Repetitive Transcranial Magnetic Stimulation on Motor Recovery after Acute Ischemic Stroke

Amal Salah Eldien El Motayam[1], Walid M. Reda Ashour[1], Ahmed E. Elsayed[2], Mohammed Samir Ibrahim[2], Rania S. Nageeb[1]

[1] Neurology Department, Faculty of Medicine, Zagazig University, Egypt
[2] Neurology Department, Kobri El-Koba Military Complex, Cairo, Egypt.
Email: drmsi200200@gmail.com

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Abstract

Background: Transcranial magnetic stimulation (TMS) is one of the emerging techniques which assist in targeting rehabilitation after stroke. Using of it has progressed dramatically over the last decade with two emerging and potentially useful functions identified. Firstly, it's used as a tool for predicting recovery of motor function after stroke, and secondly, as a adjunct treatment aimed at modifying the excitability of the motor cortex in preparation for rehabilitation. In stroke patients, much of spontaneous recovery occurred after the acute phase due to plastic alterations in the brain. The task for rehabilitation is to discover new ways which may promote and improve the brain plasticity , so that the recovery happen more quickly and more effectively. Since much of good recovery depends on lesioned hemisphere plasticity , one of therapeutic approach is to attempt to progress this plasticity by brain stimulation. Conventional rTMS modalities include high-frequency (HF-rTMS) stimulation (> one Hz) and low-frequency (LF-rTMS) stimulation (⩽ one Hz). High-frequency stimulation typically enhances motor cortex excitability of the stimulated area, whereas low-frequency stimulation usually gives a reduction in excitability. The mechanisms by which rTMS modulates the brain are rather complex, although they seem to be related to the phenomena of long-term potentiation and long-term depression.

Keywords: Repetitive transcranial magnetic stimulation, Brain infarction, Motor function, Outcome

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Introduction

Repetitive Transcranial magnetic stimulation (rTMS) is a non-invasive means by which evaluation of the function and structure of the central nervous system is implemented. A stimulation coil introduces a magnetic field over a specific area of a participant's scalp, inducing a secondary electrical current within cortical parenchyma **(1).**

It is a specific stimulation paradigm distinguished by the execution of a sequence of sequential stimuli on the likewise cortical region at different frequencies and inters sequence intervals. It can transiently change the excitability of the excited cortex, with both local and remote consequences outlasting the stimulation period **(2).**

Repetitive Transcranial Magnetic Stimulation applies to any alliance of more than two pulses delivered with a time interval of two seconds or less (frequency of 0.5–1 Hz) with the capability to provide diverse consequences than the isolated pulses. This entails delivery of short bursts or trains of three to four pulses at high frequency (10–20 Hz, i.e. with a time interval between pulses around 50 ms) and of long

periods of stimulation (until 20–30 min) at a fixed frequency, with or without interference by stimulation-free intervals in between discharges **(3).**

Stimuli are given as single pulses, usually with three to five seconds between every stimulus. Depending upon the wanted neuro-physiological index, stimuli may either be applied at a single cranial site or systematically over a predefined grid, in a manner identified as 'mapping' **(4).**

Mechanism of action of Repetitive Transcranial Magnetic Stimulation (rTMS):

The fundamental principle behind mechanism of rTMS action remains identical across protocols and works on Faraday's principle, i.e., an alternating electric field causes a dynamic magnetic field of a few teslas, which in turn produces a perpendicular electric current in conductors in the near region, i.e., a population of neurons **(5).**

The magnetic stimulation produces electrical fields (voltages measured between 2 points) that, in turn, produce electric currents to swirl in the body. More particularly, a magnetic stimulator involves a capacitor discharge system connected to an external coil of wire, which creates a throb of current within the coil and hence a pulse of the magnetic field. Meanwhile, this coil is situated nearby the body; this offers currents to flow in the tissue **(6).**

Long-lasting influences on the brain depends on changing synaptic strength or causing anatomical changes such as alterations in dendritic spines or sprouting. Since the anatomical changes may well be a secondary consequence of prolonged changes of synaptic strength, the basic logic of rTMS stimulation is to change synaptic strength **(7).**

Recent studies investigated cellular and molecular mechanisms underlying efficacy rTMS. It is induced neuronal electric field which activates voltage-dependent calcium channels, N-methyl-D-aspartate receptor and calmodulin-dependent protein kinase II, along with promoting changes in the release of dopamine, glutamate and gamma-aminobutyric acid**.** These alterations elicit calcium influx, excitatory postsynaptic potential, inhibitory postsynaptic potential and activation of molecular pathways critical for plasticity, such as Akt/mammalian target of rapamycin, mitogen-activated protein kinase/extracellular signal-regulated protein kinase 1/2 and ribosomal protein S6 **(8), (9), (10).**

