well-being following ischemic stroke.

Data analysis

Statistical analyzes were performed using SPSS, version 29 (SPSS Inc., USA). Categorical variables are expressed as numbers and proportions (%), continuous variables as mean ± standard deviation or median, interquartile range and minimal-maximal values. The Chi-square test, the Student's *t* test and the Mann–Whitney test were used for group comparison. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 26 patients were enrolled in this study, consisting of 13 men and 13 females with a mean age of 72.2 ± 12.3 years. Of these patients, 11 had strokes located in the left hemisphere, 10 in the right hemisphere, and 5 had bihemispheric strokes. Cortical damage was identified in 2 patients, subcortical damage in 11 patients, and cortico-subcortical damage in 13 patients. In terms of comorbidities, arterial hypertension was diagnosed in 23 patients, type 2 diabetes mellitus in 9, dyslipidemia in 24, and nicotine abuse in 6. The median baseline NIHSS was 5, and the median time from stroke onset to first intervention was 3 days. Patients were randomly assigned to one of two groups: 13 patients received therapeutic rTMS and 13 patients received placebo rTMS. No statistically significant differences were observed between the two groups in terms of baseline demographic and clinical characteristics. A detailed summary of the demographic and clinical characteristics of the study cohort is presented in Table 1.

In the statistical analysis of the selected outcome measures, we observed a statistically significant reduction in the NIHSS score in the therapeutic rTMS group compared to the placebo group ($p < 0.001$), indicating a greater improvement in clinical impairment. Furthermore, patients receiving therapeutic rTMS showed a statistically significant improvement in FMA-UE scores compared to the placebo group ($p = 0.012$). Although an increase in FMA-LE scores was also observed in the therapeutic rTMS group, this change did not reach statistical significance ($p = 0.082$). No significant differences were found in changes in the MAshS or MAS between the two groups ($p = 0.968$ and $p = 0.340$, respectively). Regarding functional activity, patients in the therapeutic rTMS group showed significant improvements in BI and FIM scores compared to the placebo group ($p = 0.017$ and $p = 0.003$, respectively), indicating greater functional independence. Electrophysiological evaluations of MEPs – amplitude, latency, and CMCT – did not show statistically significant changes between the groups. A summary of the statistical results is provided in Table 2, with a graphical representation of the significant changes in the NIHSS, FMA-UE, FIM and BI scores shown in Figures 1–4.

DISCUSSION

In the context of ischemic stroke, the use of rTMS primarily targets two key mechanisms – neuroplasticity and interhemispheric inhibition (IHI). Neuroplasticity, defined as "-the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections" (Mateos-Aparicio & Rodríguez-Moreno, 2019), can be promoted by rTMS by influencing cortical excitability, but clear evidence in favor of the early use of plasticity-enhancing interventions after stroke is still limited and

