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ORIGINAL ARTICLE

Transcranial Magnetic Stimulation in Neurology: What We Have Learned From Randomized Controlled Studies

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ABSTRACT

Background. Initially developed to excite peripheral nerves, magnetic stimulation was quickly recognized as a valuable tool to noninvasively activate the cerebral cortex. The subsequent discovery that repetitive transcranial magnetic stimulation (rTMS) could have long-lasting effects on cortical excitability spawned a broad interest in the use of this technique as a new therapeutic method in a variety of neuropsychiatric disorders. Although the current outcomes from initial trials include some conflicting results, initial evidence supports that rTMS might have a therapeutic value in different neurologic conditions. **Methods.** We reviewed the results of clinical trials of rTMS on four different disorders: stroke, Parkinson's disease, chronic refractory pain, and epilepsy. We reviewed randomized, controlled studies only in order to obtain the strongest evidence for the clinical effects of rTMS. **Results.** An extensive literature review revealed 32 articles that met our criteria. From these studies, we found evidence for the therapeutic efficacy of rTMS, particularly in the relief of chronic pain and motor neurorehabilitation in single hemisphere stroke patients. Repetitive TMS also seems to have a therapeutic effect on motor function in Parkinson's disease, but the evidence is somewhat confounded by the uncontrolled variability of multiple factors. Lastly, only two randomized, sham-controlled studies have been performed for epilepsy; although evidence indicates rTMS may reduce seizure frequency in patients with neocortical foci, more research is needed to confirm these initial findings. **Conclusions.** There is mounting evidence for the efficacy of rTMS in the short-term treatment of certain neurologic conditions. More long-term research is needed in order to properly evaluate the effects of this method in a clinical setting.

KEY WORDS: *Chronic pain, epilepsy, Parkinson's disease, randomized clinical trials, stroke, transcranial magnetic stimulation.*

Introduction

Transcranial Magnetic Stimulation: Basic Principles

Magnetic stimulation was a tool developed initially for peripheral nerve excitation. However, scientists quickly realized its valuable potential to stimulate the brain cortex in a noninvasive and painless way (1). This technique is based on a fundamental law of electromagnetic physics: That current running through a wire produces a magnetic field, and conversely, that a changing magnetic field can induce a current in an electrical conductor. In transcranial magnetic stimulation (TMS), a strong alternating electric current is run through a coil of wire, creating a changing magnetic field that can be focused and restricted to small areas depending on the coil geometry

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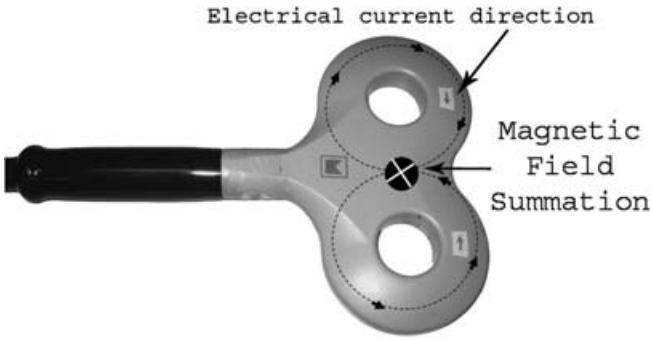

FIGURE 1. A figure-of-eight coil.

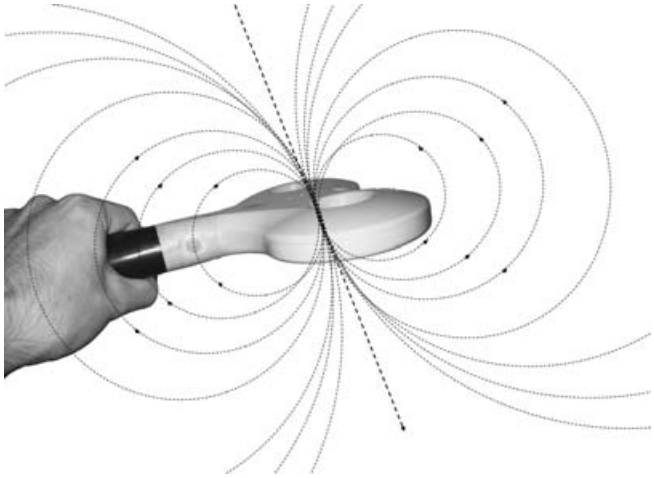

FIGURE 2. Figure-of-eight coil and approximate magnetic field lines.

and shape (2). For example, a figure-of-eight coil (Figs 1 and 2) will produce a more focused magnetic field than will a circular coil.

Thus, if one can imagine the brain's neurons as tiny wires, it is now possible to see how transcranial magnetic stimulation works: The magnetic field from the coil passes unimpeded through the skin and bone of the skull, interacting with the wire-like neurons of the cortex. Because the field is rapidly changing, it is able to induce a current in the neurons (axons), forcing action potentials to occur. For example, a TMS "pulse" applied to the primary visual cortex often induces small visual apparitions called phosphenes in human subjects (Fig. 3).

