Transcranial magnetic brain stimulation in post-stroke motor recovery

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation method that can modulate excitability of the human cortex. It has 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 for the potential use of rTMS as clinical rehabilitative tool should be found.

Conclusions: 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.

Key words: neural plasticity, neurorehabilitation, transcranial magnetic stimulation.

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 noninvasive 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. The capacitor is connected to a casing with coil, made of copper wires. The coil is held tangentially to the scalp during a TMS procedure. A brief and time-varying magnetic field is produced when the stored charge is discharged to the coil. This magnetic field penetrates through the head tissues, and generates an electrical current in the cortical neurons under the coil. The generated current is sufficient to produce depolarization of the neuronal membranes and generate action potentials (fig. 1). 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. This stimulation can either be interrupted every few seconds [intermittent TBS (iTBS)] or can be uninterrupted [continuous TBS (cTBS)]. Intermittent TBS typically increases cortical excitability. Continuous TBS decreases cortical excitability. These 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 caused by 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 cortical sectors in the opposite (contralesional) right hemisphere to turn increasingly involved through 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].

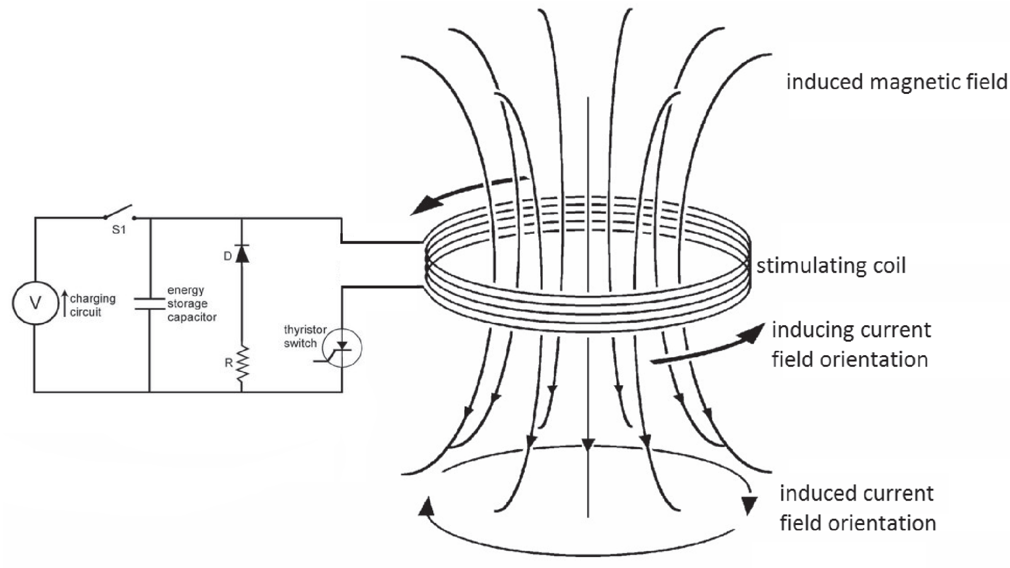

Fig. 1. The principle of the magnetic stimulator.

During the recent years there have been made some important researches. In 2009 Khedr et al., reported a therapeutic effect of rTMS in patients with post-stroke dysphagia [12]. Real and sham rTMS were compared in 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 patient. 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 after 1 month in 16 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 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 TMS group. 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 double-blinded and sham-controlled clinical trials with larger samples are needed to validate this 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. There were no adverse effects. The FMA score increased and WMFT log performance time decreased significantly at discharge. This decline was 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; $p < 0.001$). In 79 patients these changes were constant up to four weeks after discharge. Linear regression analysis found no significant relationship between baseline parameters and indexes of improvement in motor function. The authors concluded that this combined protocol was safe and clinically useful in patients with post-stroke 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. The following key words were used: "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 34 candidate articles were included in meta-analysis. These studies involved 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 18 articles included in this analysis reported adverse effects from rTMS. The authors concluded that rTMS has a positive effect on motor recovery in post-stroke patients (especially sub-cortically localized stroke). Low-frequency rTMS over the unaffected hemisphere may be more beneficial than high-frequency rTMS over the affected hemisphere.

Conclusions

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 areas of the cortex. This facilitates the phenomenon of plasticity in the affected hemisphere.

Further well-designed clinical trials with larger samples 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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