TRANSCRANIAL MAGNETIC BRAIN STIMULATION IN POST-STROKE REHABILITATION: A BRIEF REVIEW WITH A FOCUS ON MOTOR RECOVERY

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Summary
Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation method that can modulate excitability of the human cortex. It had been assumed by different research groups that suppressing the undamaged contralesional motor cortex by repetitive low-frequency rTMS or increasing the excitability of the damaged hemisphere cortex by high-frequency rTMS will promote function recovery after stroke. Thus, repetitive TMS can be an adjuvant therapy for developed neurorehabilitation strategies for stroke patients. The purpose of this brief review was to provide an overview of the methods, physiologic basis and future views of the use of inhibitory and excitatory repetitive rTMS. Recent studies have reported that rTMS can effectively facilitate neural plasticity and induce motor recovery after stroke. The best rTMS pattern has not been established, a stronger evidence behind the potential use of rTMS as clinical rehabilitative tool should be found.
Key words: neural plasticity, neurorehabilitation, transcranial magnetic stimulation

Rezumat. Stimularea magnetică transcraniană a creierului în reabilitarea post-strok: scurt reviu asupra recuperării motorii
Se prezintă o analiză în revistă a metodelor, bazelor fiziologice și potențialul viitor a aplicării tehnicilor de stimulare inhibitoare și excitatoare prin stimulare magnetică transcraniană repetată (SMTr). Stimularea magnetică transcraniană este o metodă de stimulare neinvazivă a creierului prin care este posibil de a modula excitabilitatea cortexului uman. Stimularea magnetică transcraniană poate fi aplicată ca un tratament adjuvant în programe de neuroreabilitare modernă. Mai mult, studiile recente au demonstrat că stimularea magnetică transcraniană facilitează eficient procesul de plasticitate neuronală și induce recuperarea motorie după stroke. Cu toate acestea, patternul optimal de rTMS încă nu a fost stabilit, sunt necesare dovezi mai vaste pentru implementarea rTMS ca unui instrument de reabilitare clinică.
Cuvinte-cheie: plasticitate neuronală, neurorecuperare, stimulare magnetică transcraniană

Резюме. Транскраниальная магнитная стимуляция мозга после инсульта: реабилитация двигательной функции
Проведен краткий обзор методов, физиологических основ и перспектив использования техники ингибирующей и активирующей транскраниальной магнитной стимуляции (ТМС). Повторная ТМС является не инвазивным методом нейростимуляции, при помощи которого возможно модулировать возбудимость коры головного мозга. ТМС может применяться в качестве адъювантной терапии в современных программах нейрореабилитации для пациентов, перенесших острое нарушение мозгового кровообращения. Последние исследования показали, что ТМС может эффективно способствовать процессу нейропластичности и вызывает восстановление двигательных функций после инсульта. Тем не менее, оптимальный паттерн применения ТМС пока невыявлено, необходимо продолжение поиска более убедительных доказательств потенциального использования ТМС как клинического инструмента реабилитационного процесса.
Ключевые слова: нейропластичность, нейрореабилитация, транскраниальная магнитная стимуляция

Stroke is the leading cause of adult disability in the world and the burden of stroke is expected to increase in the next 20 years [1]. At present, there are limited effective interventions for patients with acute stroke [2]. Consequently, the management of most patients with stroke remains primarily focused on secondary prevention and rehabilitation [3]. In addition, brain recovery and rehabilitation will also be a prioritised field in future stroke research [4].

Transcranial magnetic stimulation (TMS) is a focal non invasive brain stimulation technique that can modulate excitability of the brain cortex [5]. TMS is based on the principle of electromagnetic induction. A TMS stimulator device consists of capacitors that store large electrical charges, which is connected to a casing with coil of copper wires. The coil is held tangentially to the scalp during a TMS procedure. When the stored charge is discharged to the coil, a brief and time-varying magnetic field is produced. This magnetic field penetrates through the skull, and depending on stimulation intensity, coil shape, and coil orientation, an electrical current is generated

