Transcranial Magnetic Stimulation in the Treatment of Neurological Disease

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ABSTRACT

Transcranial magnetic stimulation (TMS) holds great potential in the treatment of a host of neurological conditions due to its ability to focally modulate—suppress or enhance—activity in targeted cortical brain regions and modify activity across specific brain networks. Results from early trials in a number of neurological indications are presented, including stroke rehabilitation, Parkinson’s disease, tinnitus, chronic pain, migraine, and epilepsy. We emphasize both the challenges, such as the limited efficacy to date in tinnitus, as well as the opportunities, such as the use of TMS in epilepsy caused by focal/cortical lesions. However, to establish TMS as a clinically valuable neurological therapeutic intervention, a number of hurdles must be overcome, including accurate targeting of the treatment, characterization of its therapeutic benefit for specific patients/symptoms, proof of efficacy in multicenter trials that are adequately blinded and powered, proof of the durability of the effects, and assessment of potential adverse effects of cumulative dose and repeated application. [Psychiatr Ann. 2014; 44(6):299–304.]

Transcranial magnetic stimulation (TMS) utilizes electromagnetic induction to generate current in human brain tissue, thereby influencing cortical excitability and modulating behavior. Over the past two decades, there has also been a concerted effort to develop the therapeutic potential of TMS for a wide variety of neuropsychiatric disorders. This effort has had the most success in the treatment of depression, where the beneficial effects of TMS have been established in large multicenter trials, approval from the U.S. Food and Drug Administration (FDA) has been obtained, and TMS has been adopted into clinical practice. Outside of depression, the therapeutic potential of TMS has also been explored in a wide range of neurological conditions. Preliminary results are promising, with beneficial effects often seen in disorders with limited therapeutic alternatives. However, challenges remain as many of the studies are small, efficacy is variable, and the clinical utility is uncertain. Despite these limitations, TMS holds great promise in the therapeutic armamentarium for neurology, but its broader application in clinical practice will require larger multisite controlled...
studies with precise, mechanistically based anatomical targets and optimized stimulation parameters. In this article, we provide a qualitative overview of evidence for the use of TMS in the treatment of neurological disease.

GENERAL CONSIDERATIONS

Reported applications of TMS in the treatment of neurological diseases are growing rapidly. In part, this intense exploration of the clinical utility of TMS is driven by some unique features of this technology, which include the ability to focally target a specific brain region or brain circuit without producing any systemic side effects (in contrast to pharmacological therapy), and the ability to directly engage and utilize cortical plasticity mechanisms. Nonetheless, efficacy and clinical utility remain elusive, in large part due to the fact that TMS modulates activity in specific brain networks that map onto specific symptoms or disabilities of a given disease, rather than more globally reversing the pathophysiology of the disease itself. In this sense, TMS might be better conceptualized as a potential therapeutic intervention to target core symptoms of neurological disorders (eg, slowness of movement, impulse control problems, pain), regardless of the underlying disease, rather than as a therapeutic alternative for a given etiopathogenic entity.

Although most published studies report beneficial results, many are small, proof-of-principle studies, the placebo response may be substantial, and the adequacy of blinding regarding the treatment intervention is a significant concern. In particular, the production of a sham coil that is capable of producing similar tactile and auditory stimulation of “real” stimulation but does not produce cortical activation has proven quite challenging. For this reason, the results of crossover designs are difficult to interpret with confidence, and parallel-group studies are necessary to truly establish efficacy. In the current article, we concentrate on the results of randomized, parallel-group, sham-controlled studies. Because clinical significance requires durable effects (at least when discussing the use of TMS in chronic disease), we also emphasize studies with multiple sessions, in which the effects of treatment were assessed at least several days after the end of stimulation. Of note, in the United States, FDA approval for the use of TMS in neurological conditions has only been obtained for a device and treatment protocol for the abortive therapy of migraine.

MOTOR REHABILITATION AFTER STROKE

After motor stroke, the reorganization and recruitment of intact secondary motor pathways, both ipsi- and contralesionally, are involved in the residual...
function and recovery of the affected limb.\(^3\) However, relative hyperactivity of the contra-lesional primary motor cortex may cause excess transcallosal inhibition of the lesioned hemisphere,\(^4\) thereby limiting functional recovery. Consequently, TMS trials have attempted to increase the excitability of the lesioned hemisphere, decrease the activity of the unaffected motor cortex, or both (\textbf{Table 1}).