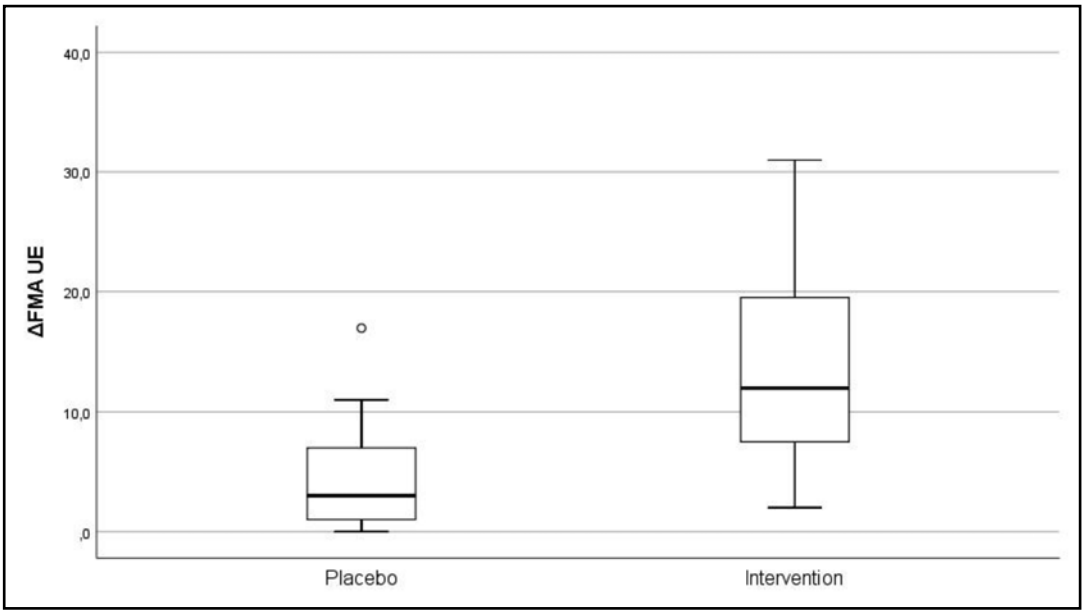

Fig. 2. Comparison of changes in clinical testing scores (Fugl-Meyer Assessment for Upper Extremity; FMA-UE) in the therapeutic rTMS group versus the placebo group of patients.

inconclusive (Adeyemo *et al.* 2012). The concept of IHI assumes that, under normal circumstances, each hemisphere exerts an inhibitory effect on the contralateral hemisphere, maintaining a functional balance. After stroke, this balance is disrupted due to a reduction in IHI of the affected hemisphere, leading to overactivity of the unaffected hemisphere. This interhemispheric imbalance is believed to hinder full recovery, a phenomenon repeatedly observed in patients with chronic stroke (Murase *et al.* 2004; Ward & Cohen, 2004). To compensate for this interhemispheric imbalance, rTMS protocols are generally used that facilitate / increase the excitability of the ipsilesional motor cortex (high-frequency-rTMS /HF-rTMS/ or intermittent theta burst stimulation) or inhibit / reduce the excitability of the contralesional motor cortex (low-frequency-rTMS or continuous theta burst stimulation) (Kadosh, 2014).

Numerous studies have explored the potential benefits of rTMS, particularly with protocols that inhibit the unaffected hemisphere or facilitate the affected hemisphere (Ayache *et al.* 2012; Lüdemann-Podubecká *et al.* 2015; Sebastianelli *et al.* 2017; Zhang *et al.* 2017a; Lefaucheur *et al.* 2020; Tang *et al.* 2022). Recent systematic reviews and meta-analyses have become more optimistic and support the use of rTMS to improve motor functions after ischemic stroke (Chen *et al.* 2022; Zhang *et al.* 2024). Despite these promising findings, there remains a consensus within the research community regarding the need for larger cohort studies to better assess the efficacy of rTMS in restoring motor functions after ischemic stroke (Ayache *et al.* 2012;

