Therapeutic applications of repetitive transcranial magnetic stimulation in clinical neurorehabilitation

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Summary

Transcranial magnetic stimulation (TMS) was introduced nearly 20 years ago and has since been developed as a sophisticated tool for neuroscience research. It is an excellent technique that complements other non-invasive methods for studying human brain physiology. The aim of the present study was to review the basic concepts and principles of the repetitive TMS (rTMS) technique, gathering evidence of its applications in neurorehabilitation.
Several clinical studies have reported that sessions of rTMS can improve some or all of the motor symptoms associated with Parkinson's disease, dystonia and stroke. However, since these changes are transient, it is premature to propose these applications as realistic therapeutic options, even though the rTMS technique has shown itself to be, potentially, a modulator of sensorimotor integration and neurogenesis.
Future work in this area promises to advance our understanding of the pathophysiology of a wide range of neurological conditions, generate widely applicable diagnostic tools for clinical neurophysiology, and perhaps establish neuromodulation as a viable therapeutic option in neurorehabilitation.

KEY WORDS: neurogenesis, neuroplasticity, neurorehabilitation, rTMS, sensorimotor integration.

Introduction

It is now almost thirty years since Merton asked Morton to build a high-voltage electrical stimulator capable of activating muscle directly rather than through its small nerve branches. He had the idea that this device would also be able to stimulate the motor areas of the human brain through the intact scalp (transcranial electrical stimulation, TES), and he was right.
Merton and Morton used brief, high-voltage electric shocks to activate the motor cortex and produce a relatively synchronous muscle response, the motor-evoked potential (MEP). It was immediately clear that this would be useful for many purposes, but one problem with TES is that it is painful on account of its activation of pain fibers in the scalp. Five years later, Barker and colleagues showed that it was possible to stimulate both nerve and brain using external magnetic stimulation or transcranial magnetic stimulation (TMS), with little or no pain (1). TMS is now commonly used in clinical neurology to study central motor conduction time. Depending on the stimulation parameters used, TMS can excite or inhibit the brain, allowing the functional mapping of cortical regions and the creation of transient functional lesions. It is now widely used as a research tool to study aspects of human brain physiology including motor function, vision, language and the pathophysiology of brain disorders. It may also be useful as a therapeutic tool, particularly in neurorehabilitation (2,3). Since its introduction as a non-invasive method of stimulating the human brain, repetitive TMS (rTMS) has provided a potential means of modulating cortical excitability and function. Depending on essential stimulation frequency parameters and on the number of trains of stimuli delivered, rTMS can produce lasting up- or down-regulation of the corticospinal system (3).
The present study reviews the basic concepts and principles of the rTMS technique, gathering evidence of its applications in neurorehabilitation.

Transcranial magnetic stimulation: basic principles

Transcranial magnetic stimulation exploits the principle of inductance (discovered by Michael Faraday in 1838) in order to transmit electrical energy across the scalp and skull without the pain of direct percutaneous electrical stimulation. TMS, as currently used, was introduced by Anthony Barker in 1985 and the technique provided, for the first time, a non-invasive, safe, and – unlike TES – painless method of activating the human motor cortex and assessing the integrity of the central motor pathways (1). Since its introduction, the use of TMS in clinical neurophysiology, neurology, neuroscience, and psychiatry has spread widely, mostly in research applications, but increasingly with a view to clinical aims. It involves placing a small coil of wire on the scalp and passing a powerful and rapidly changing current through it. This produces a magnetic field that passes unimpeded and relatively painlessly through the tissues of the head (4).
The site of stimulation of a nerve fiber is the point, along its length, at which current sufficient to cause depolarization passes through its membrane. The capacity of TMS to depolarize neurons depends on the "activating function", which causes transmembrane current to flow and can be described mathematically as the spatial derivative of the electrical field along the nerve. Accordingly, stimulation will take place at the point where the spatial derivative of the induced electrical field is maximum. When the stimulation reaches a bent nerve point, even though the fiber bends across the induced electrical field, the current will still continue in a straight line and pass out of the fiber across the membrane (5). Thus, the spatial derivative of the electrical field along the nerve is critical, and makes bends preferential points of stimulation. These characteristics of TMS cause it to differ from TES in several ways. The peak strength of the magnetic field is related to the magnitude of the current and the number of spirals of wire in the coil. The operator can control the intensity of the stimuli by changing the intensity of the current flowing in the coil, thus changing the magnitude of the induced magnetic field and of the secondarily induced electrical field. The focus of the magnetic field depends on the shape of the stimulation coil. The two shapes most commonly used are the figure-of-eight coil and the circular-shaped coil (4). The former provides more focal stimulation, allowing fairly detailed mapping of cortical representation. The latter induces a more widely distributed electrical field and allows bihemispheric stimulation, which is particularly desirable in the study of central motor conduction times. Operators can also control the frequency of the delivered stimuli, which will critically determine the effects of TMS on the targeted region of the brain (6). The location of a stimulation coil is also dependent on the operator: different brain regions can be stimulated to evoke different behavioral effects. Anatomically precise localization of stimulation can be achieved using a frameless stereotactic system. The magnetic field, in turn, induces a much weaker electrical current in the brain. The strength of the induced current is a function of the rate of change of the magnetic field, which is determined by the rate of change of the current in the coil. In order to produce enough current to excite neurons in the brain, the current passed through the coil must change within a few hundred microseconds (4-6).
The stimulators and coils currently in production develop about 1.5-2 Tesla (T) at the face of the coil and are thought to be able to activate cortical neurons at a depth of 1.5-2 cm beneath the scalp (5). Even though TMS with conventional equipment appears to penetrate no deeper than the cortex, it may affect cells transsynaptically at some distance from the site of stimulation, as shown by its effect on distant cortical and subcortical sites detected by means of positron emission tomography (PET). Some neurological disorders may involve or be caused by an impairment of cortical excitability or altered interactions between cortical and subcortical structures, detectable by TMS. Furthermore, TMS can be used to modify intracortical excitability and activate distant cortical, subcortical, and spinal structures along specific connections (4).