Initial physiologic studies showed two main characteristics that render TMS a valuable tool for the treatment of neuropsychiatric disorders: 1) duration of the effects: The effects of repetitive TMS (rTMS—ie, when several pulses are applied consecutively) on cortical excitability outlasts the period of stimulation (3,4); 2) opposite modulatory effects can be induced such that either a facilitation or an

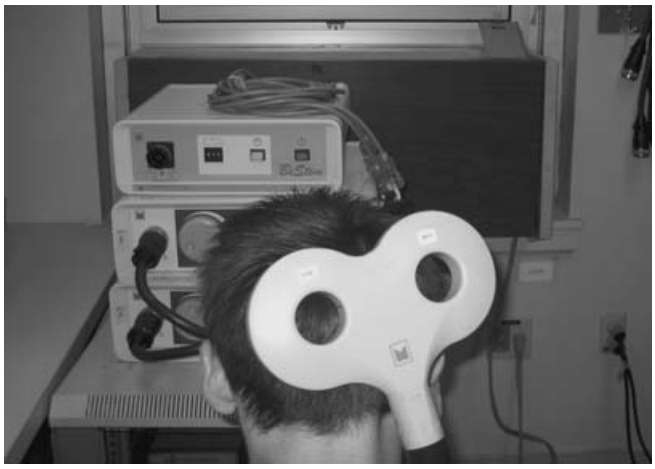

FIGURE 3. A subject receiving transcranial magnetic stimulation (TMS) over his occipital cortex.

inhibition of cortical activity is possible depending on the frequency of stimulation (3–5).

Several animal and human studies have established that rTMS modulates brain cortex activity noninvasively (6–11). This modulation may range from suppression to facilitation of activity in the targeted cortical area as measured by single-pulse TMS and neuroimaging techniques, depending on the stimulation parameters (particularly frequency of stimulation) (12,13). While low-frequency rTMS (1 Hz) decreases the excitability of targeted cortical regions resulting in measurable behavioral changes, high-frequency rTMS (20 Hz) often has the opposite effects (5,12), rendering this technique an attractive clinical tool.

Following these neurophysiologic data, several studies have been performed focusing on the use of rTMS to obtain clinical gains in neuropsychiatric diseases, such as in major depression, Parkinson's disease, and epilepsy. In the wake of these first studies, the use of rTMS for the treatment of major depression developed rapidly, whereas its uses in other neurologic conditions were slower to progress. Several reasons may account for this difference, including difficulty in patient enrollment, lack of clinical efficacy, mixed results, or less interest in alternative therapies.

Review Search Methods and Exclusion Criteria

This current study reviews the clinical studies of rTMS in four main areas of neurology: pain, epilepsy, stroke, and Parkinson's disease. In order to provide a reliable report, we included only the randomized, placebo-controlled studies published in English and German from January 1985 to August 2006 that aimed to evaluate the clinical effects of rTMS in one of these conditions. We therefore excluded case reports, open studies, or studies written in languages other than English or German.

For each one, a framework was designed in which we summarize the available data, discuss the potential limitations and suggest the future perspectives. Relevant articles in the four main areas of focus were found using the following search criteria on the Pubmed database (www.pubmed.gov): "transcranial magnetic stimulation" and "stroke," "Parkinson's disease," "epilepsy," or "pain," respectively.

Mechanisms of Action

Several neuroimaging and animal studies have been performed to investigate the mechanisms of action of rTMS. Although this research does not provide conclusive evidence, it gives some insight into the effects of this therapy in modifying clinical symptoms of several neurological disorders.

Neuroimaging studies have been an important tool in helping to elucidate the mechanisms of action of rTMS. In summary, these studies show that rTMS 1) changes the concentration of neurotransmitters, such as glutamate and dopamine, and 2) changes brain activity both locally and distantly. A recent study by Luborzewski et al. using the technique of magnetic resonance spectroscopy in 17 patients with depression showed that 10 days of high-frequency rTMS (20 Hz) increased the concentration of glutamate in the site of stimulation (dorsolateral prefrontal cortex). In addition, the author found correlations between the intensity of stimulation and clinical changes with glutamate concentration (14). Another study has shown that 10 Hz rTMS of the dorsolateral prefrontal cortex, but not parietal cortex, induces a significant release of dopamine in the caudate nucleus as evaluated using raclopride—a marker of dopamine release—and positron emission tomography (15). This study also provides support for the use of TMS in patients with Parkinson's disease.

Neuroimaging studies also have elucidated rTMS's capability of modifying both local and distant (from the site of stimulation) neural activity. For instance, while investigating the effects of rTMS in patients with major depression, Loo et al. (16) found a differential effect on cerebral blood flow (CBF) with different stimulation frequencies. High-frequency rTMS (15 Hz) increased CBF in the inferior frontal cortices and cingulate gyrus, and decreased it in the right orbital frontal cortex, subcallosal gyrus and left uncus. Low-frequency rTMS led to increases of CBF in the right anterior cingulate, bilateral parietal cortices and insula, and the left cerebellum (16). These results show that rTMS can have both a local and widespread effect, depending on rTMS parameters, such as frequency and intensity of stimulation. In addition, Fregni et al. (17) showed in a recent study that high-frequency rTMS (15 Hz) in Parkinson's disease patients does not change the local activity of the left dorsolateral prefrontal cortex (DLPFC), but rather changes the activity in an extensive neural network associated with mood regulation—areas such as the prefrontal cortex and cingulate gyrus. Furthermore, these changes are not only correlated to clinical scores, but are also similar to the effects on CBF induced by fluoxetine, although this drug also leads to activity changes in other areas such as the occipital cortex (17). This evidence thus strongly supports the idea that, depending on the parameters of stimulation, rTMS can reliably change distant activity of an extensive neural network.