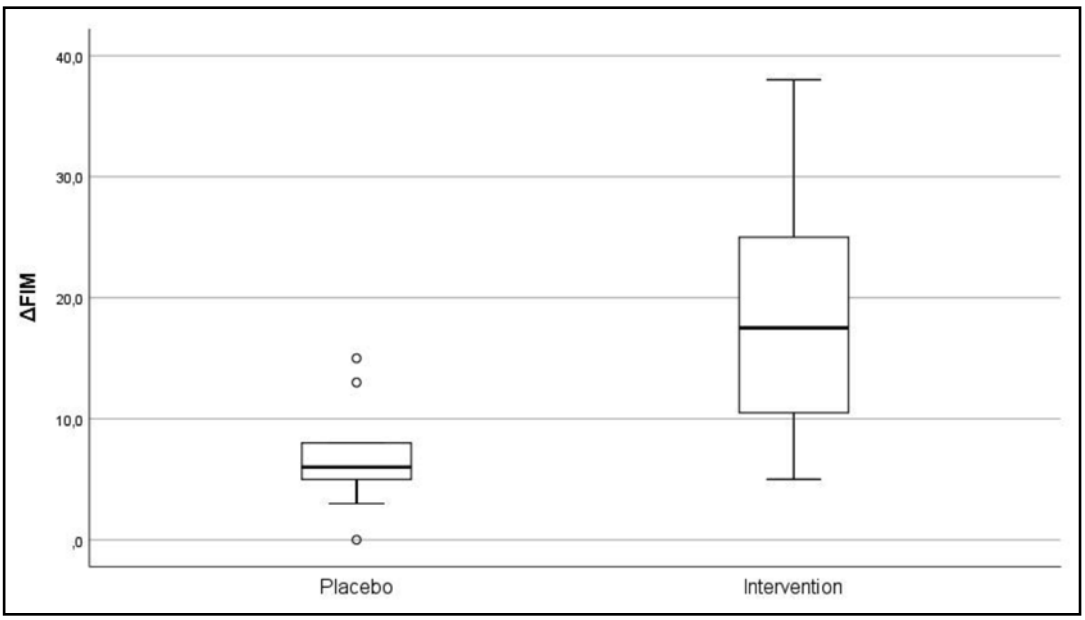

Fig. 3. Comparison of changes in clinical testing scores (Functional Independence Measure; FIM) in the therapeutic rTMS group versus the placebo group of patients.

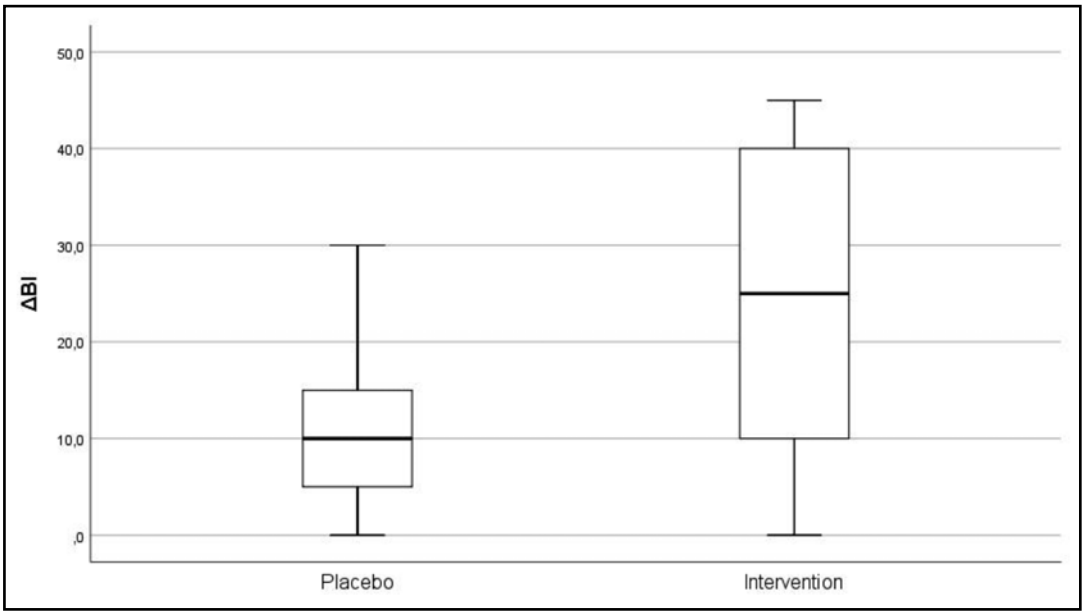

Fig. 4. Comparison of changes in clinical testing scores (Barthel Index; BI) in the therapeutic rTMS group versus the placebo group of patients.

Lüdemann-Podubecká *et al.* 2015; Sebastianelli *et al.* 2017; Zhang *et al.* 2017a; Lefaucheur *et al.* 2020; Chen *et al.* 2022; Tang *et al.* 2022, Zhang *et al.* 2024).

The primary objective of this randomized double-blind study was to evaluate the effect of 10 Hz rTMS applied to the ipsilesional hemisphere on recovery of motor functions in patients in the acute stage of ischemic stroke, compared to a placebo rTMS group. Specifically, we focused on evaluating impairment and activity, as well as electrophysiological parameters, in adult patients with motor impairment in the acute phase (within 6 days) of ischemic stroke. A total of 26 patients were enrolled in the study, 13 participants in the therapeutic rTMS group and 13 in the placebo rTMS group.