The rTMS technique: a novel tool for clinical neurorehabilitation

Repetitive TMS is the application, to a single brain area, of a train of TMS pulses of the same intensity at a given frequency, which ranges from one stimulus per second to 20 or more. The cortex is stimulated by a train of magnetic pulses at frequencies between 1 Hz and 50 Hz, in contrast to single-pulse TMS, in which the frequency of stimulation is less than 1 Hz (6). In order to develop a universal system of referring to the different types of TMS, the term "repetitive TMS" should replace the terms "rapid TMS" and "rapid-rate TMS" and be used in reference to regularly repeated stimulations delivered to a single scalp site. Instead, the term "fast" or "high-frequency" rTMS should be used to refer to stimulus rates of more than 1 Hz, and the term "slow" or "low-frequency" rTMS to stimulus rates of 1 Hz or below. rTMS can either activate or inhibit cortical activity, depending on the stimulation frequency used (4,5).
The higher the stimulation frequency and intensity, the greater the disruption of cortical function during the train stimulation. However, in the wake of the immediate effects induced during the train itself, a train of repetitive stimulation can also induce a modulation of cortical excitability. This effect may range from inhibition to facilitation, depending on the stimulation variables, particularly, the stimulation frequency (6). Lower frequencies of rTMS, in the 1 Hz range, can suppress the excitability of the motor cortex, while 20 Hz stimulation trains seem to lead to a temporary increase in cortical excitability (5). Although these effects vary among individuals, the effect of low-frequency rTMS is robust and long-lasting and can be applied to the motor cortex and to other cortical regions to study brain-behavior relations. Instead, the mechanisms by which cortical activation occurs are not entirely clear, although some authors suggest that a transient increase in the efficacy of excitatory synapses may play a role. Higher frequencies are achieved because a bipolar stimulus is shorter than a unipolar stimulus and requires less energy to produce neuronal excitation (4).
The delivery of a single pulse of TMS to the brain is very safe. rTMS can be considered a satisfactory technique for delivering high-frequency (1-50 Hz) stimulation. The effect produced can be powerful and last longer than the actual stimulation: inhibitory stimulation at around 1 Hz,

and excitatory stimulation at 5 Hz and above. However, rTMS has the potential to induce seizures even in healthy subjects. There exist safety guidelines setting out limits for frequency, intensity, and train length, and adhering to these should prevent most problems. Since capacitors charge and discharge quickly and reach high stimulation rates, rTMS has been considered a valuable technique in the research and treatment of many neurological disorders (7).

The combination of TMS and neuroimaging can be most helpful in the investigation of functional connectivity between regions in the living human brain. Furthermore, the combination of rTMS with tracer PET or magnetic resonance spectroscopy could become a novel tool for investigating neurochemical functional anatomy in health and disease. The mechanisms of the modulation of cortical excitability beyond the duration of the rTMS train are still unclear (5,6). It has been suggested that long-term potentiation and depression of cortical synapses or closely related neuronal mechanisms could explain the effect of high- and low-frequency rTMS, respectively. Animal studies suggest that modulation of neurotransmitters and gene induction may contribute to the long-lasting modulatory effects of rTMS (4,6). Therefore, rTMS may be used as a neurophysiological probe to test the functional integrity of different cortical regions, by either activating or inhibiting them.

