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Invited review

Therapeutic application of repetitive transcranial magnetic stimulation: a review

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Abstract

Transcranial magnetic stimulation (TMS), a non-invasive means of electrically stimulating neurons in the human cerebral cortex, is able to modify neuronal activity locally and at distant sites when delivered in series or trains of pulses. Data from stimulation of the motor cortex suggest that the type of effect on the excitability of the cortical network depends on the frequency of stimulation. These data, as well as results from studies in rodents, have been generalized across brain areas and species to provide rationales for using repetitive TMS (rTMS) to treat various brain disorders, most notably depression. Research into clinical applications for TMS remains active and has the potential to provide useful data, but, to date, the results of blinded, sham-controlled trials do not provide clear evidence of beneficial effects that replace or even match the effectiveness of conventional treatments in any disorder. In this review, we discuss the clinical and scientific bases for using rTMS as treatment, and review the results of trials in psychiatric and neurological disorders to date.

Keywords: Depression; Parkinson's disease; Treatment; Clinical trials; Motor cortex; Prefrontal cortex

1. Introduction

Virtually ever since its adoption as a research tool, observers have wondered whether repetitive transcranial magnetic stimulation (rTMS) could be used to treat brain diseases or improve functional deficits. Early evidence that trains of stimuli delivered to the motor cortex could produce minutes of increased (Pascual-Leone et al., 1994a) or decreased (Wassermann et al., 1996a; Chen et al., 1997) corticospinal hyperexcitability provided the impetus for studies aimed at modulating cortical tone. Small clinical trials soon followed, and the hope of clinicians and the public for non-invasive, drug-free treatments has sustained this work despite the difficulty of studying an incompletely understood procedure with several dosing parameters, without the benefit of guiding preclinical data, and often without clear hypotheses about the mechanisms of action. The absence of the large-scale commercial backing that usually supports the testing of proprietary drugs for therapeutic use has also made research in this area relatively slow and lacking in standardization. In the following sections, we review the field from the point of view of the neurophysiologically sophisticated clinician, discussing the rationales for using rTMS to treat brain disease, the scientific data supporting them, and the results of clinical studies in psychiatric and neurological diseases.

2. Experimental bases for the use of rTMS as a treatment for brain disorders

2.1. Human studies

The first published studies of the effect of rTMS on the motor cortex (Pascual-Leone et al., 1993, 1994a) described, among other effects including an epileptic seizure, the fact that high-frequency rTMS (above 5 Hz or so) could saturate the inhibitory capacity of the cortical network and produce increasing excitability as indicated by the spread of evoked activity from low threshold (hand) to higher threshold (shoulder) muscles and spontaneous jerks persisting after the end of the stimulating train. This increased excitability could also last for minutes. Milder increases in MEP amplitude were also described by Berardelli et al. (1998) immediately after brief trains of 5 Hz rTMS. Others (Wu et al.,

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2000) found facilitatory changes in the motor cortex using the paired-pulse paradigm of Kujirai et al. (1993) after treatment with 5 and 15 Hz rTMS. Where physiological rationales for the local application of rTMS to remedy putative defects of neuronal activation, for example in depression and Parkinson's disease (PD), have been offered, these data have been cited.

Lower frequencies of stimulation, in the 1 Hz range, produce inhibitory changes in the excitability of the motor cortex (Wassermann et al., 1996a) that are relatively robust and long-lasting (Chen et al., 1997). There is also evidence that these effects may generalize to other areas including the visual (Kosslyn et al., 1999) and prefrontal (Speer et al., 2000) cortices. As with higher frequency stimulation, this evidence has been invoked as a reason to use low-frequency rTMS to treat disorders where cortical hyperexcitability is posited as a cause.

Analogies to long-term synaptic potentiation (LTP) (Gustafsson and Wigstrom, 1988) and depression (LTD) (Christie et al., 1994) have been drawn to explain the effects of high- and low-frequency rTMS, respectively (see discussion of LTP below). However, at this time there is no evidence of synaptic change following rTMS in humans. A preliminary report (Touge et al., 2000) indicates that the MEP amplitude depression apparent in the resting muscle is no longer present when the muscle is voluntarily activated. If MEP depression involved a change in the efficacy of synapses in the neural pathway from the cortex to the muscle, such a change would still be detectable as a decrease in MEP amplitude during voluntary muscle activation. However, a change in the excitability of neurons in the pathway, e.g. from inhibitory inputs, would tend to disappear when the same neurons were depolarized by the excitatory voluntary input. Nevertheless, the absence of synaptic effects after short-term treatment does not rule out the induction of such changes with repeated administration.