in the cortical neurons near the coil. This current is sufficient to depolarize neuronal membranes and generate action potentials. TMS can be delivered in two main modalities: via single pulses regime or repetitively at a set number of pulses per second (repetitive TMS or rTMS). Typically, low-frequency rTMS (<5 Hz) is characterized by decreased cortical excitability, whereas high-frequency rTMS (≥5 Hz) is characterized by enhanced excitability [6]. Recently, also a new rTMS protocol, theta burst stimulation (TBS), was introduced which can produce longer-lasting and more stable changes in cortical excitability compared to standard rTMS [7]. Standard rTMS consists of single pulses of stimulation delivered repeatedly over a unit of time, while TBS consists of very rapidly delivered 3 pulses (at 50 Hz) every 200 ms, which can either be interrupted every few seconds [intermittent TBS (iTBS)] or can be uninterrupted (cTBS). ITBS typically increases cortical excitability, while cTBS decreases cortical excitability, and such changes in excitability over the motor cortex have shown to last for about an hour with more intense TBS methods [7].

Repetitive TMS for motor recovery following stroke aims to augment neural plasticity and improve motor function. The phenomenon is based on the so called *interhemispheric competition model*. This concept proposes that motor deficits in patients with stroke are causedby reduced output from the affected hemisphere and excessive interhemispheric inhibition from the unaffected hemisphere to the affected hemisphere [8]. According to *interhemispheric competition model* a competitive relation is assumed to exist between each cerebral hemisphere regarding cognitive, motor and sensory function.The rightward bias elicited by the left hemisphere is naturally stronger than that elicited by the right hemisphere. By this account, interhemispheric inhibitory connections that normally modulate and effectively suppress right hemispheric activity are disturbed due to damage in the left hemisphere, enabling areas in the contralesional right hemisphere to become increasingly involved via disinhibition.

Therefore, rTMS method achieves improvement in motor deficits by either increasing the excitability of the affected hemisphere or decreasing the excitability of the unaffected hemisphere [9]. Inhibitory noninvasive brain stimulation (NBIS) increases excitability in the ipsilesional motor cortex by reducing excessive interhemispheric inhibition from the contralesional motor cortex [10]. Excitatory NIBS over the affected hemisphere directly increases the excitability of the ipsilesional motor cortex [11].

During the recent years there have been made some important researches. In 2009 Khedr et al. reporteda therapeutic effect of rTMSat patients with post-stroke dysphagia [12]. Real and sham rTMS were compared at a group of 26 patients with mono-hemispheric stroke and post-stroke dysphagia. There were no significant differences at the baseline assessment between patients who received real rTMS and the sham group. The parameters were of 300 rTMS pulses at an intensity of 120% hand motor threshold for 5 consecutive days for each patients. Dysphagia and motor disability were assessed four times: before and immediately after the last session and then again after 1 and 2 months. Real rTMS led to a significantly greater improvement compared with sham in dysphagia and motor disability that was maintained over 2 months of follow-up. The amplitude of the motor-evoked potential (MEP) evoked by single-pulse TMS was also assessed before and at 1 month in 16 of the patients. A significant increase in the amplitude of the esophageal MEP evoked from either the stroke or non-stroke hemisphere. The authors concluded that rTMS may be a useful adjunct to conventional therapy for post-stroke dysphagia. These results need to be validated by well-designed studies.

In another study the long-term effects of combined time-locked rTMS and physical therapy (PT) intervention in chronic stroke patients with mild motor disabilities were studied (Avenanti et al., 2012) [13]. A double-blind, randomized, single-center clinical trial included a total of 30 patients. Patients received 10 daily sessions of 1 Hz rTMS over the intact motor cortex. Patients were randomly assessed to real (rTMS(R)) or sham (rTMS(S)) groups. TMS session was administered either immediately before or after PT session. Clinical assessment included dexterity, force, inter-hemispheric inhibition, and corticospinal excitability for the time of 3 months after the end of treatment. Treatment consisted of cumulative rebalance of excitability in the 2 hemispheres and a reduction of inter-hemispheric inhibition in the real TMS group. In all groups there were detected use-dependent improvements in trained abilities. These were small and transitory in sham TMSgroup. Greater behavioral and neurophysiologic outcomes were detected in the group with real TMS.Amongst the latter the improvements in the group receiving TMS before PT were robust and stable and in the other group (PT before TMS) the improvements showed a decline over time. The authors concluded that priming PT with inhibitory rTMS is optimal to boost use-dependent plasticity and rebalance motor excitability and suggest that time-locked rTMS is a valid and promising approach for chronic stroke

patients with mild motor impairment. Furthermore, the authors stated that further studies are needed to evaluate the effect of intervention order of time-locked rTMS in the same patients.