rTMS induction of neuroplasticity

Transcranial magnetic stimulation can be used in a variety of ways to induce plastic changes in the brain, and can thus be exploited to assess the brain's capacity for plasticity. Additionally, induced plastic changes can be exploited therapeutically, and this aspect will be discussed below. Although rTMS is sometimes used to disrupt cortical activity for long periods, the majority of applications take advantage of the fact that longer periods of rTMS can sometimes produce effects on cortical circuits that outlast the duration of the stimulus (8). This, in fact, makes it possible to provoke and study mechanisms of acute cortical reorganization in the healthy human brain. Most descriptive studies of the effects of rTMS have used the primary motor cortex, and have shown that rTMS can have long-term effects on corticospinal excitability, but also that the direction, magnitude, and duration of the conditioning effects are critically dependent on the stimulation variables.

Three factors influence the effect of rTMS: frequency, intensity and duration of the stimulation. It is thus important to specify all three of these parameters when describing the results of any rTMS experiment. An effective way of modulating synaptic efficacy is to activate a cell with two or more inputs, almost simultaneously. If the impulses are transmitted along the same synaptic pathway, the stimulation is referred to as homosynaptic; conversely, if they travel along different synaptic pathways, it is termed heterosynaptic (4). In general, when authors talk of "high-frequency stimulation", they are referring to frequencies of about 5 Hz and above; "low-frequency stimulation" instead refers to frequencies of about 1 Hz. As regards the strength of stimulation, rTMS at an intensity of more than about 10% above the MEP threshold in relaxed muscle is classed as "high-intensity stimulation" or suprathreshold rTMS. High frequencies of rTMS, especially at suprathreshold, produce facilitatory after-effects on corticospinal excitability (9). A 10-pulse rTMS train at 150% resting motor threshold and 20 Hz caused an increase in MEP size lasting about three minutes after the administration of rTMS (10). A 30-pulse rTMS train at 120% resting motor threshold and 15 Hz caused a shorter and smaller increase in MEP size lasting 90 seconds (11).

In the case of stimulation at intensities below the resting motor threshold, longer trains are usually required before any lasting effect is seen. For example, Maeda et al. (9) reported a facilitation of MEPs lasting two minutes after the administration of 240 pulses of 20Hz stimuli at 90% resting threshold. Notably 10Hz rTMS had no lasting effect on MEP size. Low-frequency rTMS usually results in suppression of corticospinal excitability (12). A 15-min train of 0.9 Hz applied at 115% motor resting threshold over the primary motor cortex reduced corticospinal excitability (i.e. it increased the resting motor threshold and suppressed the MEP input-output curve) for at least 15 minutes after the end of stimulation (13). Low-frequency rTMS at intensities below the resting motor threshold have a much weaker effect on corticospinal excitability as compared with suprathreshold rTMS (14). Even lower intensities (90% active motor threshold) or lower frequencies (0.1 Hz) had no lasting effect (15).

The duration of rTMS affects the duration and depth of the after-effect. Maeda et al. (9) and Touge et al. (16) both used 1Hz rTMS, at 90% and 95% resting threshold respectively. Longer periods of rTMS lead to longer and stronger reductions in excitability. Studies both of relatively short trains (<20 stimuli) and of longer trains of rTMS provide an insight into the interaction between factors promoting inhibition and factors promoting excitation. If the number of stimuli in the train was increased to 20, facilitation became prominent at high intensities (17). It was suggested that the threshold for inhibitory effects was lower than that for facilitatory effects, and that inhibition built up faster than facilitation. The result of this was that short trains tended to result in transient inhibition, whereas longer trains were likely to produce facilitation, particularly if the intensity and frequency of stimulation were high.

The potentially restorative effects of rTMS have also been tested in patients with motor cortex damage, investigating whether function can be restored and plasticity induced in patients with neglect. A recent study investigated repetitive stimulation of the contralesional hemisphere as a means of restoring interhemispheric inhibitory balances and consequently motor function and behavior (18) and showed that repetitive stimulation of the contralesional motor cortex with low frequencies led to subsequently improved motor functions. It is important to note that this rTMS-induced improvement occurred only when stimulating over the contralesional motor cortex, and not with premotor cortex or sham stimulation.

