NEW THERAPEUTIC PERSPECTIVES IN NEUROREHABILITATION: TRANSCRANIAL MAGNETIC STIMULATION

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive tool for the electrical stimulation of neural tissue, including the cerebral cortex, and is an excellent method to study brain physiology. Trains of stimuli (repetitive TMS) can modify excitability of the cerebral cortex at the stimulated site and also at remote areas along anatomo-functional connexions. Repetitive TMS is used to modulate cortical excitability in a frequency-dependent manner, for a period of time that outlasts the duration of stimulation, inducing plastic changes in the brain. Repetitive TMS may become an additional tool for early rehabilitation and might be useful for promoting cortical plasticity in neurologic patients. Its utility have been demonstrated by many clinical studies in various disabling conditions, as stroke, Parkinson disease, multiple sclerosis, spinal cord injuries, and many more, where rTMS opens a new field of therapeutic possibilities.

Key words: transcranial magnetic stimulation, neurorehabilitation, neuroplasticity

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain (1). This field can be of sufficient magnitude and density to depolarize neurons. TMS was introduced in 1985 by A.T. Barker and collegues (2) as a noninvasive and painless stimulation of neural tissue, including cerebral cortex, spinal roots and cranial and peripheral nerves (3). TMS is now commonly used in clinical neurology to study central motor conduction time and to assess the integrity of the central motor pathways, leading to a new era of research in motor and cortical function.

The technical principle of TMS consists in placing a small coil of wire on the scalp and passing a powerful and rapidly changing electrical current through it. This will induce a rapidly changing magnetic field that passes unimpeded into the surrounding tissues of the head, where it again induces an electrical field and excites cortical neurons (4), (5). Depending on the stimulation parameters used, TMS can excite or inhibit the brain, allowing the functional mapping of the cortical areas. Transcranial stimuli evoke multiple descending volleys in corticospinal neurons: the initial volley is recorded as the direct (D) wave –arising from excitation of the pyramidal cells-, the following volleys are indirect (I) waves, possibly produced by the excitation of pyramidal cells by surrounding intracortical neurons (4). The conduction time from motor cortex to spinal cord alpha-motoneurons is referred as central motor conduction time (CCT), and it is prolonged in demyelinating lesions of the pyramidal tract, in ischemic or degenerating diseases (4).

TMS can use single pulses of stimulation, pairs of stimuli separated by variable intervals, or trains of repetitive stimuli at various frequencies.

Single stimuli can depolarize neurons and evoke measurable effects – the motor evoked potentials (MEPs) - that can be recorded from muscles of the contralateral limb. Normal amplitude of the MEP reflects the integrity of the pyramidal tract and also normal function of the upper and lower motoneurons. MEP recording have clinical use in diagnosis and prognosis of neurologic diseases.

New paradigms of magnetic stimulation have been developed: repetitive TMS. Repetitive transcranial magnetic stimulation (rTMS) is the application, to a single brain area, of a train of stimuli of the same intensity and given frequency (3). These trains can modify excitability of the cerebral cortex at the stimulated site and also at remote areas along functional anatomical connections (3), (6). The cortical areas influenced by rTMS are mainly the motor cortical areas, but also the visual, parietal and prefrontal cortex. The trains will induce excitatory and inhibitory effects during and after the train, depending on their parameters (4). Their short-term and long-term effects on cortical excitability may range from inhibition to facilitation depending on the stimulation frequency (4). Lower frequencies of rTMS (above 1 Hz) will induce inhibition of motor cortex, while high frequency trains (above 20 Hz) seem to increase the cortical excitability. Thus, rTMS has been found to be a promising noninvasive treatment for a variety of neuropsychiatric conditions. (7), by modulating local cortical excitability in a frequency-dependent manner, for a period of time that outlasts the duration of stimulation (8).

The last decade has seen a rapid increase in the applications of TMS to study cognition, brain-behavior relations and the pathophysiology of various neurologic and psychiatric disorders. TMS is being increasingly combined with other brain imaging and neurophysiologic techniques including functional magnetic resonance imaging (fMRI) and EEG. Moreover, the combination of rTMS with tracer PET may become a novel tool to investigate neurochemical functional anatomy.

Many arguments for rTMS use in rehabilitation have been developed. Repeated sessions of transcranial magnetic stimulation (rTMS) are capable of changing and modulating neural activity beyond the period of stimulation. This has behavioral consequences and therapeutic potential.

Therapeutic utility of TMS has been claimed in the literature for neurologic diseases such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, or epilepsy, in rehabilitation of aphasia or of hand function after stroke, and also in pain syndromes, such as neuropathic pain, visceral pain or migraine and psychiatric disorders, such as depression, acute mania, bipolar disorders, panic, hallucinations, obsessions /compulsions, schizophrenia, catatonia, post-traumatic stress disorder, or drug craving.

Potential mechanisms of action of rTMS are under study. Because many neurological disorders are thought to involve abnormal or dysfunctional neuronal activity, it is hypothesised that the therapeutic action of rTMS may occur through modulating and reversing abnormal activity and facilitating neuroplasticity (7). The therapeutic effects could be a result from plastic changes induced in motor cortical networks (9). Motor plasticity and improved outcome with rTMS treatment can be induced either by low-frequency stimulation over the intact hemisphere (explained by a reduction in transcallosal inhibition from the former) , or by high-frequency rTMS over the injured hemisphere (which increase the MEP amplitude).

