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Transcranial magnetic stimulation in stroke rehabilitation

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Abstract
Transcranial magnetic stimulation (TMS) is a non-invasive tool for electrical stimulation of nervous system. TMS is an effective technology with potential diagnostic and therapeutic uses in various diseases. TMS can be applied as single pulses of stimulation, paired-pulse, or in trains, repetitive TMS.

In this survey we try to cover some important areas, such as biological effects, the safety issues, contraindications on TMS. According to available evidence, TMS could be an effective method for improving functional recovery of stroke patients. rTMS was able to improved motor function in the hemiplegic side, poststroke aphasia, manual dexterity and has a promising potential in neuromodulation of autonomic nervous system. Moreover repetitive TMS might become useful in the rehabilitation of patients with dementia in the attempt to restore impaired brain plasticity.

The main deficiency of rTMS is that it has no long-lasting effect on motor function in patients with stroke. Creating a home device to deliver TMS can be an important step in rehabilitating the patients with stroke. All these are supported by the available studies, but more investigations are needed to establish the clinical indication as a diagnostic or therapeutic tool in any neurological or psychiatric disease.

Key words: *rehabilitation, transcranial magnetic stimulation, stroke*

Introduction

Throughout the history of medicine, it has been very difficult to study the brain at a functional level. Until very recently, scientists were only able to understand which areas of the brain played specific roles by studying patients who had suffered brain injury. The study of brain and cognition has advanced thanks to neuroscience research methods such as brain mapping electroencephalography (EEG), computerized tomography (CT), single-photon emission computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), near-infrared spectroscopy and recently transcranial magnetic stimulation (TMS). If imaging techniques only allow researchers to view active areas of the brain during various cognitive tasks, TMS allows researchers to intervene in the activity of the brain. Using TMS it is possible to create temporary and artificial anomalies in the brain by inducing a small current in finely controlled areas (1). By targeting areas, researchers can deduce which parts of the brain are responsible for different types of cognition.

Transcranial magnetic stimulation (TMS) is a noninvasive technique for stimulating neurons in the cerebral cortex through the scalp, safely and with minimal discomfort. Initially a laboratory tool for neurophysiologists studying the human motor system, TMS it is one of the latest therapeutic methods for the treatment of various diseases and neuropsychiatric disorders, among which are: depression, anxiety, attention deficit, schizophrenia, post-traumatic stress disorder, obsessive–compulsive and bipolar disorder (2), tinnitus (3), neuropathic pain (4), migraine (5), stroke (6), epilepsy (7), Parkinson's disease (8).

TMS uses electromagnetic induction (Faraday's principle) to induce weak electric currents in specific parts of the brain. It involves the generation of a brief but strong magnetic field capable of activating cortical elements in the brain of conscious subjects without causing pain. It has been described as selective depolarization of neurons in the cerebral cortex, located between 1.5 and 2 cm below the cranial bone using magnetic pulses with specific intensity. TMS can be applied one stimulus at a time, single-pulse TMS, in pairs of stimuli separated by a variable interval, paired-pulse TMS, or in trains, repetitive TMS (9). Single-pulse TMS is used to evaluate the motor threshold (MT), motor evoked potential (MEP) responses from target muscles, MEP amplitude and onset latency to evaluate aspects of sensorimotor cortex and pyramidal tract function.

Paired-pulse TMS utilizes two individual magnetic pulses, separated by a variable inter-stimulus interval (ISI). This method is used to evaluate the short- and long interval intra-cortical inhibition and intra-cortical facilitation (9). Paired associative stimulation

(PAS) technique involves applying pairs of peripheral and central stimuli repeatedly.

When multiple stimuli of TMS are delivered in trains, one can differentiate between ‘‘conventional” which refers to the application of regularly repeated single TMS pulses (repetitive TMS) and ‘‘patterned” protocols of repetitive stimulation (10). By convention, “slow” or low-frequency TMS refers to stimulation at 1 Hertz or less, and “fast” or high-frequency TMS refers to stimulation at a frequency higher than 1 Hz. Slow rTMS decreases the excitability, while fast rTMS increases the excitability of the motor cortex (11).