Research to establish the optimal parameters for the most effective and efficient induction of neuroplasticity remains to be completed. It is known that higher-frequency rTMS over the more injured motor cortex can, compared to sham rTMS, lead to improved motor function. Thus, motor plasticity and improved outcome with rTMS can be induced either by low-frequency rTMS

over the less injured hemisphere or high-frequency rTMS over the more injured hemisphere. Takeuchi et al. (19) and Fregni et al. (20) evaluated the effects of low-frequency rTMS of the intact hemisphere after this suppressive protocol of motor cortex excitability. Takeuchi et al. (19) observed a reduction of the transcallosal inhibition from the intact hemisphere in response to rTMS of the damaged motor cortex and Fregni et al. (20) a reduction of the motor threshold in response to rTMS of the damaged motor cortex. Kim and co-workers (21) showed that high-frequency rTMS of the damaged motor cortex increased MEP amplitude. Talelli and co-workers (22) evaluated the effects of a single session of rTMS, using a novel excitatory protocol of rTMS named theta burst stimulation (TBS). They found that MEP amplitude was increased on the stroke side after TBS of the stroke hemisphere. The effects produced by rTMS on motor cortex excitability in patients with acute stroke are still unknown. Taken together, these findings using rTMS highlight the vast potential offered by this relatively new technology for assessing and promoting neuroplasticity and rehabilitation.

Effects of rTMS in sensorimotor integration

Sensorimotor integration is the continuous processing, by the motor system, of sensory afferents in order to prepare motor acts and to enhance the execution of fine motor activities. In this process, the central nervous system (CNS) integrates information coming from multiple sensory channels, allowing the performance of specific, goal-directed tasks (23). This process has been documented in the intact human cortex through experiments using TMS. The cerebral cortex is composed of cortical areas that are neither purely sensory nor purely motor, but associative, and serve higher-order integrative functions. These higher-order areas of the cortex, called association areas, associate sensory inputs with motor response and perform those mental processes that intervene between sensory inputs and motor outputs (24). Accordingly, there have been reports that alterations of sensory input may influence the excitability of projections to muscles in the opposite arm. Werhahn et al. (25) found that anesthesia of the hand and forearm of one hand increased MEPs of hand muscles in the opposite hand, and pharmacological studies suggested that this effect might be GABA-dependent. In addition, the authors found that excitability of the motor cortex in the hemisphere contralateral to the anesthetized limb was reduced compared with excitability of the motor cortex in the 'intact' hemisphere.

Kossev et al. (26) showed that enhancing, rather than decreasing, sensory input can have effects on the excitability of corticospinal projections to the opposite arm. It thus emerges that manipulations of sensory inputs can be used to induce lasting changes in motor cortical outputs. Reduction of afferent input by anesthesia causes disinhibition within the motor cortex (25) which can be associated with improved hand function after stroke (27). Increased sensory input can likewise be used to increase motor cortical output (28). Muscle vibration itself can induce changes in associations between cortical hand muscle representations (29). Sensorimotor integration is known to function abnormally in types of dystonia (30), while stroke is associated with defects in short intracortical inhibition (SICI) and interhemispheric inhibition (31). The inhibitory imbalance between the unaffected and affected hemispheres following stroke is a reasonable target for therapeutic modulation. The fact that muscle vibration has effects not only in the contralateral but also the ipsilateral hemisphere, and moreover can modulate the relationship between the two, expands the scope for targeted interventions designed to redress inhibitory imbalances in these disorders.

Therapeutic applications of rTMS in clinical neurorehabilitation

Long-lasting influences on the brain depend on changes in synaptic strength or anatomical changes (e.g. alterations in dendritic spines or sprouting), and since such anatomical changes may be a secondary consequence of extended changes in synaptic strength, the aim of rTMS is to alter synaptic strength. This effect has been seen in several neurological disorders. This modulation of cortical activity induced by rTMS is not limited only to motor areas. There is also evidence that its long-lasting effects can be provoked in areas outside the motor cortex and be associated with assessable behavioral changes (4,6). This finding raises the possibility of therapeutic applications of rTMS in order to "normalize" pathologically decreased or increased levels of cortical activity. Therefore, several experiments of various neurological disorders will be presented to demonstrate and to discuss such uses of rTMS.

Parkinson's disease

Pascual-Leone and co-workers (32) were the first researchers to report that sub-motor threshold high-frequency (5 Hz) rTMS of the primary motor cortex (M1) enhanced contralateral hand function in Parkinson's disease (PD) (five patients). There are two rationales for the use of this method in PD: first, its capacity to increase cortical excitability to thalamocortical drive, which is understood to be lacking in this disease; and second, its capacity to modify catecholamine metabolism subcortically through cortical stimulation (33). Ghabra et al. (34), investigating the effects of rTMS in 11 similar patients in the unmedicated state, found no beneficial effect on grooved pegboard test performance during or after stimulation. In fact, in an appreciable number of patients, stimulation at 90% resting MEP threshold catastrophically disrupted movement, making the task impossible. This phenomenon has been noted by others and associated with the cerebellar tremor; it was found that decreasing the stimulation intensity removed the tremor, but did not improve the task performance (35).