After inclusion, patients underwent 10 Hz rTMS or placebo rTMS. The design of the rTMS stimulation protocol was based on previous studies demonstrating the efficacy of HF-rTMS applied ipsilesionally to improve motor function (Ayache *et al.* 2012; Lüdemann-Podubecká *et al.* 2015; Tang *et al.* 2022) in the acute phase of ischemic stroke (Zhang *et al.* 2017b; Lafeucheur *et al.* 2020; Chen *et al.* 2022; Zhang *et al.* 2024).

As part of the impairment assessment, our study demonstrated a statistically significant reduction in NIHSS scores and an increase in FMA-UA scores in the 10 Hz rTMS group compared to the placebo group. However, we did not observe a statistically significant change in the FMA-LE, MAS and MAshS scores between the two groups. The more substantial improvement in upper extremity motor function, as reflected in FMA-UE, may be attributed to the anatomical location of the rTMS stimulation. The figure-of-eight coil was applied to the M1 „hot-spot" of the ipsilesional hemisphere, corresponding to the motor area of the contralateral first dorsal interosseus muscle. Due to the focal nature of the figure-of-eight coil, which induces the strongest electric current at the intersection of the two circular components, the induced electric field decreases with dispersion (Hallett, 2000; Hallett & Chokroverty, 2005). This electric field geometry means that more superficial brain regions, which correspond to the motor areas for the upper extremity, according to the classical cortical homunculus paradigm, receive greater stimulation than deeper regions, which represent the motor areas for the lower extremity. Furthermore, we observed statistically significant improvements in the FIM and BI scores, indicating enhanced functional activity in the therapeutic rTMS group. However, no statistically significant changes were found in the electrophysiological parameters of MEP, namely latency, amplitude and CMCT.

Despite the high heterogeneity of the methodologies and outcome measures in the literature, our findings align with those of several studies that have documented the positive effects of HF-rTMS applied to the ipsilesional hemisphere during the acute phase of ischemic stroke in improving motor functions (Khedr *et al.* 2005; Khedr *et al.* 2009; Khedr *et al.* 2010; Du *et al.* 2016; Guan *et al.* 2017; Du *et al.* 2019). Many of these studies used 10 Hz rTMS protocols like ours (Chang *et al.* 2010; Khedr *et al.* 2010; Sasaki *et al.* 2013; Sasaki *et al.* 2014; Sasaki *et al.* 2017; Du *et al.* 2019). However, unlike some previous studies (Khedr *et al.* 2009; Khedr *et al.* 2010; Du *et al.* 2016; Du *et al.* 2019), our study did not observe significant changes in electrophysiological parameters.

There are several limitations to this study that should be acknowledged. These include the small sample size, the monocentric nature of the study, and the strict inclusion and exclusion criteria, which, while ensuring a well-defined study population, may limit the generalizability of the findings. Furthermore, the short follow-up period precludes conclusions about the long-term

effects of rTMS on motor recovery. Future studies with larger, multicenter cohorts and extended follow-up are necessary to further elucidate the long-term impact of rTMS on motor function in stroke rehabilitation.

In conclusion, our study provides partial support for the positive effects of 10 Hz rTMS applied to the ipsilesional hemisphere on motor function recovery in patients in the acute stage of ischemic stroke. The findings suggest that rTMS, as applied in our protocol, may be a promising adjunct in the rehabilitation of patients with acute ischemic stroke and could be considered as part of comprehensive stroke care. However, the search for the optimal rTMS protocol must continue through further randomized controlled trials with larger cohorts and assessment tools. Given the variability in outcomes and the considerable heterogeneity of rTMS protocols in literature, future research should prioritize large-scale multicenter studies to better define the most effective rTMS parameters. There is a critical need for standardization of rTMS protocols, particularly in terms of stimulation site, intensity, and timing of intervention, to ensure consistency and improve generalizability of results.