Patterned rTMS refers to repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation. Most used protocols of this kind are the different theta burst stimulations (TBS) in which short bursts of 50 Hz are repeated at a rate in the theta range (5 Hz) as a continuous (cTBS) or intermittent (iTBS) train. In general, protocols of slow rTMS apply all pulses in a continuous train, whereas protocols of fast rTMS apply shorter periods of stimulation separated by periods of pause. Intermittent TBS produces enhanced cortical excitability due to long-term potentiation (12), and continuous TBS produces suppressed cortical excitability due to long-term depression (13).

Another method, called “triple stimulation technique” (TST), delivers a single magnetic pulse in association with two timed peripheral electrical pulses and is used to evaluate the integrity of neuronal pathways and can became a routine procedure to assess corticomotor conduction to distal limb muscles (14). Recently, quadripulse stimulation, repeated trains of four monophasic pulses separated by interstimulus intervals is able to produce facilitation (at short intervals) or inhibition (at longer intervals).

Biological effects of TMS

TMS short-term effects are due to changes in neuronal excitability caused by shifts in ionic balance of active neurons. Longer-lasting effects of TMS appear to depend on synaptic changes among cortical neurons, also known as long-term depression and long-term potentiation. Experiments using fMRI and TMS have revealed evidence of extremely rapid plasticity. TMS may also induce changes in neurotransmitter systems effects on glutamate AMPA receptor/NMDA receptor expression (influencing calcium ion dynamics) and hormonal axes (15).

Frontal lobe stimulation at high-frequency (HF) rTMS induced an increase of dopamine in the hippocampus. HF-rTMS over the left dorso-lateral prefrontal cortex (DLPFC) increased dopamine release in the striatum (16). rTMS may modulate tryptophan or 5-hydroxytryptamine metabolism in limbic areas in normal subjects without inducing behavioral changes (17). Also TMS can explore neurotransmitter such as gamma-aminobutyric acid (GABA), monoamine and cholinergic system (18)

rTMS may have neuroprotective effects by reducing oxidative stress, inflammation, and by increasing levels of neurotrophic factors (15).

Patients with depression seem to have reduced activity in the left prefrontal cortex, therefore, high frequency rTMS has been used to excite this area (19). In borderline personality disorder, rTMS applied over the right (1 Hz) or left (5 Hz) dorsolateral prefrontal cortex improve some symptoms, such as impulsiveness, affective instability, and anger (20).

Continuous theta burst transcranial magnetic stimulation of the lateral cerebellum modulates motor cortical excitability and improves symptoms in movement and cognitive disorders (21).

Experimental evidence suggests that focal brain stimulation can improve motor and cognitive processes, such as working memory, sustained and focused attention in healthy individuals (22), which are used today in training programs for security purposes. Elevations of mood are associated with right-sided excitation and depression with left-sided excitation. The disadvantage might be the short duration of this effect.

The main advantages of TMS are noninvasiveness and the possibility to stimulate small brain areas. TMS was approved in 2008 by the U.S. Food and Drug Administration for treatment of major depression (10).

The safety issues

TMS has been accepted as a safe method of investigating the nervous system. The peak magnetic field strength of TMS, 1.5 – 2 T, is less than in MRI technique, which produces field strengths of 3 – 8 T. The changes in neural activity induced by TMS are transient and without long-lasting effects.

In the review on TMS risk and safety, E. M. Wassermann reported such known adverse effects of rTMS: seizure induction, effects on cognition, effects on mood, transient effects on hormones and lymphocytes, transient auditory shift, pain and headache, burns from scalp electrodes (1).

A subsequent consensus conference found that seizures were “extremely rare” and mainly occurred when stimulation exceeded guidelines (10). There is some evidence that rapid rTMS has anticonvulsant properties in patients with therapeutic refractory epilepsy, but at high stimulation intensities, rTMS can evoke a seizure. However, given the large number of subjects and patients who have undergone rTMS it is suggested that the risk of rTMS to induce seizures is very low (10). Single pulse TMS and low frequency rTMS in healthy adults appear to carry little risk (1). Up to now, there is no evidence that TMS has any negative impact on blood pressure or heart rate and also on the hearing threshold of the subject. It also does not cause neuronal death or mutagenesis.

Contraindications to TMS

There are few absolute contraindications to TMS treatment such as: pregnant women, children under 6 years, patients with intracranial metallic implants, patients with cardiac pacemakers, individuals with cochlear implants and spinal cord stimulators (10).

A personal or strong family history of epilepsy is generally regarded as a contraindication for fast TMS.