Transcranial magnetic stimulation can speed up reaction time in patients with PD, and this led to the idea that rapid rTMS might be used for therapy. Early experiments indicated an enhancement in pointing performance after rTMS of M1 (36) and an improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) after rTMS (37). In another study, subthreshold rTMS of the M1 at both 0.5 Hz (600 pulses) and 10 Hz (2000

pulses), but not sham stimulation, enhanced numerous aspects of motor performance. However, these changes lasted only minutes. A more substantial and long-lasting effect of rTMS therapy appears to be produced by repeated application over a period of days (38). In the light of these findings (36-38), 36 unmedicated PD patients were randomized to one of two groups: real-rTMS (suprathreshold 5 Hz, 2000 pulses once a day to the motor cortex for 10 consecutive days) and sham-rTMS. The former enhanced all the motor section of the UPDRS, walking speed, and self-assessment scale after the sessions were over, and the benefit lasted at least one month (39). In a double-blind placebo-controlled study, eight 25Hz rTMS sessions were performed over four weeks in 18 PD patients, stimulating four cortical targets (left and right motor and dorsolateral prefrontal cortex) in each session, with 300 pulses each, at 100% motor threshold intensity. A therapeutic rTMS effect persisted for at least one month after the treatment ended (40).

In contrast to these high-frequency studies, Brusa et al. (41) instead tried to elucidate whether 1Hz rTMS may modulate L-dopa-induced dyskinesia (LID) in dyskinetic PD patients. The authors examined whether decreased excitability of the supplementary motor area (SMA) could modify LID in these patients. Moreover, they tested whether repeated sessions of 1Hz rTMS could enhance and/or prolong the beneficial effects. The results showed that 1Hz rTMS induced a transient reduction of dyskinesias. A single session of rTMS enhanced LID, in contrast to repeated sessions which failed to enhance and/or prolong the beneficial effects, without causing motor deficits or other negative effects. The authors concluded that LID may depend on augmented excitability of the SMA.

Similarly, Khedr et al. (42) set out to establish whether repeated sessions of rTMS could induce effects lasting at least one month. Fifty-five unmedicated PD patients were classified into four groups: two groups (early and late PD) received 25Hz rTMS of the motor arm and leg areas bilaterally; the third and fourth groups acted as controls for frequency (10 Hz) and for site of stimulation (occipital) respectively. All the patients received six consecutive daily sessions (3000 pulses per session). The first two groups then received a further three booster sessions (three consecutive days of rTMS) after 1, 2, and 3 months, in contrast to the third group which had just one session after the first month. The UPDRS, walking time, key-tapping speed, and self-assessment scales were performed before and after each rTMS session and before and after the monthly sessions. When compared with occipital stimulation, the early and the late groups demonstrated an improvement in all measures due to 25Hz rTMS over motor areas. The groups that received 10Hz rTMS improved more than the occipital group but less than the 25Hz groups. The effect increased gradually throughout the sessions and was then maintained for one month after they ended, with a slight reduction in efficacy. Interestingly, the booster sessions restored and maintained the effect for the next month, showing that 25Hz rTMS can lead to cumulative and long-lasting effects on motor performance.

More recently, Khedr et al. (43) verified whether frequent sessions of rTMS augment serum dopamine in PD patients and whether this correlates with changes in clinical rating scales. The authors applied a protocol of 25Hz rTMS with 3000 stimuli to the hand and leg motor areas bilaterally in twenty untreated PD patients with moderate to severe symptoms. They were measured on the UPDRS, and with an enzyme immunoassay for quantitative determination of plasmatic dopamine before and after six sessions. The result was a significant improvement in UPDRS compared with the baseline. Moreover, the serum dopamine level was also significantly increased over the same interval. A significant correlation emerged between UPDRS and serum dopamine level before and after the protocol, suggesting that the motor performance improvement in PD after the rTMS protocol may be related to an elevation in the serum dopamine concentration.

In a recent study, Fierro et al. (44) aimed to explore the lasting effects on cortical inhibition of sub-threshold high-frequency rTMS trains over M1 in patients “on” and “off” L-dopa treatment. Fourteen PD patients were assessed twice under “on” and “off” medication conditions. A paired-pulse paradigm was employed in both conditions to verify SICI and long intracortical inhibition (LICI) before and after the application of a high-frequency rTMS protocol over the M1. At baseline, SICI and LICI were found to be significantly reduced in “off” compared with “on” patients and controls. In contrast to the baseline condition, high-frequency rTMS over the M1 significantly increased SICI and LICI in “off” medication PD patients. TMS proved to be ineffective when the same patients were in the “on” state. The results showed a deterioration of the intracortical inhibition (ICI) only in unmedicated patients. Hence, the “on” and “off” states appear to be critical for rTMS effects in PD patients. Possibly, there is a positive correlation between increased cortical inhibition and clinical enhancement. It is suggested that high-frequency rTMS during the “off” state could be considered as a potential add-on treatment to diminish the need for L-dopa and thus delay the unfavorable effects of its chronic use.

