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Repetitive Transcranial Magnetic Stimulation for Upper Extremity Motor Recovery: Does It Help?

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Abstract

Purpose of Review Repetitive transcranial magnetic stimulation (rTMS) noninvasively modulates brain excitability in humans and influences mediators of plasticity in animals. When applied in humans in the months to years after stroke, potentiation of motor recovery has been limited. Recently, investigators have shifted rTMS administration into the early weeks following stroke, when injury-induced plasticity could be maximally engaged. This article provides an overview of basic mechanisms of rTMS, consideration of its interaction with various forms of neuroplasticity, and a summary of the highest quality clinical evidence for rTMS given early after stroke.

Recent Findings Studies of repetitive magnetic stimulation in vitro and in vivo have found modulation of excitatory and inhibitory neurotransmission and induction of cellular mechanisms supporting plasticity. A handful of clinical studies have shown sustained improvements in grip strength and UE motor impairment when rTMS is delivered in the first weeks after stroke.

Summary Though in its infancy, recent research suggests a plasticity-enhancing influence and modest motor recovery potentiation when rTMS is delivered early after stroke.

Keywords Repetitive transcranial magnetic stimulation · Motor recovery · Associative plasticity · Homeostatic plasticity

Introduction

Over 30 years ago, transcranial magnetic stimulation (TMS) made it possible for the first time to noninvasively and painlessly stimulate the cortex [1]. TMS is a type of noninvasive brain stimulation (NIBS) that uses electromagnetic induction to either probe cortical circuitry or cause long-lasting changes in cortical excitability. From a capacitor, a short-duration (~ 1 ms), large electric current (~ 2000 A) is discharged through a coil of wire encased in a plastic paddle. The current generates a rapidly fluctuating magnetic field which, if positioned over a conductive material, induces its own brief electric field in situ. This electric field induces action potentials in neural tissues, while the magnetic field bypasses nociceptive tissues such as the scalp or meninges. The magnetic field decays exponentially with distance, limiting the depth and extent of stimulation [2]. Cortical connectivity, however, must always be kept in mind: even focal stimulation can induce excitability effects, and may influence neuroplasticity mechanisms, at remotely connected sites.

When delivered in single or paired stimuli, TMS probes neural circuitry without long-lasting alterations in excitability. When delivered in repeating trains of stimuli, repetitive TMS (rTMS) can cause cortical excitability changes that outlast the period of stimulation by many minutes. rTMS may be delivered in trains of evenly spaced single stimuli, or in clusters of stimuli that are repeated. rTMS stimulation patterns are modeled after electrophysiology protocols that induce long-term potentiation (LTP) and depression (LTD), forms of synaptic plasticity believed to underlie learning [3]. In electrophysiology protocols, high-frequency stimulation induces LTP, whereas low-frequency stimulation induces LTD [3].

Similarly, the frequency and temporal patterns of rTMS determine its effects on cortical excitability. When delivered at rest, high-frequency rTMS (≥ 5 Hz) tends to increase excitability, whereas low-frequency rTMS (0.2–2 Hz) tends to decrease excitability [4••]. A more recent type of rTMS is theta burst stimulation (TBS), whose basic building block is a

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pattern of three 50 Hz stimuli repeated at 5 Hz [5, 6]. TBS mimics the firing patterns of hippocampal pyramidal cells in awake behaving rodents exploring a new environment [7], and stimulation with this pattern induces LTP in rat hippocampal slice [8]. In human motor cortex (M1), intermittent delivery of TBS (iTBS; TBS given for 2 s, repeated every 10 s) increases neuronal excitability, whereas continuous delivery of TBS (cTBS; TBS given in an unbroken train) decreases excitability [6]. Repetitive paired-pulse [9], quadripulse [10], paired associative stimulation [11], and disinhibition stimulation [12] are other patterned rTMS approaches, but have not yet been used for early recovery potentiation and so will not be further discussed.