2.2. Animal studies

Compared with the growing number of clinical trials with rTMS, there are surprisingly few animal studies on its basic mechanisms of action, constraining the ability to perform hypothesis-driven clinical studies. Nevertheless, the existing animal literature on rTMS effects provides useful information about a range of biological effects of rTMS, although these studies have only begun to explore the universe of possible combinations of stimulation parameter values and few of the findings have been rigorously replicated.

Several studies report that rTMS shares many, but not all, of the behavioral and biochemical actions of electroconvulsive shock (ECS) and other antidepressant treatments (for review, see Lisanby and Belmaker, 2000). Most of this work has been conducted in rodents, limiting its applicability to the actions of rTMS in humans. Due to limitations in coil size, rTMS cannot be administered focally to rodents and it seems reasonable to expect that the entire brain is receiving stimulation in most studies, whereas rTMS is considerably more focal in humans. Reported behavioral actions of rTMS in rodents include antidepressant-like effects on the Porsolt swim task (Fleischmann et al., 1995; Zyss et al., 1997, 1999; Keck et al., 2001) and apomorphine-induced stereotypy (Fleischmann et al., 1995), as well as possible antimanic-like effects on the amphetamine model of mania (Belmaker et al., 2000).

Most studies have found that high-frequency rTMS exerts anticonvulsant activity similar to the effects of ECS (Fleischmann et al., 1995, 1999). When given in sufficiently high doses, high-frequency rTMS can be proconvulsant in animals (Jennum and Klitgaard, 1996; Lisanby et al., 2001b) and in humans (Pascual-Leone et al., 1993; Wassermann et al., 1996b; Lisanby et al., 2001c). The development of a reliable animal model for the proconvulsant effects of rTMS would help to clarify the relationship between stimulation parameters and seizure risk, of obvious importance to the clinical applicability of rTMS (Lisanby et al., 2001b).

Several groups have described the effects of rTMS on neurotransmitter systems. Using different methods, two groups have demonstrated that acute treatment with rTMS in rodents modulates monoamine content and turnover (Ben-Shachar et al., 1997; Keck et al., 2000), but no effects on neurotransmitter levels or metabolites have been reported after chronic stimulation (Ben-Shachar et al., 1999). Shortly after rTMS, dopamine is reported to be reduced in the frontal cortex (Ben-Shachar et al., 1997) and increased in the striatum (Ben-Shachar et al., 1997) and the hippocampus (Ben-Shachar et al., 1997; Keck et al., 2000). Increased serotonin (5-HT) in the hippocampus was found in brain homogenates with HPLC (Ben-Shachar et al., 1997) but not in an in vivo microdialysis study (Keck et al., 2000). Reductions in arginine vasopressin release and increases in taurine, aspartate, and serine were reported in the hypothalamic paraventricular nucleus with rTMS (Keck et al., 2000). Although interesting, the regional specificity of neurotransmitter effects should be interpreted cautiously considering the lack of focality of TMS in stimulating the rodent brain.

Chronic rTMS exerts changes in receptor binding generally similar to antidepressant action, including modulation of cortical β-receptors (Ben-Shachar et al., 1999; Fleischmann et al., 1996), reduction of frontal cortex 5-HT_2 receptors (Ben-Shachar et al., 1999), increases in 5-HT_{1A} receptors in frontal and cingulate cortex (Kole et al., 1999), and increases in *N*-methyl-D-aspartate (NMDA) receptors in the ventromedial hypothalamus, basolateral amygdala, and parietal cortex (Kole et al., 1999). The persistence of these effects has yet to be determined.