Animal studies confirm and extend these findings as they show that rTMS: 1) changes the concentration of neurotransmitters, and 2) changes cellular genetic expression. In two separate studies, the same group showed that rTMS induces similar behavioral effects as electroconvulsive therapy and electroconvulsive shock in rats: effects such as the enhancement of apomorphine-induced stereotypy, reduction of immobility in the Porsolt swim test and increases in seizure threshold for subsequent stimulation (18). Later, this group showed that nine days of rTMS change the beta-adrenergic receptor binding in cortex (18) and confirmed that it leads to changes in seizure threshold similar to the effects of electroconvulsive shock and electroconvulsive therapy (18). In addition, Juckel et al. showed that stimulation of the prefrontal cortex (with electrical current, but mimicking the parameters used in rTMS) leads to an increase in limbic serotonin output as measured by microdialysis (19).

Repetitive TMS has been shown to modulate gene expression. Initially, Ji et al. showed that rTMS induces a significant increase in *c-fos* expression in the paraventricular nucleus of the thalamus area and other areas controlling the circadian rhythms (20). Hausmann et al. confirmed these results, showing that rTMS treatment for 14 days increased the transcription factor *c-fos* in the parietal cortex and hippocampus (21). Finally, rTMS induces an increase of kf-1 in rat frontal cortex and hippocampus (22). Although these results are somewhat heterogeneous because they show an induction of different factors in different areas, one also must consider the fact that the experimental parameters varied considerably between experiments, suggesting that the effects of rTMS are specific to these stimulation parameters.

Finally, rTMS effects also have been correlated to a modulation of synaptic transmission. Indeed, an enhancement of synaptic efficiency with electric stimulation has been shown for several decades (23). A recent rTMS study has shown that a similar phenomenon can be induced in humans if stimulation is performed at 50 Hz (24).

Clinical Trials of rTMS in Stroke

Recent evidence has shown that cortical stimulation with either epidural stimulation (25), transcranial direct current

stimulation (26,27), or rTMS (28,29) induces a significant improvement in motor function. The rationale of using rTMS to promote rehabilitation in stroke is based on the dysfunctional brain activity that is correlated with functional motor deficits (30). Indeed, in a recent review, Humell and Cohen stated that "transcranial magnetic stimulation could develop into useful adjuvant strategies in neurorehabilitation" (31). We reviewed then the randomized studies in this area following the framework in this review.

Randomized Clinical Trials

Five studies met our inclusion criteria. In three of these studies, the healthy motor cortex was stimulated with low-frequency (inhibitory) parameters. In the first one performed by our group, inhibitory low-frequency rTMS applied to the unaffected (contralesional) motor cortex induced a significant transient improvement in motor function as indexed by simple reaction time, choice reaction time, and pegboard test (32). A few months later, Takeuchi et al. (33) found that 1 Hz stimulation of the unaffected hemisphere transiently increased acceleration in a pinching task. Later, Fregni et al. (28) showed that five days of inhibitory rTMS applied to the healthy hemisphere induces a long-lasting effect that lasts at least two weeks after the end of treatment (28).

Another strategy of stimulation is the use of high-frequency excitatory rTMS of the affected (ipsilesional) hemisphere. Initially, Khedr et al. (29) applied 3 Hz rTMS to the affected hemisphere over a 10-day period to 26 patients suffering from acute ischemic stroke. As compared to sham TMS, patients receiving active rTMS showed a significant improvement as measured by disability scales; Khedr and colleagues conclude that rTMS might be used as an add-on therapy to normal physical and drug rehabilitation in early stroke patients (29). Subsequently, another group confirmed these results showing that motor function improves in stroke patients when high-frequency stimulation (10 Hz) is applied to the affected cortical motor areas (34) (Table 1).

The authors of these five studies all concluded that TMS can improve the outcome of stroke patients, either through inhibiting the neural tissue of the unaffected hemisphere (in order to reduce the transcallosal inhibition to the affected hemisphere), or by stimulating the hemisphere where the stroke occurred. As there are only a few studies published, it is still difficult to conclude that strategy leads to a better outcome (ie, stimulation of the affected or unaffected hemisphere). Inhibitory rTMS on the healthy hemisphere has some advantages in the form of lower risk of seizure induction and increased prediction accuracy of stimulation location (stroke lesion disturbs the electric field in the affected hemisphere (35)). Further studies should compare these two strategies of stimulation.

Clinical Trials of rTMS in Chronic Refractory Pain

The mechanisms of chronic pain are still unknown; however, recent evidence suggests that it is associated with maladaptive changes in the central nervous system following disease or injury (36). Individuals who suffer chronic pain frequently fail to improve after pharmacologic treatment aiming at the peripheral modulation of pain. One alternative to modulating the central nervous system is the use of deep brain (37) (38), or epidural stimulation (39,40). Previous to the use of TMS, this technique was the most common nonpharmacologic, central treatment for chronic pain, in which electrodes were implanted in deep (such as the thalamic nuclei) or cortical (such as the motor cortex) areas of the brain. Thus, rTMS provides an attractive noninvasive alternative method of brain stimulation for medication-resistant chronic pain patients.