In astrocytes, as well it could promote intracellular calcium release and alters glial fibrillary acidic protein and inflammatory gene expression in vitro**.** Twenty Hz rTMS suppressed proliferation of astrocytes and down-regulated the expression of neuronal nitric oxide synthase, which could potentially contribute to its beneficial effects on neuropathic pain relief**.** In microglia, long-term low-frequency rTMS (LF-rTMS) stimulation promoted their polarization to M2 phenotype without affecting the proliferation of microglia **(11).**

The therapeutic applications of rTMS after Acute Ischemic Stroke

Virtually all rTMS applications that have a therapeutic rather than investigative goal use slow frequency (one Hz) or fast-frequency (ten Hz) leading to either to change in brain cortical parameters (e.g., excitability, receptor density, and hormone levels) or to investigate brain characteristics (e.g. localization of brain function and connectivity, affects of medications on cortical excitability). It can change

brain cortical parameters while trains of stimuli are delivered in rapid sequence to discrete brain regions. **(12).**

The most common stimulation site is the primary motor cortex (M1) that causes motor evoked potentials recorded from the contralateral muscles through surface electromyography electrodes. The strength of TMS, measured as a portion of the maximal output of the stimulator, is tailored to every patient based on the motor threshold (MT) of excitability **(13).**

Resting MT (rMT) is found when the target muscle is at rest, it is defined as the minimal intensity of M1 stimulation needed to elicit an electromyography response with a peak-to-peak amplitude > 50μV in at least five out of ten consecutive trials **(14).**

In a clinical context, the evaluation of motor cortex and corticospinal tract integrity is better assessed by the following TMS outcome parameters: motor threshold, motor evoked potential amplitude, central motor conduction time, cortical silent period duration, short-interval intracortical inhibition, as well as intracortical facilitation **(15).**

The majority of studies reported that of stroke survivors are left with a residual disability such as impairment of motor , speech defects and about 50% of stroke survivors experiencing longstanding motor disability and up to 30% still requiring aid with activities of daily living six months after stroke due to the imbalance of transcallosal inhibitory pathways between both hemispheres, which may be influenced by the cerebral ischemia and by the asymmetric inhibition from the unaffected hemisphere **(16), (17).**

Motor and manual dexterity

Brain hypoxia and nutritional deficiency that can harm the brain tissues produce a series of motor symptoms and disability **(18).** Throughout the recovery process, neural plasticity is regarded as the primary mechanism that induces motor-function restoration, by gradually restoring the association among neural networks and between the brain and the muscles **(19).**

Much of the spontaneous recovery includes plastic alterations in the brain occurred in post stroke patients, so the task for rehabilitation is to discover the ways which promote and improve neuronal plasticity and the variations happen more quickly and more effectively. Since much of good recovery depends on plasticity in the lesioned hemisphere, one therapeutic approach is to attempt to progress brain plasticity in the lesioned region with brain stimulation **(20).**

The primary factors limiting poststroke functional rehabilitation are synaptic function changes, such as diminished excitability of the affected hemisphere and interhemispheric imbalance of inhibition (hereafter interhemispheric imbalance). Excessive ipsilesional hemisphere inhibition by the contralesional hemisphere after stroke seriously limits motor-function recovery because interhemispheric inhibition worsens neurological deficits via the transcallosal pathway **(21).**

Contralesional hemisphere inhibition upon the ipsilesional hemisphere is linked with post-stroke injury, which is the severer the injury, the stronger the inhibition. In addition, interhemispheric inhibition is regarded as a therapeutic target for poststroke recovery. So that this recovery is improved by decreasing transcallosal inhibition in the affected hemisphere and inhibiting excitability of the unaffected hemisphere by rTMS**.** After the acute period, it was observed that the transcallosal inhibition in the ipsilesional hemisphere was magnified, while the excitability in the contralesional hemisphere raised **(22), (23).**

In a series of sequelae after stroke, a deficit in manual dexterity would happen in two-thirds of the patients leading to significant limitation for stroke survivors who need partial or full dependence/assistance on others for activities of their daily living. Although neural rearrangement happens soon after a stroke, the natural rehabilitation of functional recovery of upper limbs has often been limited. To overcome these limits, novel strategies to intensify neural regeneration, brain structures, and functional recovery are required. Recently, rTMS has been approved as an add-on method to enhance motor function recovery after stroke **(24).**