A candidate mechanism by which rTMS may exert persistent effects is through gene induction. Three groups, using very different methods, have reported that rTMS modulates the expression of immediate early genes (Fujiki and Steward, 1997; Hausmann et al., 2000; Ji et al., 1998). A single rTMS train increased *c-fos* mRNA in the paraventri-

cular nucleus of the thalamus, and to a lesser extent in the frontal and cingulate cortices but not in the parietal cortex (Ji et al., 1998). In distinction to these acute effects, 14 daily rTMS treatments with a rodent-sized figure-of-8 coil caused a 3-fold increase in *c-fos* mRNA in the parietal cortex (Hausmann et al., 2000). No change was seen in brain-derived nerve growth factor (BDNF) mRNA expression in that study (Hausmann et al., 2000), but another group found that a longer treatment protocol significantly enhanced BDNF mRNA in the hippocampus and the parietal and piriform cortices (Muller et al., 2000). Effects on neurotrophic factors could possibly explain preliminary findings of neuroprotective (Post et al., 1999) and neuroplastic effects of rTMS, such as mossy fiber sprouting in the hippocampus following chronic rTMS (Lisanby et al., 2000). Possible effects of rTMS on neurotrophic factors might be relevant to new theories about the mechanisms of action of antidepressant medications (Duman et al., 1997), but further work needs to be done to discover whether such effects are relevant to rTMS in humans.

The putative frequency-specific effects of rTMS in humans have been likened to LTP and LTD (Weiss et al., 1997). However, attempts to test the ability of rTMS to exert LTP- and LTD-like effects have had mixed success. Wang et al. (1996) delivered 8 Hz rTMS to the auditory cortex of the gerbil and reported suppression of auditory cortex firing in 11, increases in firing in 8, and no changes in firing in 21 out of 40 trials. In another study, acute and chronic rTMS treatment enhanced the reactivity of the rat dentate gyrus to perforant pathway stimulation and interfered with the serotonergic and β-adrenergic modulation of hippocampal activity (Levkovitz et al., 1999). The net effect of these multiple actions could be either excitatory or inhibitory (Levkovitz et al., 1999).

2.3. Limitations on the usefulness of rTMS as treatment

While only very few of the very large number of possible combinations of magnetic stimulation parameters (frequency, intensity, train duration, etc.) have been tested experimentally, the issue of safety places stringent boundaries on the region of the stimulation parameter space that can be used in human studies (Green et al., 1997; Wassermann, 1998). This fact is likely to limit the efficacy of rTMS, particularly as a means to increase cortical excitability. Perhaps fortunately, the lasting excitatory effects on cortical excitability produced in rTMS experiments with frequencies in the 5–20 Hz range have been inconsistent (Maeda et al., 2000) and evanescent. The explanation may lie in the fact that in animal studies, LTP of excitatory synapses by electrical stimulation requires pulse frequencies of 50 Hz or more applied for periods of several seconds (see, for example, Keller et al., 1991). rTMS at these frequencies and analogous intensities would likely produce seizures in humans.

Another limitation is related to the depth of penetration of effective stimulating currents. With the possible exception of centrally evoked phosphenes (Marg and Rudiak, 1994), no phenomena produced by TMS in humans can be attributed to activation of sites deeper than the cortex or immediately subjacent white matter. While stimulators capable of injecting effective currents deep into the human brain could be built, their use would likely be complicated by the strength of the induced current at the surface, which might be epileptogenic or even harmful to tissue.

3. Psychiatric disorders

3.1. Depression

3.1.1. General comments

Major depression is the most thoroughly studied of the potential psychiatric applications of TMS. As a focal cortical intervention, TMS offers the possibility of targeting key brain regions involved in depression. Since depression involves a network of cortical and subcortical areas, the selection of the optimal target within this network is an empirical question. The assumption awaiting empirical validation is that the effect of TMS on the region targeted will produce local and distant effects that serve to normalize activity in the circuit on a lasting basis.

The dorsolateral prefrontal cortex (DLPFC) has been the main target for stimulation in depression. A substantial body of literature supports the theory that mood is regulated by a network of brain regions (including the prefrontal, cingulate, parietal, and temporal cortical regions as well as parts of the striatum, thalamus, and hypothalamus) and that focal lesions in this network (from infarction, tumor, or transient disruption, e.g. by the Wada procedure) can result in mood disturbances. Furthermore, depressed patients demonstrate alterations in CBF and metabolism in the dorsolateral, ventrolateral, orbitofrontal, and medial frontal regions, as well as the subgenual prefrontal and anterior cingulate cortex (see Soares and Mann, 1997; Mayberg, 1997 for reviews and Drevets et al., 1997). The first rTMS studies of mood in depression and normal individuals (see below), selected the DLPFC as a region within this network that is accessible to TMS and highly connected with other key nodes in the network, such as other prefrontal and anterior cingulate regions.