Randomized Clinical Trials

Twelve studies met our criteria for the clinical evaluation of rTMS and pain; several others (41–44) were excluded, being either an open label, case report, or an uncontrolled study. Lefaucheur et al. were the first group to explore rTMS and pain management in a series of placebo-controlled, randomized experiments (45,46). Initially, this group recruited a total of 28 patients, and used 20 min of rTMS stimulation over the area of the primary motor cortex corresponding to the perceived painful region of the body in an attempt to mimic analogous surgical stimulation procedures. These authors found that 10 Hz, but not 1 Hz stimulation, significantly reduced subjects' pain for an average duration of eight days as reported by a visual analog scale. In 2004, the same group expanded their sample size to 60 subjects, also testing a variety of chronic central pain disorders (such as thalamic stroke and trigeminal neuralgia), and confirmed that 10 Hz stimulation over the primary motor cortex (M1) is associated with a significant pain reduction. These results also were supported by Pleger et al. (47) in a sham-controlled, crossover experiment with 10 patients having complex regional pain syndrome. In this study, 10 Hz rTMS was applied to the hand area of M1, resulting in pain relief "within 30 sec," but lasting no more than 45 min post-TMS. Furthermore, Andre-Obadia et al. showed that 20 Hz, but not 1 Hz, rTMS of M1 reduces pain in a group of 14 patients with chronic pain due primarily (10 subjects) to stroke; however, sham stimulation also reduced pain in this study (48). Sham stimulation was applied using a real coil oriented perpendicular to the skull. Lastly, Canavero et al. found that 0.2 Hz stimulation over M1 seemed to produce analgesic effects in some patients, with just two trains of 10 stimuli at full output power. Patients who responded to TMS also reliably responded to the analgesic agent propofol with an $r = 0.89$ (49).

TABLE 1. rTMS and Stroke

Study	Coil shape	Site of stimulation	Stimulation parameters	Study design	*N*	Stroke characteristics	Outcome measures	Conclusions
Mansur et al. 2005 (32)	F8	Contralesional M1 and premotor areas	1 Hz, 600 pulses, 100% MT, 1 session	Crossover	10	Small vessel ischemic stroke, mild-moderate hemiparesis, subacute stroke (less than 1 years)	sRT, cRT, Perdue pegboard test, finger tapping	rTMS improves simple and choice reaction time as well as Purdue Pegboard test immediately following M1 stimulation only
Takeuchi et al. 2005 (33)	F8	Contralesional M1 (corresponding do FDI)	1 Hz, 1500 pulses, 90% MT, 1 session	Parallel	20	Subcortical infarction confirmed w/MRI, > 6 months after stroke	Pinch task (measuring force and acceleration)	Increased acceleration on pinch task and decreased transcallosal inhibition for active rTMS group; effects did not last to 30 min
Khedr et al. 2005 (29)	F8	Ipsilesional M1(correspondi ng to ADM)	3 Hz, 3000 pulses, 120% MT, 10 sessions	Parallel	52	Acute hemiplegia with single thromboembolic nonhemorrhagic infarction; 5–10 days poststroke	SSS, NIHSS, BI, MEP	Active rTMS patients improved significantly vs. sham treatment on NIH and Barthel Index Stroke scores at least 10 days poststimulation
Kim et al. 2006 (34)	F8	Ipsilesional M1 hand area	10 Hz, 160 pulses, 80% MT, 2 sessions 1 week apart	Crossover	15	Chronic hemiparetic stroke; > 3 months after stroke	Motor skill learning task: accuracy, RT, MEP amplitude	Active rTMS transiently increases motor skill learning, accuracy, RT; no long-term effects studied
Fregni et al. 2006 (28)	F8	Contralesional M1 (corresponding to FDI)	1 Hz, 1200 pulses, 100% MT, 5 sessions	Parallel	15	Single ischemic stroke, > 1 year after stroke; and mild to moderate motor deficit	JTT, sRT, cRT, Perdue pegboard test	Significant improvement across various motor tests lasting 2 weeks

ADM, abductor digiti minimi; BI, Barthel Index Scale; cRT, choice reaction time; F8, figure-of-eight; FDI, first dorsal interosseous; JTT, Jebsen-Taylor hand function test; M1, primary motor cortex; MEP, motor-evoked potentials; NIHSS, National Institutes of Health Stroke Scale; sRT, simple reaction time; SSS, Scandinavian Stroke Scale.

Khedr et al. (50) was the first group to study long-term pain relief by applying 20 Hz rTMS to M1 corresponding to the painful area over five consecutive days. They found substantial, significant pain relief (based on a visual analog scale) for both groups of their subjects—poststroke and trigeminal neuralgia—that lasted for two weeks post-treatment (50). However, in a recent study, Irlbacher et al. (51) failed to show positive effects of this therapy in patients with central and phantom limb pain. In the Irlbacher's study, they applied rTMS to M1 with a frequency of 1 Hz, 5 Hz, or 2 Hz sham for five consecutive days, and found no differences in pain amelioration across these three groups. Some methodological issues might account for this negative result such as 1) a high dropout rate—less than half of the patients completed this crossover study; 2) a short 18-day wash-out period—Khedr et al. showed that five consecutive days of stimulation can cause analgesic effects for at least two weeks—and 3) the study used 500 TMS pulses per session—a lower number as compared to other studies, most of which used more than 1000 pulses per session. Finally, it is possible that phantom limb pain is more resistant to treatment with rTMS, perhaps requiring higher intensities and doses of rTMS for effective analgesia as compared to other types of chronic pain.