In 2012 Corti et al. investigated the concurrent effects of rTMS on the excitability of corticospinal pathways and upper-limb motor function in adults after stroke, they stated that conceptually rTMS could be used therapeutically to restore the balance of inter-hemispheric inhibition after stroke [14]. In this publication rTMS has been used in 2 ways: (i) low-frequency stimulation (less than or equal to 1 Hz) to the motor cortex of the unaffected hemisphere to reduce the excitability of the contralesional hemisphere or (ii) high-frequency stimulation (greater than 1 Hz) to the motor cortex of the affected hemisphere (AH) to increase excitability of the ipsilesional hemisphere. The evidence regarding the safety and effectiveness of high-frequency rTMS to the motor cortex of the AH was reviewed. The findings of this review suggested that rTMS applied to the AH is a safe technique and could be considered an effective approach for modulating brain function and contributing to motor recovery after stroke. The authors concluded that although the studies included in this review provided important information, double-blinded, sham-controlled phase II and phase III clinical trials with larger sample sizes are needed to validate this novel therapeutic approach.

Kakuda et al. (2012) in a pilot study examined the safety and feasibility of the inpatient protocol of low-frequency rTMS (LF-rTMS) and intensive occupational therapy (OT) for post-stroke patients with upper limb hemiparesis [15, 16]. The study subjects were 204 post-stroke patients with upper limb hemiparesis (mean age at admission of 58.5 +/- 13.4 years, mean time after stroke of 5.0 +/- 4.5 years). During 15-day hospitalization, each patient received 22 combined sessions of 20-min LF-rTMS (1 Hz to the contralesional hemisphere over the primary motor area) and 120-min intensive OT daily. The OT was provided after TMS session. Fugl-Meyer Assessment and Wolf Motor Function Test were performed serially. The were no adverse effects. The FMA score increased and WMFT log performance time decreased significantly at discharge, relative to the respective values at admission (change in FMA score: median at admission, 47 points; median at discharge, 51 points; $p < 0.001$ change in WMFT log performance time: median at admission, 3.23; median at discharge, 2.51; $p < 0.001$). These changes were persistent up to 4 weeks after discharge in 79 patients. Linear regression analysis found no significant relationship between baseline parameters and indexes of improvement in motor function. The authors concluded that this combined protocol is a safe, feasible, and clinically useful neurorehabilitative intervention for post-stroke patients with upper limb hemiparesis. They stated that the effectiveness of the intervention should be confirmed in a randomized controlled study including a control group.

In a meta-analysis, Hsu et al. (2012) investigated the effects of rTMS on upper limb motor function in patients with stroke [17]. These investigators searched for RCTs published between January 1990 and October 2011 in PubMed, Medline, Cochrane, and CINAHL using the following key words: stroke, cerebrovascular accident, and repetitive transcranial magnetic stimulation. The mean effect size and a 95% CI were estimated for the motor outcome and motor threshold using fixed and random effect models. Eighteen of the 34 candidate articles were included in this analysis. The selected studies involved a total of 392 patients. A significant effect size of 0.55 was found for motor outcome (95% CI: 0.37 to 0.72). Further sub-group analyses demonstrated more prominent effects for subcortical stroke (mean effect size, 0.73; 95% CI: 0.44 to 1.02) or studies applying low-frequency rTMS (mean effect size, 0.69; 95% CI: 0.42 to 0.95). Only 4 patients of the 18 articles included in this analysis reported adverse effects from rTMS. The authors concluded that rTMS has a positive effect on motor recovery in patients with stroke, especially for those with subcortical stroke. Low-frequency rTMS over the unaffected hemisphere may be more beneficial than high-frequency rTMS over the affected hemisphere.

Thus, pairing of rehabilitative training with NIBS results in more enduring performance improvements and functional plasticity in the affected hemisphere compared with motor training or stimulation alone in patients with chronic stroke [18]. Cumulative rTMS has been shown to be important for continuous motor improvement in patients with stroke. The results of the studies indicate that neural plasticity is consolidated by rTMS intervention. Therefore, rTMS induces a more suitable environment for neural plasticity by artificially modulating the ipsilesional motor cortex, thus counteracting use-dependent plasticity impairment by facilitating plasticity in the affected hemisphere.

Further well-designed studies in larger populations are required to determine whether rTMS in stroke can improve motor function and to identify the most effective rTMS protocols for stroke treatment.

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