Dystonia

There is a different rationale for the use of rTMS in dystonia in which physiological findings reveal a decrease in ICI. Since rTMS delivered over M1 at 1 Hz can induce an increase in inhibition, this effect might improve the deficit. An initial study showed a normalization of ICI and some modest improvement in performance (45). This improvement of deficient ICI (46) and of handwriting persisted, at most, for 3 hours after application of a 30-min. train of rTMS but resulted in clinical benefits in only 2 of 16 patients studied. Although these effects are transient, the data support the concept of impaired inhibitory mechanisms in the motor cortex. Another target could be the premotor cortex (PMC), since rTMS at 1 Hz can improve the deficit in reciprocal inhibition seen in dystonia (47). Accordingly, nine patients with writer’s cramp and seven age-matched control subjects were studied using subthreshold 0.2Hz rTMS applied to the M1, SMA, or PMC (48). Stimulation of the PMC but not of the M1 significantly improved the handwriting rating in the patient group. rTMS over the other sites or using a sham coil in the patient group, and trials in the control group revealed no clinical changes.

In a recent experiment, Bäumer et al. (49) investigated

whether, as hypothesized, functional alterations make the somatosensory cortex (S1) of writer's cramp patients more vulnerable to the inhibitory effects when a subthreshold 1Hz rTMS is applied. Seven patients and eight healthy subjects were assessed. In addition, patients also were submitted to rTMS of M1. Short-latency afferent inhibition (SAI) was investigated in the relaxed first dorsal interosseous muscle through conditioning electrical stimulation of the index finger and rTMS pulses over the contralateral M1. Baseline SAI was not significantly different between groups; however, S1 but not M1 rTMS reduced SAI in the patients. Moreover, in the healthy subjects, rTMS had no effects on SAI, which is mediated mainly at the sensorimotor cortex. It was concluded that there was an irregular responsiveness of S1 to 1Hz rTMS in the patients, which may be a trait suggestive of maladaptive plasticity in the sensorimotor areas in these subjects.

Gilio et al. (50), on the other hand, verified whether 5Hz rTMS obtains similar MEP facilitation during stimulation and similar facilitatory after-effects in patients with upper limb dystonia and in healthy subjects. Protocols of 5, 10, and 20 stimuli trains were distributed at 120% resting motor threshold over the M1 with the individuals at rest. The rTMS trains were followed by single test stimuli distributed at a variety of interstimulus intervals (0.5-10 s) at 120% resting motor threshold using a conditioning-test paradigm. The effects of suprathreshold 1Hz rTMS were also evaluated. The MEP amplitude during the course of the trains and of the test stimuli was measured. In control studies, the authors investigated the effect on the MEP amplitude of afferent inputs elicited by muscle twitches after ulnar nerve stimulation. Equally, the patients and the healthy participants showed significantly increased MEP amplitude over the course of the 5Hz rTMS protocol. In addition, in both groups the MEP facilitation was found to outlast the 5Hz rTMS; nevertheless the facilitatory after-effects were more evident and long-lasting in the patients. Moreover, it was also verified that MEP amplitudes during and after 1Hz rTMS remained unchanged. Ulnar nerve stimulation did not change the test MEP amplitude. The authors concluded that patients with upper limb dystonia show an atypical recovery when assessed through MEP facilitation after suprathreshold 5Hz rTMS application, indicating an atypical pattern of short-term cortical plasticity.

Stroke

Repetitive transcranial magnetic stimulation may improve outcome after stroke by suppressing maladaptive cortical plasticity and improving adaptive cortical activity, thereby facilitating neurorehabilitation. Functional imaging studies after stroke show increased activity in undamaged brain areas (51), but the role of these areas is controversial (52). Some activation in the uninjured brain could reflect adaptive cortical reorganization that promotes functional recovery, but some changes may be maladaptive and generate the emergence of behaviors whose suppression would improve functional outcome. The symptoms after brain damage are due as much to the changes in activity across the undamaged brain as to the actual damage. In fact, contralesional neglect after stroke is not due to the lesion itself but primarily to the hyperactivity of the intact hemisphere, and 1Hz rTMS of the unaffected parietal lobe, carried out in order to suppress the excitability of the intact hemisphere, can improve contralesional visuospatial neglect after stroke (53).

