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Research article

A topical reappreasal on use of repetitive Transcranial Magnetic Stimulation in elderly patients with postischemic stroke statuses - a systematic literature review

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Abstract: Introduction: Stroke is a cerebrovascular disease with an impressive potential of disability, (multi)morbidity, and mortality among elderly patients. After stroke, a series of seque-lae represents a dynamic challenge for rehabilitation, especially for improving motor, cognitive and depressive disorders (1,2). Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive, painless, neuromodulations and neurostimulation method, which uses electromagnetic induction to administer repeated trains of pulses, with thera-peutic, diagnostic and research purposes (3–5).
Method: We performed a systematic literature review of the related literature using a widely international accepted method - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(6), by searching, filtering, and selecting profile documen-tary material. Combinations/syntaxes of keywords were searched in the following interna-tional databases: Elsevier(7), PubMed(8), PMC(9), PEDro(10), in ISI indexed journals by Web of Knowledge/Science(11) during 1/01/2019-31/12/2021. Besides the 9 articles selected to enhance our related knowledge base we have also used some works freely identified in the literature.
Results and discussions: 9 articles satisfied all the previous filtering criteria/ PRISMA steps and were selected for qualitative and detailed analysis. The benefits of rTMS, aiming to bring further insight into the responsiveness of motor deficit, depression, and cognitive impairment of the treatment, and through the favorable dynamic progress of the scores of the quantification scales used: HAMD-17/ HDRS, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assesment; SCWT, Stroop Color-Word Interference Test; WAIS, Wechsler Adult Intelligence Scale; NIHSS, National Institutes of Health Stroke Scale; Barthel Index Score; ADL, Activities of Daily Living; mRS, modified Rankin Scale; FIM, Functional Independence Measures.
Conclusions: Through this systematic review, we wish to present the perspective of the successful use of rTMS among elderly patients. We also intend for this work to be the start-ing point in the development of a doctoral study, which will include post-stroke sequelae, such as motor deficits, depressive and cognitive disorders, and through which we will strengthen scientific confidence in the tolerability and effectiveness of this type of stimula-tion for this segment of age.

Keywords: elderly, ischemic stroke, transcranial magnetic stimulation, TMS, repetitive transcranial magnetic stimulation, rTMS

1. Introduction

The aging society phenomenon produces increased stroke incidences, despite the great prevention possibilities of modern medicine, a factor that negatively counterbalances these possibilities being the global natural phenomenon - including in Romania (12).

Conventionally, "elderly" has been chronologically defined at the age of 65 years old or older (13). Demographic research shows the average life expectancies of people in the European Union (EU) countries has enhanced over the last decades, and will more than likely continue to increase, considering that "Chronic disease, frailty, and disability tend to become more prevalent at older ages, so that a population with a higher life expectancy may not be healthier" (14). European population aged 65 years and older is more than 80% affected by chronic diseases or co-morbidities generating a burden of disease and high management costs. It is foreseen that until 2060, in the European Union, the population aged 65 or above will almost double, reaching 152.6 million. Older population aged 80 years and above, will triple, reaching 62.4 million (15). The current demographic trends- decreased fertility rates and increased life expectancy- also explains the old-age dependency ratio, indicating that people over 65 years old or above relative to the group population aged 15-64, and is projected to increase in the EU over the mentioned projection period (16).

Stroke is one of the cerebrovascular diseases with major potential for mortality, (in the elderly: multi) morbidity and disability. It is the leading cause of disability and the second cause of mortality worldwide, affecting especially the aging population, and represents a dynamic challenge for rehabilitation (2,17). Most strokes occur in people >65 years old and aged patients have higher mortality and poorer quality of life after stroke compared with younger patients (18). Stroke, a debilitating disease of aging, is affecting >15 million people worldwide each year, as estimated by World Health Organization (WHO), and approximately 5.5 million people die (19).

Ischemic stroke is the most frequent subcategory and is responsible for about 87% of all strokes. "The ischemic stroke is a transient or permanent interruption of the blood supply into/through the cerebral vasculature. During ischemia, lack of oxygen and energy supply generates inflammation and oxidative damage" (1).

Stroke among geriatric patients has special clinical particularities emphasizing the severe prognostic due to age or time of its appearance. It's more likely for the elderly to experiment stroke in the morning, at the wakening time. Also, regardless the symptoms intensity, the following hours and days stroke have expanding or aggravating potential leading to temporary or permanent consequences (4).