Pain relief using rTMS also has been found while targeting areas other than M1. Fregni et al., in a preliminary study, evaluated both 1 and 20 Hz stimulation on right and left secondary somatosensory cortex (SII) in five patients

with visceral pain due to chronic pancreatitis. The results revealed a significant reduction in visceral pain for 1 Hz (right or left S1) or right SII (1 or 20 Hz) stimulation (52). Sampson et al. (53) found analgesic properties from 1 Hz stimulation of the right dorsolateral prefrontal cortex—an area often used to treat depression—in four patients with fibromyalgia. Finally, Hirayama et al. (54), exploring the effects of rTMS on different areas such as primary somatosensory cortex (S1), premotor area (pre-M), and supplementary motor area (SMA) as compared to primary motor cortex, showed that these other areas are not significantly associated with pain reduction for patients with intractable deafferentation pain (54). The summarized results of these studies can be found in Table 2.

The investigation of the use of rTMS for chronic pain has been developing rapidly, expedited in part by the extensive amount of literature reporting success in the use of epidural motor cortex stimulation in patients with refractory chronic pain; these results suggest that chronic pain is a condition that might greatly benefit from methods of brain stimulation, including rTMS. Further studies should explore alternative parameters and locations of stimulation, as the initial research into areas that also are part of the neural network of pain such as the somatosensory cortex (52) and the dorsolateral prefrontal cortex (53) has been promising and may help to maximize the clinical effects of rTMS in pain. Finally, if this treatment proves to be clinically useful, the long-term effects of this technique in chronic pain also need to be explored by large, randomized clinical trials; most of the current studies have evaluated the effects of a single session of rTMS and shown only temporary reductions in pain (a few days). Even the studies that applied longer regimens of stimulation (five sessions) showed benefits that lasted less than two months.

Clinical Trials of rTMS in Parkinson's Disease

Repetitive TMS also has been shown to be clinically useful for the treatment of Parkinson's disease, a neurodegenerative disorder of the brain's motor systems in elderly individuals. Current treatment protocols usually involve pharmacologic approaches that primarily alter the dopaminergic nitrostriatal pathways to alleviate common Parkinson's disease symptoms such as tremors and muscle rigidity (55). Nonpharmacologic approaches such as deep brain stimulation (56) and electroconvulsive therapy (57) have been shown to improve motor function significantly. Although several trials of rTMS for Parkinson's disease have been performed, they are difficult to compare as methodological discrepancies and the wide range of stimulation parameters that researchers use can cause interpretation difficulties (58). In an attempt to resolve some of these conflicts, Fregni et al. (57) conducted a meta-analysis of 12 existing studies that evaluated the effects of rTMS (and also electroconvulsive therapy) on motor function in Parkinson's disease patients using the Unified Parkinson's Disease Rating Scale (UPDRS), and concluded that rTMS has a significant, positive effect on motor function in Parkinson's disease. The data from many of the studies included in the Fregni's analysis, plus an additional few randomized, controlled studies are summarized in Table 3.

Randomized Studies Published

We found 13 studies that fit our criteria for this review. Due to the large variation in stimulation parameters and results, we organized this section of the review according to 1) area of target stimulation and 2) rTMS effects on motor function (improvement vs. worsening).

The M1 was the most common target area. In a series of two experiments, Siebner et al. applied a single session of 5 Hz stimulation to the M1 hand area and found a significant—albeit transient—improvement in both reaction time (on a pointing task) as well as bradykinesia, rigidity & tremor scores on the UPDRS (59,60). Sommer et al. in a similar study (single session of 1 Hz stimulation on M1) also found transient improvement in bradykinesia as measured by a finger tapping task (61). The first study evaluating repeated sessions of rTMS of M1 was in 2003, when Khedr et al. stimulated the M1 hand and lower limb area using a frequency of 5 Hz for 10 consecutive days, and achieved significant improvements in UPDRS movement scores for at least one month. Lastly, Lefaucheur et al. tried both 0.5 and 10 Hz stimulation of left M1, and found that either frequency significantly improves motor function for 20 min poststimulation as measured by UPDRS: While low frequencies improve motor skills bilaterally, high-frequency stimulation improves bradykinesia and rigidity contralaterally (62).

On the contrary, other studies have shown that stimulation of M1 does not improve motor movements. One study applying 5 Hz stimulation to the hand area of M1 found no significant improvement in UPDRS motor scores (63). Another report by Okabe et al. also investigated the effects of repeated sessions of M1-targeted rTMS on motor function; in contrast to the study of Khedr et al., they found no significant effects more than 16 weeks. However, the stimulation parameters were quite different between the two studies: Whereas Khedr et al. used 5 Hz stimulation with a figure-of-eight coil over 10 consecutive days, Okabe used 0.2 Hz stimulation with a circular coil once a week for eight weeks. It has been shown that repeated sessions of rTMS—when repeated within 24 hours but not after one week—lead to cumulative long-lasting changes in cortical excitability (64). Besides the interval of one week, other parameters are quite different between Khedr and Okabe's study, making the comparison between both difficult (65,66).