Beyond the frequency and pattern of stimuli, other parameters such as duration and intensity of stimulation or prior/ongoing physical activity can also affect the degree and direction of excitability changes [4••]. Importantly, because of intra- and interhemispheric neural connectivity, rTMS can also alter excitability in remotely connected areas depending on the nature of these connections. For example, 1 Hz rTMS decreases excitability in the stimulated M1 but increases excitability in the contralateral (unstimulated) M1; these changes are mediated by reduced transcallosal interhemispheric inhibition (IHI) emitted from the stimulated M1 [13, 14].

Potential Mechanisms of rTMS Influence

Although rTMS stimulation patterns and their excitability changes resemble those seen in electrophysiological preparations, LTP and LTD cannot be mechanistically assumed, not least because of major methodological differences for induction [15]. Although the physiological basis for rTMS excitability change is not well understood, recent in vitro and in vivo studies have begun to shed light on synaptic and cellular changes induced by repetitive magnetic stimulation (rMS; absent the "T" because preparations lack a cranium) [15, 16].

At the synapse, high-frequency rMS has been found to modulate both excitatory and inhibitory neurotransmission. After application of 10 Hz rMS to mouse entorhinohippocampal slice, transmission at excitatory synapses steadily increases up to 6 h. These excitatory changes are underpinned by increased insertion and clustering of alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, enlargement of dendritic spines on postsynaptic neurons, and requirement of *N*-methyl-D-aspartate (NMDA) receptor activation for induction [17]. At inhibitory synapses, the same stimulation protocol reduces inhibitory transmission. These inhibitory changes are underpinned by a reduction in the number and size of synaptic $GABA_A$ receptor clusters [18]. The investigators noted that unlike classical LTP, pyramidal cell excitability increased gradually and transiently after rMS and suggested that disinhibition of inhibitory circuitry rather than direct excitation of excitatory circuitry was the mechanism of action [18].

At the cellular level, rTMS/rMS influences cellular signaling, immediate early gene expression, neurotrophin production, and neurotransmitter release—all of which participate in the induction and/or maintenance of LTP/LTD (see excellent in-depth reviews in [16••, 19••]). For example, repeated daily 20 Hz rTMS in awake behaving rats increases brain-derived neurotrophic factor (BDNF) and phosphorylated (activated) AMPA receptors, although 1 Hz rTMS does not [20]. rTMS also alters cortical protein expression and activity of cortical inhibitory interneurons in a frequency-dependent manner: iTBS but not cTBS leads to suppression of inhibitory interneurons, the expression of activity-dependent proteins, and better tactile maze learning in rats [15]. Furthermore, rTMS is strong modulator of dopaminergic, GABAergic, and glutamatergic neurotransmission in both animals and humans [16••]. Collectively, this basic research points to the engagement of cellular machinery by rTMS (particularly excitatory rTMS) that could promote plasticity and ensuing behavioral changes. An important point is that excitability changes may indicate the engagement of molecular and cellular mechanisms that mediate plasticity, or excitability changes may modulate plasticity directly, as discussed below.

rTMS Interaction with Plasticity

Despite apparent engagement of plasticity machinery, rTMS given by itself does not cause long-lasting behavioral change in humans. Rather, it must be paired with training to affect behavior. If given with rehabilitation therapy after stroke, the interaction of rTMS with various types of plasticity warrants consideration. There are three types of plasticity in this context: associative plasticity (a.k.a. activity-dependent or Hebbian plasticity), homeostatic plasticity (a.k.a. metaplasticity), and injury-induced plasticity (a.k.a. endogenous or spontaneous plasticity).