Neuropsychiatric and motor disorders are common sequelae after stroke, emphasizing neurocognitive disorders such as dementia, depression, and anxiety as well as motor impairments such as hemiparesis (contralateral to the lesioned cerebral hemisphere), spasticity and dexterity in the paretic arm, hand, and gait disturbance (2).

Almost 80% manifest motor impairments, 40% have moderate motor deficit and about 15-30% have severe permanent disability (2). At the same time, in the spectrum of neuropsychiatric and cognitive disorders, 25-30% of stroke survivors suffer from depression and 12.2% have dementia (5,20). Marital status (unmarried, widow/ widower), feminine gender, psychiatric family history, genetic factors, absence of social and family emotional support, and physical or intellectual disability can form a predisposition for Post Stroke Depression (PSD) (4). Studies have demonstrated a connexion between depression and the stroke site, with a predilection for left hemisphere (5).

Compared to Alzheimer's Dementia, Vascular Dementia (VD) is the second most common globally, accounting for about 20-30% of all dementia cases, with a lower surviving rate, 3 to 5 years. Its presence it's linked to a future stroke and each stroke is a prediction factor for developing dementia (3,20,21). Alvarez-Sabin et al. they stated that

"Cognitive decline after stroke is more common than stroke recurrence. Stroke doubles the risk of dementia and is a major contributor to vascular cognitive impairment and vascular dementia" (22).

These consequences lead to a reserved outcome associated with a decreased quality of life by impacting the physical, mental, and social functionality of the daily life activities, generating ultimately an even higher mortality rate. Also, is the reason for a prolonged hospitalization and high hospitalization costs.

Neuroplasticity is a restorative brain process. It starts immediately after the ischemic event, considered to be a spontaneous healing, that shows the human brain's ability to restore the damaged neural network using the intact hemisphere, contributing to motor and cognitive improvements (1). Usually, when spontaneous neuroplasticity is not complete, the patient's recovery can be enhanced by adding rehabilitation methods, aiming to improve motor and cognitive functionality, reduce the patient's dependence or it's chance to institutionalization, and ultimately reduce mortality. Physical and Rehabilitation Medicine uses methods such as Constraint-Induced Movement Therapy (CIMT), Strength Training, Mirror Therapy, Computer Based Training Programs/ Virtual Reality (VR)/ Augmented Reality (AR), considering ergotherapy or occupational therapy gold standard in post-stroke rehabilitation (17).

Despite the numerous existing rehabilitation methods, each patient's evolution is unique and is dependent to the neuroplasticity process, the injury's location, biological, psychological and environmental factors (23).

New innovative methods such as Non-Invasive Brain Stimulation (NIBS), Transcranial Direct Current Stimulation (tDCS) or repetitive Transcranial Magnetic stimulation (rTMS) are gaining field for post-stroke therapeutic approaches for motor and depressive disorders, as well as cognitive impairment (2,5,20).

rTMS is a non-invasive neurostimulation and neuromodulation brain stimulation technique, which uses electomagnetic induction to change the level of cortical excitability, in order to either cause hyperpolarization or depolarization of the cortical neurons. A coil generates electric currents administred in repeated trains of pulses in variabil intensity, frequency, and duration, with minimal discomfort or painless. It is used since 2008 with the Food and Drug Administration's (FDA) approval for Multi-Drug Depression (MDD), but lately also for therapeutic, diagnostic and research purposes in a variety of neurological and psychiatric conditions, such as Obsessive Compulsive Disorder (OCD), Post Traumatic Stress Disorder (PTSD), addictions to drugs, Parkinson's Disease, Tinnitus. In addition, recently it has been reasearched to be useful, in some studies more than others, in the rehabilitation of post-stroke patients, mentioning aphasia, hemiparesis/hemiplegia, spasticity, depression and cognitive disorder (2,3,5,20,24–26).

Although stroke is widely spread around the globe, the acces to innovatively high expensive therapies such as rTMS is impossible or hard to obtain for low income contries. It is reachable for high income countries, such as USA, Korea, Japan, Denmark, Italy or Poland (27).

Considering the overwhelming incidence of ischemic compared to hemorrhagic stroke, the present systematic review is based on updating the usefulness of rTMS in this pathology.