Much of the spontaneous recovery from stroke after the acute phase involves plastic changes in the brain. The task for rehabilitation is to find ways of facilitating this plasticity so that the changes occur more rapidly and more completely. Since a good recovery depends to a great extent on the plasticity in the lesioned hemisphere, one therapeutic approach is to try to increase brain plasticity in the lesioned region through brain stimulation. In one study, 15 patients with chronic hemiparetic stroke performed a complex, sequential finger motor task using their paretic fingers after either 10Hz or sham rTMS of the ipsilesional M1. Changes in the behavior and corticomotor excitability before and after the intervention were evaluated by measuring the movement accuracy, the movement time, and the MEP amplitude. rTMS was found to produce a significantly larger increase in MEP amplitude than the sham rTMS, and the plastic change was positively associated with enhanced motor performance accuracy. Another approach to brain stimulation is to target the contralesional side. The contralesional M1 inhibits the ipsilesional M1 via transcallosal inhibition (TCI) (21). The study by Takeuchi et al. (19), mentioned earlier, investigated whether decreased excitability of the contralesional M1 induced by 1Hz rTMS could enhance motor performance of the injured hand in stroke patients by decreasing in the TCI. Compared with the sham stimulation, rTMS reduced both the amplitude of MEPs in the contralesional M1 and the TCI duration, and immediately induced an increase in pinch acceleration of the injured hand, even though a plateau in motor performance had been achieved as a consequence of the previous motor training. This enhancement in motor function after rTMS was significantly associated with a reduced TCI duration (19).

Liepert et al., in a double-blind study of real versus placebo rTMS (54), investigated whether inhibitory 1Hz rTMS over the contralesional M1 improved motor performance of the damaged hand in acute stroke. Twelve patients early after subcortical stroke (acute phase, 7 days) were submitted to a crossover design (1200 stimuli of real and sham rTMS). The protocol of stimulations was balanced across subjects and the stimulus intensity was subthreshold (90% motor threshold at rest). Motor function was tested by grip strength recordings and Nine Hole Peg Test (NHPT) performances before and after each rTMS session. When contrasted with sham stimulation, real rTMS enhanced NHPT results; however, no significant results for grip strength in the damaged hand were observed. No change in performance was recorded for the undamaged hand. NHPT baseline measures in a subgroup of patients suggested stable motor performance prior to the rTMS sessions. Such findings indicate that therapeutic rTMS applications over the contralesional hemisphere are viable in the acute phase of stroke and can transitorily improve the dexterity of the damaged hand.

Another recent experiment examined the effect of inhibitory 1Hz rTMS, applied over the M1 of the uninjured hemisphere, on the dexterity of the injured hand in subcortical stroke patients. All individuals performed a

grasp, lift and hold task using an instrumented object and the index finger and thumb, for both the injured and uninjured hand. This protocol was applied prior to (baseline) and following 1Hz rTMS over the vertex (control stimulation) and the M1 of the uninjured hemisphere. In contrast to baseline, 1Hz rTMS applied over the uninjured M1, excluding the vertex, enhanced the efficiency and timing of grasping and lifting with the injured hand. These findings suggest an interhemispheric competition concept and, moreover, strengthen the argument in favor of rTMS as a novel tool for stroke rehabilitation (55).

Di Lazzaro et al. (56) recently evaluated the effects of TBS on cortical excitability in acute stroke, exploring in 12 patients the effects of facilitatory TBS of the damaged hemisphere and of inhibitory TBS of the undamaged hemisphere on cortical excitability to single-pulse TMS bilaterally. To this end, the effects of TBS application in the patients were contrasted with those observed in the control group of age-matched healthy subjects. It was verified that both the facilitatory TBS in the damaged M1 and the inhibitory TBS in the undamaged M1 generated a significant increase in the amplitude of MEPs derived from stimulation of the damaged hemisphere. It was thus shown that facilitatory TBS over the stroke hemisphere and inhibitory TBS over the intact hemisphere, in the acute phase, augment the excitability of the damaged M1.

Mechanisms of action of rTMS in neurogenesis

Several cellular mechanisms have been suggested to be involved in the behavioral/neurofunctional outcome of rTMS. For instance, low- and high- frequency rTMS modify the intracortical connections in different ways and even remote neuroplastic changes can occur in both brain hemispheres in rTMS-treated stroke patients. Furthermore, serotonergic fibers have been observed to grow in lesioned spinal cord submitted to rTMS. Moreover, new exciting mechanisms of rTMS have been explored in PD and stroke. The release of dopamine after rTMS has been associated with the symptomatic improvement of PD, and the neurogenesis of new cells with dopaminergic identity described in animal experiments has been suggested to play a role in the slower progression of PD after rTMS (57).