TABLE 2. rTMS and Chronic Pain

Study	Stimulation site	Stimulation parameters	Study design	*N*	Etiology of pain	Outcome measures	Conclusions
Lefaucheur et al. 2001 (45)	M1 corresponding to the painful area	10Hz, 1000 pulses, 80% MT, 1 session	Crossover	14	Trigeminal neuralgia, thalamic stroke	Visual analog scale	Significant but transient reduction in pain
Lefaucheur et al. 2001 (46)	M1 corresponding to the painful area	10 Hz and 1 Hz, 1000 pulses, 80% MT, 1 session	Crossover	18	Thalamic stroke, brainstem lesion, brachial plexus lesion	Visual analog scale	Significant but transient reduction in pain only after 10 Hz rTMS
Canavero et al. 2002 (49)	M1 corresponding to painful area	0.2 Hz, 20 pulses, 100% machine output, 1 session	*a	9	Brain ischemia, spinal cord injury or syringomyelia	Visual analog scale/numerical rating scale	Mixed results, 3 out of 9 patients reported significant pain relief for not more than 16 hours. The TMS pain relief also was strongly correlated to propofol-induced pain relief.
Brighina et al. 2004 (78)	Left dorsolateral prefrontal cortex	20 Hz, 400 pulses, 90% MT, 12 sessions every other day	Parallel	11	Chronic migraine	Number of migraine attacks, number of ingested pills	Significant long-term reduction in both number of headaches as well as amount of medicine ingested; effects lasted for at least 2 months after treatment
Lefaucheur et al. 2004 (62)	M1 corresponding to the painful area	10 Hz, 1000 pulses, 80% MT, 1 session	Crossover	60	Thalamic stroke, brainstem lesion, brachial plexus lesion, spinal cord lesion, trigeminal nerve lesion	Visual analog scale	Significant but transient reduction in pain
Pleger et al. 2004 (47)	M1 of the hand area	10 Hz, 120 pulses, 110% MT, 1 session	Crossover	10	Minor trauma, radial fracture, luxation of 2nd and 3rd fingers, fracture of navicular	Visual analog scale	Reduction in pain for 45 min
Khedr et al. 2005 (50)	M1 corresponding to the painful area	20 Hz, 2000 pulses, 80% MT, 5 consecutive days	Parallel	48	Trigeminal neuralgia, poststroke	Visual analog scale, LANSS	Significant reduction in pain, up to 2 weeks poststimulation
Fregni et al. 2005 (52)	Right secondary somatosensory cortex	1 Hz, 1600 pulses, 90% MT, 1 session	Crossover	5	Chronic pancreatitis (visceral pain)	Visual analog scale	Significant but transient reduction in pain
Hirayama et al. 2006 (54)	M1 corresponding to the painful area and somatosensory, premotor and supplementary area	5 Hz, 500 pulses, 90% MT, 1 session	Crossover	20	Post-stroke, spinal cord lesion, trigeminal neuropathy, brachial plexus injury, peripheral neuroma operation, cauda equina lesion	Visual analog scale, McGill pain questionnaire	Significant reduction in pain after M1 stimulation only as compared to other areas of stimulation
Sampson et al. 2006 (53)	Right dorsolateral prefrontal cortex	1 Hz, 1600 pulses, 110% MT; 5 x/week for 4 weeks	*b	4	Fibromyalgia	Visual analog scale	15–27 week reduction in pain across all four subjects
Irlbacher et al. 2006 (51)	M1 corresponding to pain	1 and 5 Hz, 500 pulses, 95% MT, 5 consecutive days	Crossover	27	Central and phantom limb pain	Visual analog scale	No significant effects compared to sham group
Andre-Obadia et al. 2006 (48)	M1 hand area (abductor digiti minimi)	1 and 20 Hz, 1600 pulses, 90% MT, 1 session each	Crossover	14	Central supratentorial or brain-stem poststroke pain, spinal cord injury, peripheral lesion	Visual analog scale, global subjective assessment	Pain improvement after 20 Hz and sham stimulation, but not after 1 Hz stimulation. Only 20 Hz stimulation predicted the efficacy of subsequent invasive motor cortex stimulation

All studies in this table used figure-of-eight coils; LANSS, Leeds assessment of neuropathic symptoms and signs.
*a—Study design specifics, control conditions, as well as the blinds for the study were not given. A crossover design is most likely.
*b—Part of a double-blind sham-controlled trial for major depression and borderline disorder; only one patient received sham stimulation.