2. Materials and Methods

In order to identify the current state of knowledge of this topic, we previously carried out a systematic review of the related literature through the method of filtering and selecting profile documentary material, widely used and accepted at the international level: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Figure 1) (6). We searched, using contextually, combinations/syntaxes of keywords in the following international databases: Elsevier(7), PubMed (8), PMC (9), PEDro (10), articles published in English in ISI indexed journals by Web of Knowledge/Science (11) during 1/01/2019-

31/12/2021. Seven sets of words, keyword combinations/ syntaxes for database search have been used: "elderly" + "ischemic stroke" + "transcranial magnetic stimulation", "elderly" + "ischemic stroke" + "repetitive transcranial magnetic stimulation", "elderly" + "ischemic stroke" + "TMS", "elderly" + "ischemic stroke" + "rTMS" (Table 1). We identified through database searching 498 articles. After removing the duplicates, we obtained 237 ISI articles, and 36 articles were excluded. 134 articles were full text assessed for eligibility, and 125 articles were excluded with reasons. After, full text reading for eligibility, 9 articles were included in the qualitative synthesis (Fig. 1). In order to enhance our related knowledge base we have used also some works freely identified in the literature.

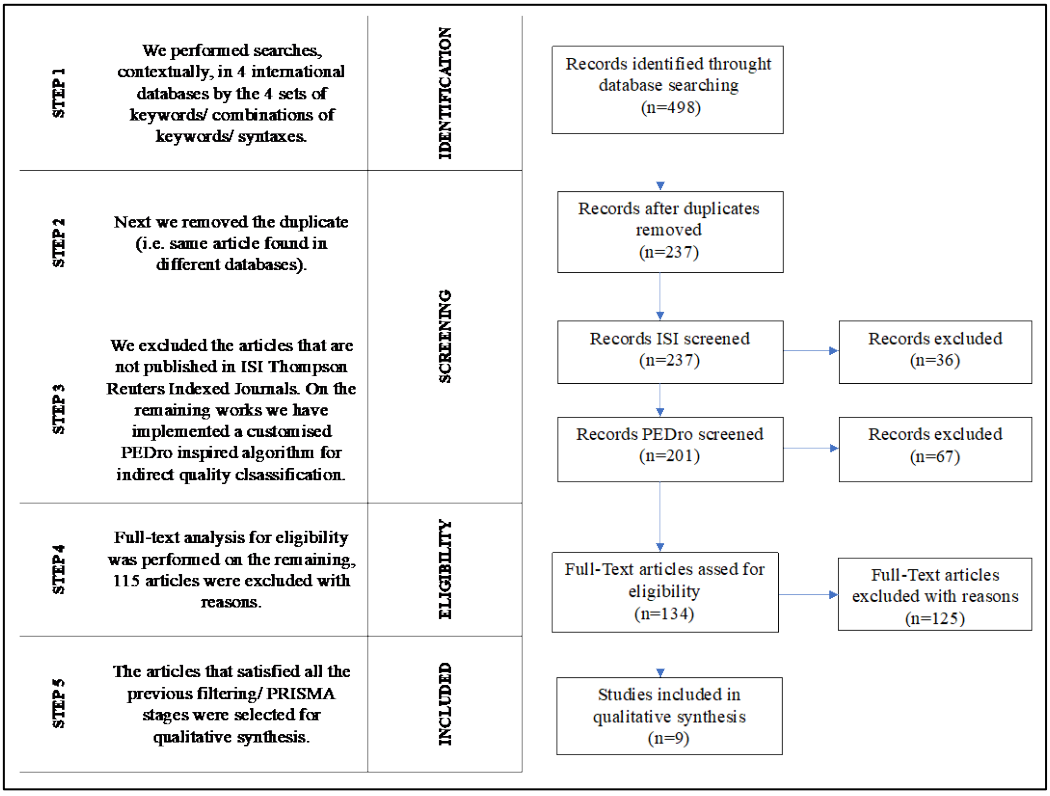

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram relating to our literature systematic review.