ACKNOWLEDGMENTS

Funding
This study was supported by a grant of Comenius University in Bratislava (UK/253/2022) and by a research grant of Scientific Grant Agency (VEGA 1/0022/23).

Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical approval

This study was conducted as a part of larger prospective randomized double-blind placebo-controlled trial (title „Effect of different types of non-pharmacological intervention on motor function recovery in patients after stroke") that was approved by the Ethics Committee of the University Hospital Bratislava on 30 May 2022. Each participating patient signed an informed consent form upon inclusion in the study.

REFERENCES

1 Adeyemo BO, Simis M, Macea DD, Fregni F (2012). Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke. Front Psychiatry. **3**: 88.
2 Ayache SS, Farhat WH, Zouari HG, Hosseini H, Mylius V, Lefaucheur JP (2012). Stroke rehabilitation using noninvasive cortical stimulation: motor deficit. Expert Rev Neurother. **12**(8): 949–972.
3 Bates KA, Rodger J (2015). Repetitive transcranial magnetic stimulation for stroke rehabilitation-potential therapy or misplaced hope?. Restor Neurol Neurosci. **33**(4): 557–569.
4 Du J, Tian L, Liu W, Hu J, Xu G, Ma M et al. (2016). Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial. Eur J Neurol. **23**(11): 1666–1672.
5 Du J, Yang F, Hu J, Hu J, Xu Q, Cong N et al. (2019). Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: Evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. Neuroimage Clin. **21**: 101620.
6 GBD 2019 Stroke Collaborators (2021). Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. **20**(10): 795–820.
7 Guan YZ, Li J, Zhang XW, Wu S, Du H, Cui LY, et al. (2017). Effectiveness of repetitive transcranial magnetic stimulation (rTMS) after acute stroke: A one-year longitudinal randomized trial. CNS Neurosci Ther. **23**(12): 940–946.
8 Hallett M, Chokroverty S (2005). Magnetic stimulation in clinical neurophysiology. 2nd ed. Philadelphia: Elsevier, Butterworth, Heinman.
9 Hallett M (2000). Transcranial magnetic stimulation and the human brain. Nature. **406**(6792): 147–50.
10 Chang WH, Kim YH, Bang OY, Kim ST, Park YH, Lee PK (2010). Long-term effects of rTMS on motor recovery in patients after subacute stroke. J Rehabil Med. **42**(8): 758–764.
11 Chen G, Lin T, Wu M, Cai G, Ding Q, Xu J, et al. (2022). Effects of repetitive transcranial magnetic stimulation on upper-limb and finger function in stroke patients: A systematic review and meta-analysis of randomized controlled trials. Front Neurol. **13**: 940467.
12 Kadosh RC (2014) The Stimulated Brain. 1st ed. Academic Press.
13 Katan M, Luft A (2018). Global Burden of Stroke. Semin Neurol. **38**(2): 208–211.
14 Khedr EM, Abdel-Fadeil MR, Farghali A, Qaid M (2009). Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol. **16**(12): 1323–1330.
15 Khedr EM, Ahmed MA, Fathy N, Rothwell JC (2005). Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology. **65**(3): 466–468.
16 Khedr EM, Etraby AE, Hemeda M, Nasef AM, Razek AA (2010). Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. Acta Neurol Scand. **121**(1): 30–37.
17 Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018) Clin Neurophysiol. **131**(2): 474–528.
18 Lüdemann-Podubecká J, Bösl K, Nowak DA (2015). Repetitive transcranial magnetic stimulation for motor recovery of the upper limb after stroke. Prog Brain Res. **218**: 281–311.
19 Mateos-Aparicio P, Rodríguez-Moreno A (2019). The Impact of Studying Brain Plasticity. Front Cell Neurosci. **13**: 66.
20 Murase N, Duque J, Mazzocchio R, Cohen LG (2004). Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol. **55**(3): 400–409.
21 National Health Information Centre (2024). Health Statistics Yearbook of the Slovak Republic. Bratislava (Slovakia): National Health Information Centre. https://www.nczisk.sk/Documents/rocenky/2022/Zdravotnicka_rocenka_Slovenskej_republiky_2022_en.pdf
22 OECD (2023). Health at a Glance 2023: OECD Indicators. Paris (France): OECD Publishing.
23 Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al.. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines (2021). Clin Neurophysiol. **132**(1): 269–306.
24 Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. **120**(12): 2008–2039.
25 Sasaki N, Abo M, Hara T, Yamada N, Niimi M, Kakuda W (2017). High-frequency rTMS on leg motor area in the early phase of stroke. Acta Neurol Belg. **117**(1): 189–194.