Associative plasticity is the strengthening (LTP) or weakening (LTD) of synaptic transmission resulting from correlated or uncorrelated firing, respectively, between pre- and postsynaptic neurons [21]. Repetitive motor training evokes LTP in rat motor cortex [22, 23]. The excitability effects of rTMS have been proposed to "gate" this associative plasticity, facilitating its induction but not causing it directly [24•]. Mechanistically, excitatory rTMS may temporarily reduce inhibitory interneuronal control of principal cortical neurons and so mildly depolarize them, biasing the NMDA receptor toward activation [24•, 25]. When paired with training protocols, excitatory rTMS would be expected to facilitate LTP induction, as evidenced by improved motor and somatosensory learning in humans [24•]. Inhibitory rTMS, conversely,

may be expected to facilitate LTD induction, though evidence for behavioral disruption is less conclusive [24•]. Gating effects have been found recently in mature cats, where real-time optical imaging was used to investigate the effects of rTMS on cortical reorganization [26•]. After 10 Hz rTMS was applied to visual cortex, animals were passively exposed to specifically oriented visual stimuli for 30 min. Immediately following stimulation, visual cortical neurons showed a transient increase in excitability, with neurophysiologic characteristics suggesting neural disinhibition. Established visual maps initially destabilized after rTMS, then reorganized in favor of the new stimulus orientation, persisting until recordings ended at 6 h [26•]. These changes were not observed with 1 Hz or sham stimulation. These results suggest the high-frequency rTMS sensitizes cortex to subsequent interventions that induce associative plasticity at the cortical map level. Whether these map changes translate to behavioral changes, e.g., improved task-based responses to the new stimulus orientation, has yet to be examined.

Homeostatic plasticity should also be considered with delivery of NIBS. Homeostatic plasticity regulates the directionality and extent of associative plasticity based on recent neuronal activity [27]. It prevents saturation or under-use of the synapse, keeping its activity within a responsive, physiological range [28]. Synaptic homeostatic mechanisms include a sliding threshold for LTP/LTD induction [29], scaling of synaptic strength [30], changes in the balance of excitatory and inhibitory synapses [31], and constraints on dendritic spine size change [32]. These mechanisms act on a slower time scale (hours to days) than associative plasticity [27]. rTMS may be used to generate homeostatic plasticity as a "priming" approach, where a targeted area/network is given more "room to move" in preparation for the subsequent induction of associative plasticity [24•]. Typically, inhibitory rTMS is applied at some interval before a training protocol; this approach has been shown to potentiate motor learning in healthy human subjects [24•]. Thus if training is undertaken after rTMS, NIBS-induced homeostatic plasticity may influence the direction or degree of associative plasticity, depending on the valence of rTMS and the timing of training thereafter.

Finally, injury from the stroke itself incites a robust neuroplastic response in the perilesional cortex and interconnected areas [33, 34••]. Mechanisms include altered tonic and phasic GABAergic signaling, promotion and suppression of axonal sprouting, dendritic remodeling, neuro- and gliogenesis, and upregulation of transcription factors that activate genes supporting neuronal excitability and LTP induction [34••, 35]. Injury-induced plasticity underlies a time-limited critical period that is believed to last only weeks in humans [34••]. In animals, injury-induced plasticity potentiates learning brought about through training protocols, presumably via augmentation of associative plasticity [33]. For example, as injury-induced plasticity wanes in the weeks following stroke in rats, so too does the behavioral benefit of identical doses of upper limb training, with accompanying decreases in dendritic branching and complexity in the contralesional cortex [36]. This observation underscores an important point about the timing of interventions after stroke: to maximize benefit, they must be given early enough to engage injury-induced plasticity in the post-stroke critical period.

Animal Models of Repetitive Motor Cortex Stimulation in Early Stroke

To date, no animal studies have investigated the effects of repetitive magnetic stimulation, with or without rehabilitation, after stroke. However, two recent rodent studies used optogenetic stimulation to repetitively stimulate the motor cortex after stroke [37, 38]. While optogenetic stimulation has far greater focality and cellular specificity than conventional magnetic stimulation, it shares an endpoint of repetitively depolarizing cortical neurons; thus this approach may inform our understanding of rTMS effects in the injured brain.