TABLE 3. rTMS and Parkinson's Disease

Study	Coil shape	Site of stimulation	Stimulation parameters	Study design	*N*	"On-off" status	Outcome measures	Conclusions
Siebner et al. 1999 (59)	F8	M1 hand area contralateral to affected limb	5 Hz, 1000 pulses, 90% MT, 1 session	Crossover	12	"Off" state	Pointing RT and accuracy	Reaction time for pointing movements decreased transiently after active rTMS, accuracy not affected
Ghabra et al. 1999 (63)	F8	M1 of the dominant hemisphere	5 Hz, *a, 80–85% MT, 1 session	Crossover	11	"Off" state	UPDRS	No significant effects as measured directly following stimulation
Siebner et al. 2000 (60)	F8	M1 hand area contralateral to affected limb	5 Hz, 2250 pulses, 90% MT, 1 session	Crossover	10	"Off" state	UPDRS	Improvement of UPDRS (bradykinesia, rigidity and tremor) one h poststimulation
Boylan et al. 2001 (67)	F8	Supplementary motor area	10 Hz, 2000 pulses, 110% MT, 1 session	Crossover	10	"Off" state	UPDRS, RT/MT, spiral analysis	Transient worsening of performance on spiral drawing task, increased RT 30–45 min poststimulation
Shimamoto et al. 2001 (69)	C	Bilateral frontal lobes	0.2 Hz, 30 pulses × 2, 700 V, 1 × /week over 2 months	Parallel	18	"On" state	ADL, UPDRS	Significant long-term improvement on both ADL and UPDRS motor function, as assessed after 1 and 2 months
Sommer et al. 2002 (61)	F8	M1—ADM contralateral to dominant hand	1 Hz, 900 pulses, 120% MT, 1 session	Crossover	11	*b	CURS	Transient improvement of bradykinesia (as measured by finger tapping)
Ikeguchi et al. 2003 (68)	C	Bilateral frontal lobes and occipital cortex	0.2 Hz, 30 pulses × 2, 70% maximum output, 1 session	Partial crossover (*c)	12	"On" state	ADL, UPDRS	Significant ADL and UPDRS motor improvement one week after M1 rTMS
Okabe et al. 2003 (65)	C	Bilateral M1 (FDI) and occipital cortex	0.2 Hz, 100 pulses, 110% active MT, 1 × /week for 8 week	Parallel	85	*d	UPDRS	No significant improvement of M1 rTMS as compared to occipital stimulation or sham over 16-week evaluation
Khedr et al. 2003 (66)	F8	M1 lower limb area and hand ADM	5 Hz, 2000 pulses, 120% MT, 1 × /day for 10 days	Parallel	36	"Off" state	UPDRS, walking speed, self-assessment scale	Significant long-term improvement in UPDRS score for the duration of at least 1 month
Fregni et al. 2004 (79)	F8	Left dorsolateral prefrontal cortex	15 Hz, 3000 pulses 110% MT, 1 × /day for 10 days in 2 week	Parallel *e	42	"On" state	ADL, UPDRS	Small improvement in motor function (indexed by ADL scores) after 8 weeks; no significant interaction effect; no significant change in UPDRS
Lefaucher et al. 2004 (62)	F8	Left M1 corresponding to FDI	0.5 Hz, 600 pulses; 10 Hz, 2000 pulses, 80% MT, 1 session each	Crossover	12	"Off" state	UPDRS, Purdue Pegboard, CAPSIT	0.5 Hz stimulation improved UPDRS score (rigidity bilaterally) and walking; 10 Hz also improved UPDRS score (contralateral rigidity and bradykineesia), 20 min poststimulation
Dias et al. 2006 (70)	F8	Left DLPFC	15 Hz, 3000 pulses, 110% MT, 10 sessions	Parallel	30	"On" state	Mood (quality of life) and voice parameters	LDPFC stimulation significantly improves mood but does not improve voice parameters (intensity and fundamental frequency)
Lomarev et al. 2006 (71)	Solid Core coil *f	Left and right M1, left and right DLPFC	25 Hz, 300 pulses, 100% MT to M1, 8 sessions over 4 weeks	Parallel	18	"On" state	UPDRS, walking test, complex hand task	Significant decrease in RT for executing walking and complex hand movements; 1 month therapeutic effect

ADL, the Schwab and England Activities of Daily Living Scale; ADM, abductor digiti minimi; CAPSIT, core assessment program for surgical interventional therapies; CURS, Columbia University Rating Scale; F8, figure-of-eight coil; FDI, first dorsal interosseous muscle; UPDRS, unified Parkinson's disease rating scale.

*a—Number of pulses not provided.

*b—Subjects were tested at the same time each day, approximately 30 min before the next anti-Parkinsonian medication dose.

*c—Used occipital stimulation as a control in six of the patients, 2 of whom did not receive frontal stimulation.

*d—Subjects were simulated when the anti-Parkinsonian drugs had a "moderate effect"—and cannot be characterized as either in the "on" state or the "off" state.

*e—Sham group received fluoxetine treatment.

*f—Neotonus Neopulse coil.

In addition to M1, areas such as the SMA and the prefrontal cortex have been used as sites of stimulation. In 2001, Boylan et al. tested rTMS of the SMA (at 10 Hz) and found a worsening of complex motor function as measured by spiral drawing (67). On the other hand, stimulation of a large area of the prefrontal cortex with a circular coil at a frequency of 0.2 Hz resulted in a remarkably similar improvement in motor function as shown by Ikeguchi et al. (68) with a single rTMS session and Shimamoto et al. (69) with eight-week rTMS sessions. Motor function in these studies was measured by the Schwab and England Activities of Daily Living Scale and the UPDRS (68,69).

Recently, Dias et al. stimulated the DLPFC at 15 Hz and showed no changes in voice characteristics after rTMS treatment—the results after stimulation of the motor cortex corresponding to mouth area is not reported in this review as this was an open-label experiment (70). Finally, a recent study published in March 2006 demonstrated a cumulative effect of rTMS stimulation; 18 Parkinson's subjects received 25 Hz stimulation bilaterally to their DLPFC and M1 more than four weeks and eight stimulation sessions. Simple and complex motor movements became significantly smoother, and effects lasted for at least one month following the end of stimulation (71). The results of these studies are summarized in Table 3.