In one seminal early randomized sham-controlled trial involving 52 patients in the acute phase of stroke recovery, a 10-day course of standard rehabilitation therapy combined with high-frequency repetitive TMS (rTMS) to ipsi-lesional primary motor cortex (M1) improved motor function compared to sham stimulation.\(^5\) Several subsequent studies have generally (but not always) reproduced positive effects of high-frequency ipsi-lesional rTMS, with sustained benefits.\(^6\) Low-frequency stimulation of the contra-lesional hemisphere has also been studied in several trials. In one early study,\(^7\) five sessions of low-frequency rTMS were applied to the contra-lesional M1 of 15 patients with chronic (>1 year) stroke, aiming to suppress cortical excitability. Real stimulation resulted in significant motor improvement in the affected (paretic) hand, with benefits persisting for at least 2 weeks. However, subsequent trials have had mixed results, with only some demonstrating a benefit from contra-lesional stimulation. Parallel-group, sham-controlled studies comparing high-frequency ipsi-lesional versus low-frequency contra-lesional stimulation have also yielded inconsistent findings, with no pattern consistently demonstrating superiority across studies. Recent preliminary work in chronic stroke patients suggests that application of both contra- and ipsi-lesional rTMS may be superior to either protocol alone.\(^8\) Meta-analyses assessing whether rTMS has beneficial effects in motor stroke recovery have had conflicting results, with one recent study suggesting a clear and significant benefit\(^6\) while another did not.\(^9\)

In summary, results from a number of studies suggest that rTMS may aid in motor recovery after stroke, with benefits seen up to 1 year after intervention; however, there is considerable heterogeneity in results across trials, and different stimulation parameters appear to be needed depending on cortical target (contra- versus ipsi-lesional). In this context, it is important to realize that the widely held assumption that high-frequency rTMS enhances activity in the targeted cortical region, while low-frequency rTMS suppresses it, remains insufficiently demonstrated, might be different across brain regions and in patient populations, and shows substantial interindividual variability. Further studies with adequate sample sizes are needed that carefully measure the individual effect of rTMS and address issues of optimal timing of stimulation (acute, subacute, or chronic setting), location of stimulation (ipsi-lesional, contra-lesional, or bilateral), and whether combining brain stimulation with rehabilitation techniques might further enhance recovery. The latter is a particularly appealing therapeutic approach but will also require careful study of the optimal timing for the combination (eg, should brain stimulation and other interventions be applied one after the other or concomitantly?).

### TABLE 1.

<table>
<thead>
<tr>
<th>Condition</th>
<th>(N)</th>
<th>Target and Efficacy(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor stroke</td>
<td>515</td>
<td>Ipsilesional M1 (+/-), contralesional M1 (+/-), bilateral M1 (+)</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>343</td>
<td>M1 (+/-), SMA (+), DLPFC (-), vertex (-), lateral cerebellum (-)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>299</td>
<td>Left auditory cortex/left temporal lobe (+/-), left temporoparietal junction (-)</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>230</td>
<td>M1 (+/-), DLPFC (+/-), vertex (-), secondary somatosensory cortex (+)</td>
</tr>
<tr>
<td>Migraine</td>
<td>164</td>
<td>Primary occipital cortex (+)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>148</td>
<td>Single superficial neocortical focus or malformation of cortical development (+), deep seizure focus (-), vertex (-)</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>70</td>
<td>Dorsolateral prefrontal cortex (+)</td>
</tr>
<tr>
<td>Hemispatial neglect</td>
<td>63</td>
<td>Left posterior parietal cortex (+), right parietal cortex (+)</td>
</tr>
<tr>
<td>Aphasía</td>
<td>22</td>
<td>Right inferior frontal gyrus, pars triangularis (+)</td>
</tr>
</tbody>
</table>

DLPFC = dorsolateral prefrontal cortex; M1 = primary motor cortex; SMA = supplementary motor area; TMS = transcranial magnetic stimulation.

\(^a\) Includes the number of patients within peer-reviewed, published randomized, parallel-group placebo-controlled clinical trials with clinical outcomes measured at least 1 week after the end of treatment, as of June 1, 2013.

\(^b\) The efficacy of target sites is rated based on the presence of positive and/or failed trials (+ At least one trial reporting a significant effect of repetitive TMS (rTMS) over sham; – One or more trials reporting no significant effect of rTMS over sham).
MOVEMENT DISORDERS

The strongest evidence for the clinical utility of focal brain stimulation comes from the success of deep brain stimulation (DBS) in movement disorders. It is thus appealing to explore whether the success of DBS in these patients can be replicated with noninvasive brain stimulation. Randomized controlled trials including more than 300 Parkinson’s disease (PD) patients have investigated the impact of rTMS on PD movement scores (Unified Parkinson’s Disease Rating Scale III), dyskinesias, or depression. High-frequency stimulation of M1 has shown beneficial results, and may be more effective than stimulation at other sites (ie, supplementary motor area [SMA], dorsolateral prefrontal cortex [DLPFC], vertex, or lateral cerebellum), which have generally shown nonsignificant effects (with the exception of SMA). However, the effects of M1 stimulation have been heterogeneous across trials, emphasizing the need for multisite studies based on the specific parameters used in successful trials. Of note, repeated sessions of high-frequency rTMS to the left DLPFC, although not effective for treatment of motor symptoms, does appear to improve depression in patients with PD. Outside of PD, the only parallel-group, randomized controlled trial of rTMS is for spinocerebellar ataxia, where a single study has reported that cerebellar rTMS can have a beneficial effect on walk time.