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Keywords/ "syntaxes sets	Elsevier	Pub Med	PMC	PEDro	Total
"elderly" & "ischemic stroke" & "transcranial magnetic stimulation"	0	0	189	0	189
"elderly" & "ischemic stroke" & "repetitive transcranial magnetic stimulation"	0	0	101	0	101
"elderly"& "ischemic stroke" & "TMS"	0	0	123	0	123
"elderly" & "ischemic stroke" & "rTMS"	0	0	85	0	85
Total	0	0	498	0	498

Table 1. Keywords/ "syntaxes" selected for our article and the results found in mentioned database.

3. Results and Discussion

rTMS may facilitate the neurorehabilitation process, imitating the natural phenomenon of the brain's neuroplasticity, in order to reestablish the interhemispheric neural network balance by suppressing the contralesional hemisphere neuroexcitability. This principle may present some strong pathways similarities with a neurorehabilitation method CIMT-based on a behavioral approach, but rTMS is a more elegant and elevated approach towards modulating a interhemispheric imbalanced inhibition. Low frequency (LF) considered to be up to 1 Hz, suppressive, diminishes neural excitability, inducing long-term depression (LTD), while high frequency, above 5 Hz is activator and generates long-term potentiation (LTP). Thus, the high frequency is applied over the damaged motor cortex and the low frequency is applied over the uninjured area (2,3,24,26).

rTMS studies in Motor Disorders

A systematic review (2) mentions 1 meta-analysis in post-stroke motor rehabilitation considering using rTMS has limited possibilities of recovery, with no significant increase of motor function on Activities of Daily Living (ADL) scale or Barthel Index Score (25).

A more recent systematic review discussed a significant rTMS effect for upper limb synergies, muscle strength, sitting and standing balance and improvements on ADL scale, especially within the first 3 months post-stroke. Timed training by modulating the periods of behavioural activity and stimulation, led to a overall effect size better than stimulation alone (28). Also, it could not determine on the short term follow up the long-term effect of rTMS, considering that long-term evaluation should be performed (25).

Some findings mention that is no consensus on the best frequency, either low or high, or if is best suited for acute or chronic post-stroke patients. Recent trials are showing a difference between HF and LF stimulation, considering that the overall outcome may improve when 10 Hz frequency is used over the affected cortical site, for upper extremity motor recovery. Still, there is limited research on applying HF-rTMS over the ipsilesional site (29).

Regarding the improvement of walking, balance and motor function of the lower limbs, different effects obtained after stimulation were observed. Thus, HF rTMS applied ipsilesionally induces large-scale effects, and applying LF-rTMS over the contralesional cortex does not produce improvements. In addition, intermittent theta burst stimulation (ITBS) produces a small effect when applied contralesionally and bilaterally (30).

Other studies conclude that rTMS combined with other therapies could obtain a better outcome for the patient (31). Still, it was found no significant improvement in motor function using additional rehabilitation interventions, such as CIMT (2).

rTMS studies in Vascular Depression/ PSD

Various types of studies included in systematic reviews (24,26) have concluded on the therapeutic effects of TMS. Open rTMS trials have proven to successfully decrease Hamilton Depression Scale (HDRS) scores, with a 25% rate of response compared to baseline. Prospective, randomized, controlled trials show a signifiant difference between real and sham stimulation, emphasizing a a meaningful regression and remission rates quantified by HDRS scores.

According to some initial studies in which the age factor was discussed regarding the effectiveness of rTMS in depression in the elderly, it was highlighted that they could respond less to the stimulation effect. It was considered that the stimulation effect would be prevented from propagating due to cerebral atrophy related to advanced age, which would change the distance between the coil and the cortex, as well as the density of the cerebrospinal fluid. However, subsequent studies have shown that rTMS is a viable and successful option for treating depression in the elderly by increasing the stimulation

intensity, as cerebral atrophy in the case of the elderly is also associated with a lower resting motor threshold (rMT) (32).

The majority of used protocols administred 10 Hz frequency over the left dorso-lateral-prefrontal-cortex (DLPFC) with a variable rMT intesity, between 100%-110%, during 10 sessions improving verbal fluency, visuospatial memory, and short-term depressive simptomes, and delayed remissions (26).

Some findings show no contraindication or bias in simultaneous association between antidepressants and rTMS therapy, but performed experiments continued after stimulation with an atidepressant (citalopram), and only a fraction of the patients relapsed (26).

By ameliorating the depressive symptoms, some studies showed an improvement in ADL scores, which explains that using rTMS therapy for PSD can also improve motor disability secondary to increasing the patient volition to better perform in physical therapy (24).