In the first study, rats were given a large motor and premotor stroke [37••]. Three days later, animals received one of the following interventions: 2 weeks of 10 Hz optogenetic stimulation to the contralesional motor cortex followed by 2 weeks of grasp training, 2 weeks of stimulation followed by 2 weeks of rest, 2 weeks of rest followed by 2 weeks of training, or no intervention at all [37••]. Lesioned animals that received repetitive stimulation demonstrated significantly improved grasp and forelimb recovery relative to animals without stimulation. By 5 weeks post-stroke, only lesioned animals with both stimulation and training achieved grasp success rates that were comparable to their premorbid baseline, with restoration of normal grasping kinematics [37••]. These behavioral improvements were accompanied by functionally relevant sprouting of contralesional corticospinal fibers into the stroke-denervated spinal cord.

In the second study, mice were given a somatosensory and striatal stroke [38]. Five days later, they received 10 days of 10 Hz optogenetic stimulation to the ipsilesional motor cortex. Animals did not undergo rehabilitation training, but were freely behaving during and after stimulation. Relative to non-stimulated lesioned mice, stimulated mice had improved functional recovery in a balance and ambulation task. Stimulation also resulted in the upregulated expression of activity-dependent neurotrophins and plasticity markers, particularly in the contralesional hemisphere [38].

In both studies, early repetitive stimulation of corticospinal neurons after stroke appears to induce a plasticity-supporting environment, robust rewiring, and functional improvement that surpasses that arising from injury-induced plasticity alone. Behavioral, neuroanatomical, and molecular changes were not observed in stimulated rodents who did not have

strokes, pointing to a unique interaction between brain stimulation and the post-stroke milieu. Interestingly, behavioral improvements occurred despite a delay between stimulation and formal training, or in the absence of formal training. This observation raises the possibility that early stimulation in conjunction with injury-induced plasticity may shape the neural substrate toward a more effective recovery system. It remains to be seen how low-frequency stimulation affects plasticity in an animal stroke model, and whether the above effects would be borne out with magnetic stimulation.

Human rTMS Trials in Early Stroke

In human motor recovery after stroke, the administration of rTMS has largely been motivated by the interhemispheric competition model. It posits that IHI becomes imbalanced after stroke, leading to maladaptive inhibition of the ipsilesional hemisphere by the contralesional hemisphere [39]. A common rationale is thus to use rTMS to "rebalance" the circuitry of IHI, by administering either excitatory rTMS to the ipsilesional hemisphere or inhibitory rTMS to the contralesional hemisphere. The relevance of the interhemispheric competition model to early recovery has recently come under scrutiny. We and others have found that IHI is normal in the subacute stage when behavioral recovery is most dynamic, and becomes abnormal only chronically, well after recovery has plateaued [40, 41]. These observations suggest that targeting IHI is less relevant for recovery potentiation, and that aiming for neurophysiological correction may be misguided. However, ipsilesional and contralesional cortical motor areas are relevant targets given their participation in recovery [34], and rTMS may modulate their plasticity mechanisms, as detailed above.

The majority of rTMS studies in humans have taken place 6 or more months after stroke (chronic stage), well after the post-stroke critical period had ended. Behavioral effects have been disappointingly scant in these chronic stroke studies [42]. Such is the case for the recently completed NICHE (Navigated Inhibitory rTMS to Contralesional Hemisphere) trial, the largest phase III study to date to investigate the effects of rTMS on UE motor recovery [43•]. This randomized, double-blinded, sham-controlled trial enrolled nearly 200 patients 3–12 months after stroke (80% ischemic). Patients received 1 Hz rTMS or sham stimulation to the contralesional M1, three days per week over 6 weeks. Stimulation was followed by an hour of task-oriented training. Motor impairment was assessed with the UE Fugl-Meyer (UE-FM) scale. At 6 months post-treatment, there were no significant group differences in the percent of patients with a clinically meaningful improvement in motor impairment; both groups gained approximately 8 points on the UE-FM scale. Of note, ~ 70% of the subjects were enrolled more than 6 months after stroke, with the remainder enrolled 3–6 months after stroke. This author speculates that the opportunity to meaningfully engage injury-induced plasticity had passed, as the majority of patients were stimulated outside of the post-stroke critical period. These important negative results point to the inefficacy of 1 Hz contralesional rTMS when delivered too late after stroke.