It has been suggested that rTMS can specifically improve manual dexterity which is defined as the ability to coordinate the fingers and efficiently manipulate objects, and is of crucial importance for daily living activities **(25).**

As reported in a recent study during the first week after stroke onset if rTMS applied to the affected brain hemisphere, excitatory potential in the paretic limb is obtained, it interacts with the good rehabilitation predictors; their absence is linked with poor rehabilitation. The underlying theory of rTMS treatment in stroke is based on “upregulating” the lesioned hemisphere or “downregulating” the sound hemisphere **(26).**

After stroke rTMS if utilized in high- frequency (five Hz) over the affected hemisphere which is hindered while low-frequency (< one Hz) can be applied over the intact hemisphere to lessen its excitability, leading to functional recovery. It was also used bilaterally, one Hz rTMS over the sound hemisphere and 10 Hz over the affected hemisphere which revealed improved motor training effect on the paretic hand **(16).**

Conventional rTMS modalities include high-frequency (HF-rTMS) stimulation (> one Hz) and low-frequency (LF-rTMS) stimulation (⩽ one Hz). High-frequency stimulation typically enhances motor cortex excitability of the stimulated area, whereas low-frequency stimulation usually gives a reduction in excitability. The mechanisms by which rTMS modulates the brain are rather complex, although they seem to be related to the phenomena of long-term potentiation and long-term depression **(14).**

Early study assessed forty-eight patients with acute ischemic stroke after being classified into three groups. The first two groups received real rTMS over motor cortex (3 and 10 Hz respectively) of the affected hemisphere and the third group received sham stimulation of the same site, daily for five consecutive days. Disability was assessed before, after fifth sessions, and then after 1, 2, 3 and 12 months. Cortical excitability was assessed for both hemispheres before and after the second and fifth sessions. A significant difference was found indicating that real and sham rTMS had different effects on rating scales. This was because real rTMS produced greater improvement than sham that was evident even at one year follow-up. These improvements were associated with changes in cortical excitability over the period of treatment. The results concluded that real rTMS over motor cortex can enhance and maintain recovery and may be a useful add on therapy in treatment of acute stroke patients **(27).**

In a randomized, double-blind study, **Du et al., (28) (29)** compared the effects of high-frequency versus low-frequency rTMS on motor recovery during the early phase of stroke. A total of 69 first-ever ischemic stroke patients with motor deficits were randomly allocated to receive five daily sessions of 3-Hz ipsilesional rTMS, 1-Hz contralesional rTMS or sham rTMS in addition to standard physical therapy. The results revealed that rTMS groups manifested greater motor improvements than the control group, which were sustained for at least 3 months after the end of the treatment sessions.
Later on they comprehensively assessed the effects of high- and low-frequency rTMS on motor recovery in early stroke patients, using a randomized controlled trial. Sixty hospitalized, first-ever ischemic stroke patients (within 2 weeks after stroke) with motor deficits were randomly allocated to receive, in addition to

standard physical therapy, five consecutive sessions of either: (1) High-frequency rTMS at 10 Hz over the ipsilesional primary motor cortex (M1); (2) Low-frequency (LF) rTMS at 1 Hz over the contralesional M1; (3) sham rTMS. The study revealed motor improvement was significantly larger in the two rTMS groups than in the control group.

More recently **Guo et al., (30)** investigated the functional reorganization of the motor network after rTMS in stroke patients with motor dysfunction and compared between the effect of high-frequency rTMS and low frequency. A total of thirty-three subcortical stroke patients were enrolled and assigned to the HF-rTMS group, LF-rTMS group, and sham group. Each patient of rTMS groups received either 10.0 Hz rTMS over the ipsilesional primary motor cortex (M1) or 1.0 Hz rTMS over the contralesional M1 for 10 consecutive days. They cleared that both HF-rTMS and LF-rTMS have a positive effect on motor recovery in patients with subcortical stroke and could promote the reorganization of the motor network. HF-rTMS may contribute more to the functional connectivity reorganization of the ipsilesional motor network and realize greater benefit to the motor recovery.

In a systematic review; a total of 10 studies covering 257 stroke patients were included by matching the inclusion criteria, involving both rTMS with high (≥5 Hz) and low frequency (<5 Hz). The results confirmed enhancing effects of rTMS on the lower-limb motor ability (e.g., gait and balance) of stroke patients. In conclusion, there were positive effects of rTMS on the lower limb motor ability of stroke patients. It was also found that 15- to 20-min course of rTMS for 2 to 3 weeks was the most common one, and 1 Hz and 10 Hz were the most commonly used low and high frequencies, respectively. These results have significant clinical applications for patients with weakened lower limb mobility after a stroke **(31).**

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