The therapeutic promise of rTMS is limited because the mechanisms of action of rTMS are not completely understood and therefore it is difficult to determine which treatment protocols are appropriate for specific neurological conditions (7).

The aim of therapeutic rTMS will be to "normalize" pathologically decreased or increased cortical activity (5). By changing the frequency of stimulation, it may be possible to up- or down-modulate cortical excitability for therapeutical benefit in different brain areas.

Therapeutic utility of repetitive TMS in neurorehabilitation have been demonstrated by many clinical studies in various disabling conditions, as stroke, Parkinson disease, multiple sclerosis, spinal cord injuries, and many more, where rTMS opens a new field of therapeutic possibilities.

Repetitive TMS in stroke patients:

Motor recovery typically reaches a plateau 6 months after the stroke (10), leaving 50-75% of individuals with chronic functional impairments (11).

MEPs after cortical stimulation of the damaged hemisphere are absent in patients with hemiplegia, and with low amplitude and increased motor threshold in patients with paresis.

Post-stroke recovery is based on plastic changes in the central nervous system that can compensate the loss of activity in affected brain regions. Neuroreabilitation programs improve function partly by enhancing cortical reorganization (12).

In stroke, the affected hemisphere is inhibited not only by the infarct itself, but also by an increased inhibitory effect of the contralateral (unaffected) hemisphere (disequilibrium of the transcallosal inhibitory pathways between the two primary motor areas) (13).

Repetitive TMS modulates cortical excitability and could be used to restore the balance of interhemispheric inhibition after stroke.

Functional recovery may be obtained when rTMS is applied at high-frequency (around 5Hz) over the motor cortex of the affected hemisphere in order to reactivate hypoactive regions, or when rTMS is apllied at low-frequency (< 1 Hz)over the motor cortex of the disinhibited, unaffected hemisphere in order to reduce its excitability and restore defective inhibition (10), (12).

Studies suggest that sessions of rTMS may improve some of the cognitive symptoms after a stroke, as aphasia and visuospatial neglect.

Other studies have demonstrated that rTMS effects are enhanced when used with repetitive facilitatory exercises of the affected limbs (14), performed during motor rTMs sessions or immediately after them.

The somatosensory system plays an important role in acquisition of new motor skills in stroke patients (15). Accordingly, modulating the excitability of the somatosensory cortex may influence motor learning, via reciprocal cortico-cortical afferents. Stimulation with high-frequency rTMS of the primary sensory cortex of the affected hemisphere will increase motor learning in patients with chronic stroke (8).

Repetitive TMS in Parkinson disease:

The clinical presentation of PD is related to abnormal neuronal activity within the basal ganglia and cortical regions, including the primary motor cortex (6). Cortical dysfunction has been documented in PD by functional neuroimaging and neurophysiologic studies showing either hypo- or hyper-activation of various brain areas (9).

Repetitive TMS can be used to modify activity of such cortical areas.

Motor cortex stimulation could impact the cortico-basal ganglia-thalamo-cortical circuits involved in motor control, ameliorating parkinsonian symptoms (9).

Significant clinical effects have been obtained by stimulating different cortical regions, especially primary motor cortex of PD patients, with low- and high-frequency rTMS.

High-frequency (excitatory) rTMS decreased rigidity and bradikinesia in the upper limb contralateral to the stimulation, and low-frequency (inhibitory) rTMS reduced upper limb rigidity bilaterally and improves walking (16).

Clinical application of rTMS in PD patients is limited by the short duration of effects after the time of stimulation, however, rTMS could be an alternative or a complementary technique to deep brain stimulation (9).

Repetitive TMS in multiple sclerosis:

In multiple sclerosis (MS) spasticity is a major cause of disability, impacts quality of life and is only partially influenced by drugs. Repetitive TMS have been tried to modulate cortical excitability of the lower limb motor area, in order to influence the pathologically disinhibited spinal circuits.

Studies have demonstrated that high-frequency rTMS applied over the prmary motor cortex may improve spasticity by enhancing pyramidal tract excitability (17), (18).

Repetitive TMS in spasticity treatment for patients with spinal cord injuries:

In spinal cord injuries damage to descending pyramidal tract, that normally exert spinal segmental control over muscle tone, is thought to play an important role in spasticity (19). High-frequency rTMS applied over the primary motor cortex will increase its excitability and increase corticospinal inhibitory input, that will further reduce segmental spinal excitability and limb spasticity (19). Optimal reorganization of remaining spinal circuits can contribute to recovery of the ambulatory function (20). Repetitive TMS sessions produced significant improvement of the lower-extremity motor score (LEMS) and of walking speed, and reduced spasticity in lower limbs. (20), (21).

Other authors have demonstrated in patients with chronic incomplete cervical spinal cord injury an improvement in motor score and in upper limbs function after 5 days f rTMS sessions applied over the motor cortex (22)

Conclusion: Most claims of therapeutic utility of TMS in neurorehabilitation need further support and evidence-based clinical trial data, but the potential clinical significance is huge, affecting a large number of patients with debilitating conditions. Repetitive TMS has opened a new field of investigation of neural circuits, and is developing as a potential therapeutic tool for patients with neurologic diseases.

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