Preliminary accelerated rTMS protocols have been safely and viabily researched in PSD, including elderly patients, from 2 weeks to 6 months post-stroke, using high frequency rTMS, 20 Hz over the left DLPFC, at 110% rMT, for five sessions/day, for 4 days in a row, having a total of 20 sessions. A pause of 10-15 min was necessary between daily sessions. The patients have been short-term and long-term folowed up, until 3 months, and HAMD scores were impressively improved, all evolving from a "depressed" status" (HAMD>= 8), to a "non-depressed" (HAMD<8). In term of remission rates, 100% were in remission after TMS, and only one patient presented a 47% reduction the baseline score depression at the 3 months follow-up. The study may have presented a self selection bias, based on the insclusion of patients without motor impairments on the Functional Independence Measures (FIM), National Institutes of Health Stroke Scale (NIHSS) or modified Rankin Scale (mRS) scores, which implies the suggestion to further research involving dependent patients (5).

The subacute/subchronic PSD stages are the ones to benefit the most from rTMS, but some studies showed that stimulation can have some positive results when used in chronic stages (5).

rTMS studies in Vascular Cognitive Disorder (VCD)

Randomized, controlled, crossover, blinded studies (24,26) have shown main findings using TMS for improving VCD. First improvement in the Stroop Color-Word Interference Test (SCWT) after the stimulation of DLPFC, but not for the primary Motor Cortex (M1), and the second improvement in the digit symbol subtest of the Wechsler Adult Intelligence Scale (WAIS), regardless of the stimulation site. Other neuropsychological tests presented no measurable effect of rTMS therapy. Most of the studies that mention improvents for post-stroke cognitive disorder have also used scales such as: Mini-Mental State Examination(MMSE) and Montreal Cognitive Assesment (MoCA).

For this type of trials, stimulation was performed a combined TMS tehnique, by administering a 1 to 10 Hz frequency, continous or repetitive, at 100% rMT, over the left DLPFC (active) and left M1(control), for a total of 4 sessions, 2 for continous and 2 for repetitive)(3,26). Also, other studies mention using a 10Hz frequency for vascular cognitive impairment (3).

In order to determine a better view over the vascular lesion, cognitive vascular impairment and neuroplasticity, multiple studies performed close analyses on the neurobiology of the brain when using TMS, showing for post-stroke patients a decrease in long-term potentiation-like in the affected hemisphere, but also a capacity of motor modulation between hemispheres (33). Still, therapeutic rTMS studies for for humans with VCD are lacking (20).

However, for the post-stroke sequelae, large trials are lacking in order to determine this type of stimulation's benefits, depending on the variable stimulation parameters across rTMS research, based on frequency, intensity and pulses. There is no consensus on the most suitable rTMS paradigma, no standardized treatment protocol, as studies mentions variable stimulation parameters (2,28).

The results of the studies indicate variable results, both for the improvement of motor function at the level of the upper and lower limbs, as well as for the cognitive or depressive disorder, indicating better results at some levels than at others. For example, the best results seem to be obtained by the treatment of depressive disorder in adults, but research on the geriatric population shows that some age-related variables, as explained above, can influence the application of the rTMS paradigm and implicitly the obtained result. However, the outcomes seem to be trustworthy and encourage the use of this method for elderly patients as well, despite the biological, anatomical, and physio-pathological elements that differentiate them from the young population.

4. Conclusion

rTMS is a new therapeutic method, successfully used in treating a multiple variant of disorders, in some more useful than in others. However, even though this method is mentioned in the research field, current data for some disorders are still lacking or in developing. The cerebral changes occurring in the anatomy and cerebral physiopathology of the elderly can influence to some extent, according to different researches, the customization of the stimulation protocol and the responsiveness of the patients. Also, the multitude of used methodologies of administration and the lack of a standardized protocol, generate elements of confidence lack in the studies' related findings. That is why it is necessary to strengthen the current research by conducting trials, especially on this age segment, to account for better opinions and expectations regarding the usefulness of rTMS after stroke in the geriatric population.

Thus, motivating our choice for initiating the doctoral research in this field and hoping to be able to bring new research perspectives from the upcoming doctoral study.

Author contributions.
All authors have equal contribution.

Conflict of interests:
The authors declare no conflicts of interests.

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