A special risk is occult substance abuse or dependence (alcohol, caffeine, drugs), conditions associated with altered seizure risk. Conditions of increased risk of inducing epileptic seizures related to the protocol of stimulation are: TMS applied on more than a single scalp region, prolonged PAS protocols, high-frequency rTMS protocol with parameters of stimulation exceeding the known safety limits reported (10).

A screening standard questionnaire for rTMS candidates should be considered. This survey of fifteen questions will follow if the patient had: epilepsy or seizure; syncope, severe head trauma, hearing problems, metal in the brain (except titanium), cochlear implants, an implanted neurostimulator, cardiac pacemaker, a medication infusion device, a surgical procedures of spinal cord, spinal or ventricular derivations, if he/she taking medications, if she is pregnant, if they did undergo TMS or MRI in the past (10). Affirmative answers to one or more of questions should be carefully analyzed by the treating physician.

The application of transcranial magnetic stimulation in stroke patients

Stroke is one of the most frequent neurological disabilities worldwide. An important proportion of the survivors are left with residual disability such as motor limbs impairments, speech impairment, swallowing difficulties, and cognitive impairment.

Beside the destruction of the motor structures, imbalance in informational systems and reaction mechanisms responding to damage plays important role in causing neurological dysfunction. Stroke may affect the balance of transcallosal inhibitory pathways between both hemispheres. The damage hemisphere may be affected by the cerebral ischemia and by the asymmetric inhibition from the unaffected hemisphere. In first week of stroke, if after the TMS stimulation of the affected brain hemisphere, excitatory potential in paresis limb is obtained it correlates with good predictor rehabilitation, their absence is associated with poor rehabilitation (23).

The underlying concept of rTMS treatment in stroke is based on “upregulating” the lesioned hemisphere or “downregulating” the intact hemisphere (24). After stroke rTMS applied in high- frequency (5Hz) over the affected hemisphere which is inhibited by the process or by the unaffected hemisphere can improve cortical excitability and reorganization (25). rTMS at low-frequency (< 1 Hz) can be applied over intact hemisphere in order to reduce its excitability leading to functional recovery. It was also used bilateral rTMS, 1 Hz rTMS applied over intact hemisphere and 10 Hz over affected hemisphere which revealed improved motor training effect on the paretic hand (24).

Emara et al. recently compared 5Hz ipsilesional stimulation with 1Hz contralesional stimulation over ten days and found that both groups had improvement in motor function and disability scales that lasted up to 12 weeks post-intervention (12).

Khedr et al. found that dual rTMS improved motor function in the hemiplegic side in patients with acute ischemic stroke and also can be used for rehabilitation of poststroke aphasia (27). Reduction of the excitability of the right peri-sylvian area in a nonfluent aphasia, can lead to an improvement. Using rTMS in order to suppress the right homologue of Broca area, showed improvement in picture naming after 2 months stimulation, the benefit obtained lasting up to 8 months in chronic aphasia patients (28). In a systematic review, Sebastianelli et al. found that low-frequency rTMS over unaffected hemisphere may have therapeutic utility after stroke (29).

Recently McIntyre et al. evaluated the effectiveness of rTMS in improving spasticity after stroke (30). Using Modified Ashworth Scale as main outcome 10 studies met the inclusion criteria: two randomized control trials and eight uncontrolled pre-post studies. In the uncontrolled pre-post studies they found significant improvements in Modified Ashworth

Scale for elbow, wrist, and finger flexors. However the two available RCTs failed to find a significant rTMS treatment effect on Modified Ashworth Scale for the wrist (30).

Zhang et al. evaluated the short- and long-term effects of rTMS on upper limb recovery after stroke and they show that 5-session rTMS and intermittent theta burst stimulation in the acute phase of stroke significantly improved short-term and long-term manual dexterity (31). Also they conclude that intermittent theta burst stimulation is more beneficial than continuous theta burst stimulation (31). hemisphere may has important effect on post-stroke dysphagia (32). For acquisition of new motor skills the sensory system is important. Application of 5 Hz rTMS over the ipsilateral sensory cortex enhances motor learning after stroke (33). Sasaki et al. found that high-frequency rTMS produced a more significant increase in grip strength and tapping frequency than low-frequency rTMS (34).

Autonomic nervous system (ANS) in association with motor and sensory components of the central nervous system is responsible for the rapid, continuous, accurate and unconscious control of physiological functions, such as heart rate, blood pressure, respiratory rate, body temperature, gastrointestinal motility and cognition. This physiological relationship between somatic nervous system and ANS could be described as an autonomic-motor pattern. In stroke, disturbances of these two components may co-exist and rehabilitation of both is necessary for a better outcome. Sympathetic hyperactivity and parasympathetic dysfunction may be responsible for autonomic disturbances in stroke.