TINNITUS

Tinnitus is the phantom perception of sound or noise in the absence of an acoustic stimulus. A number of placebo-controlled trials have explored the utility of repeated sessions of rTMS therapy, typically targeted to the left or contralateral (to the side of tinnitus in patients with unilateral tinnitus) secondary auditory cortex or temporal/parietal junction, with variable results. A recent Cochrane meta-analysis concluded that there is very limited support for the use of rTMS for the treatment of patients with tinnitus. In the largest study to date, published after the Cochrane analysis, low-frequency rTMS to the area within the auditory cortex of maximal activity in a positron emission tomography produced no improvement over sham stimulation on the principal outcome measure, although beneficial results were reported on some secondary measures. Overall, although some early studies have promising results, these findings have not been consistently replicated. Indeed, across all parallel-group studies in tinnitus, the mean improvement with rTMS over sham 1 month after the end of stimulation is often less than 10%, suggesting that any observed benefit is of relatively small magnitude and of rather questionable clinical significance. The reasons for these disappointing results are elusive, given a known cortical target that can be reached with rTMS. Auditory information is represented bilaterally in the cortex, however, perhaps requiring bilateral stimulation.

CHRONIC PAIN

TMS trials have attempted to normalize dysregulated corticothalamic pain networks across a wide range of conditions. Most studies apply high-frequency rTMS to M1, perhaps because of extensive projections to the thalamus and subthalamic structures. Randomized parallel-group, sham-controlled studies applying high-frequency rTMS to M1 have demonstrated beneficial results in chronic neuropathic pain, fibromyalgia, and complex regional pain syndrome, with some studies demonstrating sustained benefits with continued intermittent stimulation. One recent study in fibromyalgia patients also demonstrated improvements in quality of life. Stimulation of other regions has shown more heterogeneous effects. Of note, the individual response to rTMS therapy is significantly correlated with the response to subsequent epidural motor cortex stimulation, suggesting that rTMS might be useful to help guide the decision as to whether the implantation of an intracranial stimulator is appropriate. However, studies involving transcranial current stimulation (tCS) may have more consistently beneficial effects and may be more straightforward to implement clinically. Further research is needed to assess for impact on quality of life, the durability of benefits, the independent effect on depression, and the efficacy when used in combination with other treatment modalities.

MIGRAINE

One large double-blind, parallel-group, sham-controlled, randomized trial study reported utility of single-pulse TMS as an abortive therapy for acute migraine. A total of 201 adult patients with migraine headaches were randomized to receive either real or sham single-pulse TMS therapy to the occiput. TMS resulted in significantly higher pain-free response rates than sham stimulation at 2, 24, and 48 hours. Based on these results, FDA approval was obtained for the device (Spring TMS Total Migraine System, eNeura Inc., Baltimore, MD) in 2013. It is worth noting, however, that in the above trial, many clinically relevant secondary endpoints were negative, including headache response, global relief, and total disability time. In chronic migraine, preliminary small studies have suggested beneficial effects of high-frequency rTMS to the left dorsolateral prefrontal cortex, but not over the vertex.

EPILEPSY

Epilepsy, a disorder characterized by recurrent seizures, is thought to be due to cortical network hyperexcitability. Several studies have attempted to suppress excess cortical excitability in patients with medication-refractory epilepsy. The results appear inconsistent, with some trials demonstrating a significant, sustained reduction in seizure frequency, whereas others showed no
significant benefit of rTMS. The inconsistency is likely due to the variability of patient populations, as well as distinct rTMS methodologies used in each trial. Specifically, studies applying rTMS directly to superficial epileptogenic foci demonstrated more consistent benefit than disorders with deep or multifocal foci,\textsuperscript{23} likely because of the spatially restricted effect of rTMS, emphasizing the importance of appropriate patient selection and navigated application (Table 1). A recent sham-controlled, single-institution study with a large patient population supports these conclusions.\textsuperscript{24} On a related note, in the single largest published series of rTMS therapy for the treatment of epilepsy partialis continua, rTMS therapy resulted in durable cessation of seizure activity in 2 of 7 patients.\textsuperscript{25} Larger multisite studies are necessary to confirm the beneficial effects of rTMS in patients with focal epilepsy.