Because the stimulation parameters and target areas can vary so widely across studies, it is difficult to make any definite conclusions concerning the effects of rTMS on Parkinson's patients. In addition, it is often difficult to control for effects such as the interaction between TMS and the influence of dopaminergic drugs, as well as the different stages of subjects' disease. Nevertheless, studies such as the meta-analysis of Fregni et al. (57) lend evidence to the idea that rTMS may have an overall positive effect on the treatment of motor symptoms in Parkinson's disease. More research is needed in order to evaluate the most effective stimulation parameters for motor improvement, as well as the long-term therapeutic benefits of rTMS on Parkinson's disease symptoms.

Clinical Trials of rTMS in Epilepsy

The use of rTMS to treat epilepsy is derived from an increasingly large body of literature suggesting that stimulation of certain brain areas may lessen the frequency of seizures in affected individuals (72). Magnetic stimulation may provide an attractive alternative to medication resistant disorders, or to individuals who are either unable (ie, epileptic focus in the eloquent cortex) or wish not to have surgery. A review by Jing-Yu Chang (73) shows that about 10% of epileptic cases—several million people—"can be classified as medically intractable, unresponsive to drug treatments and without a defined epileptic focus amenable to surgical removal." Previous to rTMS, the only potential alternative was the use of deep brain stimulation techniques (73). Although rTMS may represent a potential therapeutic alternative for these studies, the development in this area has been slow and only two randomized studies have been published to date as discussed below.

Randomized Clinical Trials

There have only been two studies to date that meet the criteria for this review. Theodore et al. (74) performed the first randomized controlled trials and found that active 1 Hz rTMS applied to the epileptogenic focus (as indexed by electroencephalograph) does not significantly alter the number of seizures in epileptic subjects as compared to a sham control group, although there was a trend toward improvement ($p = 0.06$). It should be noted that the Theodore's study also recruited subjects whose epileptogenic zones were not of neocortical origin, but were rather located in deep structures, such as the mesial temporal area. Indeed, patients with neocortical foci had a greater reduction in seizure frequency as compared to those with mesial temporal foci (74). Although there is evidence that rTMS can modulate distal neural structures, it most directly affects the neural tissue directly tangential to the coil as its field decreases in strength as a square function of distance (75). This suboptimal stimulation for some subjects may have caused the overall study to not reach significance.

Based on the fact that patients with cortical foci might have a greater response to rTMS, Fregni et al. (76) performed a subsequent randomized, sham-controlled trial using similar parameters as the study of Theodore et al., but recruited subjects whose epileptic foci were of neocortical origin. Using 1 Hz stimulation for 20 min over a five-day period, Fregni et al. found a significant decrease in the number of seizures between the active rTMS group and those receiving sham treatment. This effect was apparent both in the days following, as well as more than two months after treatment, thus showing a long-lasting modulatory effect (76).

These two studies demonstrate that the effects of rTMS for epilepsy are still unclear. Although both randomized studies suggest the notion that the population who can most benefit from rTMS therapy are patients with cortical epileptogenic foci, further larger studies are still necessary to confirm the positive results of Fregni et al. (76). Another potential limitation of the use of rTMS in patients with refractory epilepsy is the interaction between rTMS and antiepileptic drugs. In a recent study, Fregni et al. (77) showed that the inhibitory effects of 1 Hz rTMS are only obtained when the plasma concentrations of valproate are low. In contrast, high valproate concentrations with 1 Hz rTMS increases rather than decreases brain activity (77). Therefore, further trials should test for the clinical effects of this interaction and also perhaps investigate the use of rTMS as a monotherapy. The results of these studies are summarized in Table 4.

TABLE 4. rTMS and Epilepsy

Study	Coil shape	Site of stimulation	Stimulation parameters	Study design	*N*	Outcome measures	Conclusions
Theodore et al. 2002 (74)	F8	Epileptogenic focus (as determined by electroencephalograph)	1 Hz, 900 pulses, 120% MT, 2 ×/day for 1 week	Parallel	24	Number of seizures	No significant differences between test groups as measured at 2 and 8 weeks poststimulation
Fregni et al. 2006 (76)	F8	Area corresponding to the malformation of cortical development	1 Hz, 1200 pulses, 70% maximum stimulator output, 5 sessions	Parallel	21	Number of seizures, epileptiform discharges in electroencephalograph, cognitive evaluation	Significant decrease of seizures in active group; effect duration greater than 2 months

Final Remarks

As a relatively new therapy, rTMS has already enjoyed a wide variety of important clinical and research applications, and yet still has a great deal of potential for novel uses and therapies. This review has presented some of the mounting evidence for the efficacy of rTMS in treating stroke, pain, Parkinson's disease, and epilepsy. These successes herald a hopeful future; one that should include and concentrate on extending the duration of therapeutic efficacy for these neurologic disorders, as well as continuing to find original uses for rTMS and the optimal stimulation parameters for specific conditions.

Additionally, more research needs to be done in assessing the long-term therapeutic uses of rTMS, and particularly to compare the efficacy and safety of this approach with standard therapies such as pharmacotherapy. Finally, one of the main priorities in future clinical trials of rTMS is the use of new tools to continue assessing both the short-term and long-term of safety of this technique.

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