In humans, the right insular cortex appears to play a predominant role in establishing sympathetic tone and the left insular cortex in parasympathetic tone. Patients with right insular cortex ischemia had frequent arrhythmias, higher blood pressure and norepinephrine levels compared to those with left insular cortex ischemia. The most targeted areas used in rTMS are the dorsal lateral prefrontal cortex and the primary motor area which seem to have large connections with structures involved in vegetative function. rTMS has considerable clinical potential for use in stroke rehabilitation due to their non-invasiveness and safety, ease of use, and the possibility to combine it with other methods. rTMS has a promising potential in neuromodulation of ANS and can be used as a tool for rebalancing disturbed autonomic functions. An acute ischemic lesion can affect autonomic nervous system responses at cardiac level and may lead to an increased risk of arrhythmia (35). Autonomic imbalance associating increased sympathetic activity occurs more frequent after right hemisphere ischemic stroke (36). Preventing sympathetic hyperactivity and arrhythmia could be achieved by TMS (37).

Brain-Derived Neurotrophic Factor (BDNF) has an important role in neuronal plasticity. Niimi et al. showed that the combination of rehabilitation and low-frequency rTMS may improve motor function in the affected limb, by activating BDNF (38).

Adult neurogenesis plays important roles in synaptic plasticity and memory. It is reported that rTMS stimulation of the rat thalamus increased adult neurogenesis. In preclinical studies in murine model of vascular dementia, rTMS was able to improve cognitive deficits by modified hippocampal synaptic plasticity and increased BDNF (39). Also low-frequency rTMS may promote hippocampal synaptic plasticity through increased expression of the Bcl-2 and reduced expression of Bax in VaD model rats (40).

Moreover repetitive TMS might become useful in the rehabilitation of patients with dementia in the attempt to restore impaired brain plasticity. Cortical excitability is increased in Alzheimer's disease and in vascular dementia, and short-latency afferent inhibition is normal in vascular dementia, but suppressed in Alzheimer's disease (41). Bentwich et al. combined rTMS with cognitive training in Alzheimer’s disease patients who were treated for more than two months with cholinesterase inhibitors. These patients were subjected to daily rTMS-cognitive training sessions (5/week) for 6 weeks, followed by maintenance session (2/week) for an additional 3 months. They demonstrated a significant improvement in Alzheimer Disease Assessment Scale-Cognitive after 6 weeks of treatment (42).

The principle of rehabilitation in stroke is that repetitive programs may promote mechanisms of neural plasticity. The main deficiency of rTMS is that it has no long-lasting effect (6 months after onset) on motor function in patients with stroke (43). That's why creating a home device to deliver TMS can be an important step in rehabilitating the patients with stroke.

Currently proven “functional therapies” include constraint-induced movement therapy, mirror therapy, functional electric stimulations, use of robotic assisted devices and virtual reality, are considered methods that can promote recovery after stroke (44-48). In the future combining these techniques with rTMS could theoretically improve the patients' care and to promote a better neurorehabilitation after stroke.

In conclusion the main areas of TMS application are: the investigation of cortical and spinal excitability, functional mapping, neuronal plasticity and connectivity, and the treatment of some neurological and psychiatric disorders. TMS has become an invaluable tool to understand neurophysiological processes and will also become a therapeutic strategy in the near future.

Changing the public perception regarding brain stimulation may be an even bigger challenge. Patients tend to be reluctant when hearing of treatments involving brain stimulation. However if the procedure and the benefits that result from it are properly explained to them, most patients will be reassured and will accept to follow it.

The results are indeed very rewarding and patients regain confidence and joy of life when they can walk or talk normally again, or wake up without feeling depressed. TMS might provide a new insight into the pathophysiology of the nervous system, and can be used in all areas of cognitive neuroscience. All these are supported by the available studies, but more investigations are needed to establish the clinical indication as a diagnostic or therapeutic tool in any neurological or psychiatric disease.

To conclude, we argue that TMS therapy should be directed to goals of total rehabilitation of the patient, this allowing for their return to work and a decent quality of life. According to available evidence, cortical magnetic stimulation could be an effective method for improving functional recovery of stroke patients.

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