COGNITIVE REHABILITATION

TMS has also been applied in cognitive rehabilitation of patients with post-stroke aphasia and hemispatial neglect, and in neurodegenerative disorders such as Alzheimer’s disease and frontotemporal dementia. In aphasia, most trials have focused on low-frequency stimulation to the right hemispheric homologue of Broca’s area, in the right inferior frontal gyrus. Although several small studies have shown a benefit, small changes in the location of stimulation can produce opposite effects, the trials that have been conducted are typically small (<25 patients), the clinical significance of the observed improvements is uncertain, the optimum target of stimulation debated, and the most appropriate combination with speech therapy undetermined.\textsuperscript{26, 27}

In hemispatial neglect, small therapeutic trials of rTMS have shown fairly consistent promising results. Driven by the framework that neglect is driven by an altered interhemispheric balance of spatial attention, most trials have evaluated the impact of low-frequency rTMS protocols on the intact left parietal region. One sham-controlled randomized trial applied serial sessions of continuous theta-burst TMS (cTBS) to the left parietal region, with the assumption that this will suppress cortical activity in the targeted brain region, and demonstrated significant improvements in visuospatial neglect for 2 weeks.\textsuperscript{28} Critically, another study demonstrated that repeated sessions of cTBS not only decreased spatial neglect but also reduced disability in activities of daily living.\textsuperscript{29} Larger, multisite randomized clinical trials are necessary to confirm and extend the above findings.

In Alzheimer’s disease, small pilot studies have also reported beneficial effects with high-frequency stimulation of the dorsolateral prefrontal cortex on specific cognitive functions, notably attention and working memory. One recent small pilot study in 15 patients tested the utility of repeated sessions of high-frequency real versus sham stimulation to six different sites, in combination with (real vs. sham) cognitive training, with the aim of affecting multiple cognitive domains.\textsuperscript{30} Beneficial effects with real stimulation/cognitive training were noted several months after the start of treatment. However, the study design does not permit an assessment of whether the observed benefit is due to TMS or cognitive training. No large-scale, parallel-group trials of TMS in Alzheimer’s disease have been reported to date.

OUTSTANDING ISSUES, PRACTICAL CONSIDERATIONS, AND FUTURE DIRECTIONS

Current studies support the notion that TMS holds promise as a therapeutic option in neurological disorders, with significant variability across conditions. However, most studies are relatively small randomized, placebo-controlled, parallel-group trials limited in number, the induced effects somewhat variable, and the question of what interventions to combine with TMS to maximize the effects underexplored.

One particular concern in future clinical trials is the need for adequate sham stimulation.\textsuperscript{2} TMS produces a tapping sensation with stimulation of trigeminal afferents, an auditory “clicking” sound in which bone conduction plays a significant part, and contraction of the frontalis and temporalis muscles at higher intensities. Tilting the coil at 90 degrees, a commonly used sham technique, avoids these sensations, which can lead to unblinding. Although sham coils have been constructed, the adequacy of blinding has not been rigorously assessed within clinical trials. The difficulty of constructing an adequate sham emphasizes the importance of a parallel-group design and TMS-naïve subjects.

Careful target selection is another critical issue. The importance of precise targeting has been best demonstrated in epilepsy, where rTMS targeted specifically to the seizure focus has a significant benefit, whereas rTMS to other regions has no effect.\textsuperscript{23} Similarly, efficacy in treating stroke-induced aphasia treatment may require the precise stimulation of the pars triangularis versus opercularis.\textsuperscript{26} The use of neuroimaging and frameless stereotaxy to spatially guide stimulation may increase efficacy across future trials. As mentioned above, TMS modulates activity in specific brain networks that map onto specific symptoms or disabilities, regardless of the disease that is causing them. In this sense, TMS might be better conceptualized as a potential therapeutic intervention to target core symptoms of neurological disorders. Thus, clinical trials have to be properly designed, and careful patient selection and characterization is crucial.

Further insights into the impact of TMS on local and network brain activity are also needed. The common talk of “inhibitory” versus “excitatory” rTMS is potentially misleading. The widely held assumption that high-frequency rTMS enhances activity in the targeted cortical region whereas low-frequency rTMS suppresses it re-
mains insufficiently demonstrated, might be different across brain regions and in patient populations, and shows substantial interindividual variability.

An overarching concern regarding the studies to date is that almost all of the trials have been conducted at single institutions, and multisite studies with larger sample sizes are critically needed to establish the generalizability across centers and patient populations.

Despite all these limitations and the need for future studies, the available evidence supports the potential clinical utility of TMS in some neurological conditions, many of which have few alternative therapeutic options. Ultimately, proof of clear therapeutic benefit and integration into broad clinical practice is likely to require multicenter, parallel-group, placebo-controlled clinical trials conducted with a clear rationale for application of a particular protocol to a specific site, data-driven hypotheses of expected effects, careful patient selection, and individualized neuronavigated stimulation.

REFERENCES

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