Earlier delivery of rTMS after stroke positions it to engage with injury-induced plasticity. Discussed here are recent high-quality studies administering rTMS the early months after stroke. Those discussed are randomized, blinded, sham-controlled, and have well-matched study groups; importantly, they also use measures believed to best read out neural reorganization (e.g., strength, UE-FM score) [44]. Although some studies have shown benefits of early rTMS at the activity and participation levels [45, 46], their outcome measures may be contaminated by compensatory movements, limiting conclusions about effects on true reorganization [44]. Also excluded from discussion are studies that use subjective appraisals, such as visible muscle twitch to determine stimulation intensity [47, 48], as this limits replication and could lead to inconsistent neural modulation and behavioral response.

A pair of studies initiated stimulation within the first weeks after stroke. Volz and colleagues enrolled 26 ischemic stroke patients within 2 weeks post-stroke and delivered rTMS for five consecutive days [49]. Patients were given iTBS to the ipsilesional M1 or the parieto-occipital vertex (control group), followed immediately by 45 min of standardized rehabilitation focusing on hand motor function. Relative to the control group, the M1-iTBS group had significantly greater recovery of grip strength one day post-intervention relative to baseline, increasing 21% in the iTBS group vs. 10% in controls. At follow-up more than 3 months after stroke, strength remained significantly higher in the iTBS group than in controls (~ 85% vs. 63% normalized grip strength, respectively). The iTBS group also showed greater preservation of motor network connectivity compared to the control group. The authors suggested that M1-iTBS may beneficially limit network degradation after stroke [49].

Long and colleagues enrolled 62 stroke patients (half ischemic, half hemorrhagic) within 3 weeks post-stroke and delivered rTMS for 15 consecutive days [50]. Patients received either 1 Hz rTMS to the contralesional hemisphere, a combination of 1 Hz rTMS to the contralesional hemisphere followed by 10 Hz rTMS to the ipsilesional hemisphere, or sham stimulation. All patients received an hour of UE task-oriented training, with unclear timing relative to stimulation. Immediately following intervention, both stimulation groups showed significant improvements in UE-FM scores (~ 5–6 point gains) relative to sham (~ 1 point gain). By 3 months, the combined-rTMS group had significantly higher UE-FM scores than the 1 Hz rTMS and sham groups (UE-FM score ~ 48 vs. ~ 42, respectively; sham score ~ 40). This study brings up an interesting approach of doubly modulating the

ipsilesional hemisphere, through remote effects (contralesional 1 Hz rTMS) paired with direct effects (ipsilesional 10 Hz rTMS).

Another pair of studies enrolled patients slightly later after stroke, although likely still within the critical period. Li and colleagues enrolled 127 ischemic stroke patients within 2 months and delivered rTMS for 5 days per week over 2 weeks [51]. Patients received either 1 Hz rTMS to contralesional hemisphere, 10 Hz rTMS to ipsilesional hemisphere, or sham stimulation. All patients received 40 min of UE rehabilitation therapy, including task-oriented training, with unclear timing relative to stimulation. Immediately following the stimulation period, the rTMS groups showed comparably and significantly increased UE-FM change scores relative to sham (sham: ~ 4 point gain; rTMS groups: ~ 16 point gain). rTMS-stimulated patients also had increased central motor conduction times in the ipsilesional corticospinal tract, which may indicate improved tract connectivity [51]. A limitation of this study is that it did not have an extended follow-up to evaluate the longevity of effects.

Not all stroke studies using early rTMS have found an effect. Seniow and colleagues enrolled 40 stroke patients (nearly all ischemic) within 2 months after stroke and delivered rTMS for 5 days per week over 2 weeks [52]. Patients received either 1 Hz rTMS or sham stimulation to the contralesional hemisphere, immediately followed by 45 min of neurodevelopmental training (i.e., postural training to support coordinated UE movements). Both groups had comparable gains in UE-FM scores immediately (~ 10 points) and 3 months (~ 17–18 points) following the intervention. It is possible that the choice of paired rehabilitation therapy may have influenced recovery; neurodevelopmental training is generally less effective than task-oriented training for recovery of UE motor control and function [53, 54]. The low stimulation intensity of rTMS (90% resting motor threshold) may also have induced counterintuitive ipsilesional effects, as low-intensity rTMS can reduce excitability in the contralateral M1 of healthy subjects [55].