26 Sasaki N, Kakuda W, Abo M (2014). Bilateral high- and low-frequency rTMS in acute stroke patients with hemiparesis: a comparative study with unilateral high-frequency rTMS. Brain Inj. **28**(13–14): 1682–1686.

27 Sasaki N, Mizutani S, Kakuda W, Abo M (2013). Comparison of the effects of high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. J Stroke Cerebrovasc Dis. **22**(4): 413–418.

28 Sebastianelli L, Versace V, Martignago S, Brigo F, Trinka E, Saltuari L, et al. (2017). Low-frequency rTMS of the unaffected hemisphere in stroke patients: A systematic review. Acta Neurol Scand. **136**(6): 585–60.

29 Tang Z, Han K, Wang R, Zhang Y, Zhang H (2022). Excitatory Repetitive Transcranial Magnetic Stimulation Over the Ipsilesional Hemisphere for Upper Limb Motor Function After Stroke: A Systematic Review and Meta-Analysis. Front Neurol. **13**: 918597.

30 Turčanová Koprušáková M (2019). Transkraniálna magnetická stimulácia – Základné princípy a využitie v neurológii. Vysokoškolské skriptá. [(Transcranial Magnetic Stimulation - Basic principles and applications in neurology. University scripts")]. 1st ed. Martin (Slovakia): Univerzita Komenského v Bratislave, Jesseniova lekárska fakulta v Martine.

31 Valovičová K, Šiarnik P, Klobucká S, Goldenberg Z, Machalová E, Riečanský I, et al. (2022). Protokol projektu s názvom „Vplyv rôznych typov nefarmakologickej intervencia na obnovu motorických funkcií u pacientov po cievnej mozgovej príhode". [(Project protocol "Effect of different types of non-pharmacological intervention on the recovery of motor function in patients after stroke")]. Lek Obz. **71**(10): 381–387.

32 Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y (2020). Burden of Stroke in Europe: Thirty-Year Projections of Incidence, Prevalence, Deaths, and Disability-Adjusted Life Years. Stroke. **51**(8): 2418–2427.

33 Ward NS, Cohen LG (2004). Mechanisms underlying recovery of motor function after stroke. Arch Neurol. **61**(12): 1844–1848.

34 World Health Organization (2001). International Classification of Functioning, Disability, and Health. Geneva: World Health Organization.

35 World Health Organization (2024). The top 10 causes of death. Published August 7, 2024. Accessed November 5, 2024. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

36 Zhang JJY, Ang J, Saffari SE, Tor PC, Lo YL, Wan KR (2024). Repetitive Transcranial Magnetic Stimulation for Motor Recovery After Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials With Low Risk of Bias. Neuromodulation. Published online September 24, 2024.

37 Zhang L, Xing G, Fan Y, Guo Z, Chen H, Mu Q (2017b). Short- and Long-term Effects of Repetitive Transcranial Magnetic Stimulation on Upper Limb Motor Function after Stroke: a Systematic Review and Meta-Analysis. Clin Rehabil. **31**(9): 1137–1153

38 Zhang L, Xing G, Shuai S, Guo Z, Chen H, McClure MA, et al. (2017a). Low-Frequency Repetitive Transcranial Magnetic Stimulation for Stroke-Induced Upper Limb Motor Deficit: A Meta-Analysis. Neural Plast. **2017**: 2758097.

39 Zohuri B, McDaniel P (2022). Transcranial Magnetic and Electrical Brain Stimulation for Neurological Disorders. 1st ed. Academic Press.