Therapeutic interventions involving the recruitment of adult endogenous stem cells to replace degenerated neurons are of substantial importance in neurorehabilitation. Neurogenesis occurs in discrete regions of the adult mammalian brain. The subventricular zone (SVZ) and the subgranular zone (SGZ) in the hippocampal dentate gyrus are two regions of the mammalian adult brain that show neurogenesis throughout the lifespan. Indeed, neuronal precursors are found and continue to proliferate in the SVZ and SGZ of the adult rodent forebrain (58). Neurogenesis in those specific brain areas can be regulated physiologically (59) and in pathological conditions (60) and is also the focus of therapeutic interventions. It has been shown that induced status epilepticus triggers dentate granule cell neurogenesis in the adult rat (61). Moreover, hippocampal ischemia increases cell proliferation and neurogenesis in the rat dentate SGZ, but not in the SVZ in the adult gerbil (62), while focal cerebral ischemia induced by middle cerebral artery occlusion leads to a marked increase in cell proliferation in the rodent SVZ (63). A frontoparietal cortical lesion was found to induce an increased cell number in the SVZ of adult rats (64). Finally, recent data have shown the neurogenesis in the SVZ to be beneficial in the motor recovery of an experimental model of PD.

It is possible that neurogenesis may contribute to some of the effects of rTMS on neuroplasticity and rehabilitation after brain lesions. In fact, TMS was found to induce neurogenesis in the rat SVZ and to prevent the motor alterations induced by lesions of the nigrostriatal pathway. Dopamine depletion seemed to be responsible for a reduction in precursor cell proliferation in the SVZ of PD patients and experimental animals (65). Differences between SVZ-derived precursor cells were shown in dopamine-producing neurons in rats with unilateral 6-OHDA lesions of the substantia nigra after a 60-day 60Hz, 0.7 mT rTMS treatment (58,66). Moreover, a reduction in amphetamine-induced rotations in animals receiving rTMS has been shown to be correlated to the number of new dopaminergic cells supposedly exhibiting the electrophysiological properties of mature dopaminergic neurons and presenting spontaneous postsynaptic potentials (66). In this way, rTMS, unlike drugs which have a symptomatic effect in PD, may be a valid causative treatment for PD. These results may explain the slower progression of PD observed in humans after rTMS (67).

The experimental evidence of rTMS-induced neurogenesis in specific brain regions and the described actions of rTMS (with regard to changes in neurotransmitter release, transsynaptic efficiency, signaling pathways and gene transcription as well as secretion of neuroprotective molecules and neuronal viability) (68) underline the potential of rTMS also as a new strategy for regenerating the lesioned CNS, particularly after ischemic injury. Cerebral ischemia can also increase neurogenesis both in the SGZ and in the SVZ of the adult brain (63) and this seems to be associated with the activation of the NMDA receptor (69). The neuronal precursors of the SVZ migrate to the ischemic zone of the adjacent striatum (70) and, through the rostral migratory stream and the lateral cortical stream, to the ischemic zone of the cerebral cortex where the damaged neurons are differentiated and replaced (67). Despite the potential for application of rTMS, its effects on neurogenesis post-stroke are not known; however, the migration of neurogenesis from the SVZ to the area around the stroke lesion has been proposed as an additional mechanism furthering functional recovery (66).

Concluding remarks

Since its introduction nearly 20 years ago, TMS has evolved into a sophisticated tool for neuroscience research. It is an excellent technique and complements other non-invasive methods for studying human brain physiology. The rTMS technique is a non-invasive and effective methodology with potential for therapeutic use. In this review, we have cited several studies in patients with PD, dystonia and stroke, which have indicated that sessions of rTMS can improve some or all of the motor symptoms associated with these conditions. rTMS may become an additional tool for early neurorehabilitation

and might be useful for promoting cortical plasticity in neurological patients. However, these changes are transient and it is premature to propose these applications as realistic therapeutic options, even though the rTMS technique has shown itself to be, potentially, a modulator of sensorimotor integration and neurogenesis. Functional imaging of the region of interest could highlight the capacity of rTMS to bring about plastic changes of the cortical circuitry and hint at future novel clinical interventions. As new coils and new patterns of stimulation are developed, we are likely to see the emergence of even more innovative ways of using this technique. Combined non-invasive techniques can be used in imaginative ways. In this manner, electroencephalography could be used to establish exactly where and when to deliver a TMS pulse in order to obtain maximum advantage. Although further developments are needed to make the effects more robust and longer lasting, future work in this area promises to advance our understanding of the pathophysiology of a wide range of neurological conditions, generate widely applicable diagnostic tools for clinical neurophysiology, and perhaps establish neuromodulation as a viable therapeutic option in neurorehabilitation.

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