Future Directions

Despite years of investigation into modifying motor outcomes post-stroke with rTMS, studies delivering it early post-stroke remain relatively rare. As discussed above, there is increasingly strong evidence from animal models that rTMS engages cellular and synaptic mechanisms that support plasticity, which builds a mechanistic rationale for its use in stroke. The clinical evidence for efficacy after stroke in humans, however, is less robust. For definitive determination of efficacy, the field still requires large, well-designed phase III trials of rTMS administered in the first weeks after stroke, with motor impairments measured well after the stimulation period to determine enduring efficacy.

Other important methodological considerations should be kept in mind. First and foremost, NIBS studies (and neurorehabilitation studies in general) need to better account for the content and amount of rehabilitation training performed during the study. What and how much is trained during "conventional therapy" varies by therapist, patient, and institution; unfortunately, only 2–5% of stroke recovery trials have reported training dose [56]. In animal stroke models, higher training doses lead to greater gains in behavioral function [57]. Thus training doses that are not matched across stimulation groups would not only directly contribute to different behavioral results, but would also be differentially potentiated by stimulation—a combination leading to an over- or underestimation of NIBS effects. Lack of reporting also limits generalization of the intervention to clinical practice. To ensure that observed NIBS effects are not attributable simply to differences in training we have begun to develop an approach to objectively measure rehabilitation training dose [58].

A second methodological point is that the timing of rehabilitation training relative to brain stimulation needs to be clearly reported. As discussed above, rTMS may act by facilitating associative plasticity and/or by activating homeostatic mechanisms. Which effect predominates is likely determined by the timing of training relative to stimulation. This documentation is not only important for generalization to clinical practice, but would also further clarify the primary plasticity-engaging mechanisms of rTMS.

Third, the parameter space of rTMS is large, and optimal stimulation parameters for maximal clinical efficacy have yet to be identified. A good first step is the comparison of different frequencies and hemispheric targets within the same study [48, 51]. It is also important to model the spatial extent of the stimulation; two studies discussed above used a round coil [50, 51] whose stimulation is less focal than the conventional figure-of-eight coil [2]. This raises an interesting possibility that modulating wider swaths of perilesional cortex might be an effective approach in the post-stroke brain, which has yet to be investigated. Overall, iTBS/cTBS appear to generate more consistent neurophysiological effects across individuals [4••], but whether these excitability effects translate to more consistent behavioral effects, particularly after stroke, remains to be determined.

Finally, the optimal patient characteristics that predict benefit from rTMS are not completely known. Inter-individual variability in excitability changes from stimulation has long been recognized [4••], and the response of plasticity mechanisms to stimulation may similarly follow suit. Particularly after stroke, the application of rTMS will likely not be monolithic. Investigators will need to determine how rTMS interacts with ischemic versus hemorrhagic stroke, the extent of ipsilesional damage, the extent of ipsilesional and contralesional pathway

upregulation, the timing post-stroke, and the patient's genetic makeup (e.g., BDNF polymorphism), among others. Clearly, there is much work still to be done.

Conclusions

The administration of rTMS in humans early after stroke is in its infancy. Mechanistically, rTMS may engage the injury-induced plasticity elicited by the stroke, potentiate the associative plasticity elicited by rehabilitation training, induce homeostatic plasticity, or act by some combination of all. A handful of recent studies the first months after stroke have shown promising reductions in motor impairment when rTMS is given in conjunction with rehabilitation training. Although large well-designed clinical trials are still needed in this post-stroke critical period, preliminary evidence points to modest efficacy of early rTMS to potentiate UE motor recovery.

Compliance with Ethical Standards

Conflict of Interest Heidi M. Schambra reports grants from NIH/NINDS during manuscript preparation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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