The method commonly used to locate the DLPFC on the subject's head was first described by Pascual-Leone et al. (1996a). In this study, effects on implicit motor learning, a function for which the DLPFC is thought to be important, were obtained with rTMS delivered to a site located 5 cm anterior to the optimal location for producing MEPs in a hand muscle. No procedure was used to optimize the effect by varying the stimulation site and no effort was made to use a proportional system that would take into account differences in head size and shape. Nevertheless, while nearly all studies in mood and depression have used this inherently

unreliable means of targeting stimulation, there has been no independent confirmation that the DLPFC is the optimal location to produce antidepressant effects with rTMS, or that the DLPFC is being reliably or effectively stimulated using this localization procedure. Indeed, studies using post hoc MRI localization of coil position demonstrate considerable variability in coil distance from the middle prefrontal gyrus (Kozel et al., 2000; McConnell et al., 2001). This distance may be correlated with clinical efficacy (George et al., 2000), strongly arguing for a more reliable method of coil placement and selection of stimulation intensity.

Another important caution regarding rTMS treatment studies in all disorders, but particularly in depression, is using appropriate controls. Adequate blinding and realistic shams are particularly important in view of the high placebo response rate in depression. Placebo response rates in depression trials range from 30 to 50%, and drug–placebo differences are typically 18–25% (Brown, 1994; Trivedi and Rush, 1994; Schatzberg and Kraemer, 2000). In a review of the US Food and Drug Administration database on patients enrolled in placebo-controlled trials of new antidepressants, the overall response rate was 30.9% for placebo, compared with 41.7% for established antidepressants, and 40.7% for investigational drugs (Khan et al., 2000). This problem is compounded for rTMS because device-based treatments may exert an enhanced placebo effect compared with placebo pills due, in part, to the elaborate rituals involved in delivering the treatment and the reliance on high technology (Kaptchuk et al., 2000). One can readily conceive that TMS, with its impressive-sounding name, its ability to cause involuntary movements as if by magic, its discomfort, and its bulky and sophisticated-looking equipment, might be particularly effective in producing placebo responses.

One mitigating factor to be weighed against the possibility of an enhanced placebo response rate due to the device-based treatment is the medication resistance of the patient population. Treatment-resistant patients tend to have lower placebo response rates and the majority of patients in TMS trials have been drawn from this population. Indeed, the sham response rates in several trials have been low (from 0 to 25%). This low sham response rate helped to make the effects of active TMS statistically distinguishable from sham in some studies (45% difference between active and sham in George et al., 2000; 24% difference between active and sham in Klein et al., 1999). However, in some trials of treatment-resistant patients, the response rates to active TMS were as low as the sham response rates and no clinically meaningful effects of active TMS were seen (Padberg et al., 1999; Berman et al., 2000; Loo et al., 1999).

Because TMS using conventional coils must be administered by an individual who is aware of the treatment condition, truly blind conditions have generally not been possible. Many investigators have dealt with the issue of clinician blinding by keeping the clinical raters unaware of the treatment condition. The optimal sham manipulation to serve as a placebo for the procedure of TMS remains an open issue. Tilting the stimulating coil off the head approximates the acoustic and somatosensory artifacts experienced with active TMS, but inadequate tilting can result in possibly significant cortical stimulation that could exert clinical effects under some conditions (Loo et al., 2000; Lisanby et al., 2001a). The physical sensation of sham and active TMS can differ substantially under some conditions and may effectively unblind the subjects in within-subject crossover trials. The development of sham coils that produce realistic auditory artifacts and scalp sensations that may also be similar to those of real coils may soon aid this situation. However, to date, these devices have not been widely tested. Another potential confound in therapeutic trials of rTMS is the 'dosage' of the sham (Kaptchuk et al., 2000). In other words, active stimulation that affects brain function in any way is likely to exert a stronger placebo effect than inactive sham, no matter how realistic.

3.1.2. Mood studies in healthy subjects

Three studies (George et al., 1996; Pascual-Leone et al., 1996b; Martin et al., 1997) showing transient effects of TMS applied to the DLPFC on subjective mood rating scales in normal volunteers suggested a potential mood-altering action. It is important to note, however, that these effects were small and not clinically apparent. In fact, the study by George et al. (1996) failed to replicate the change in visual analog ratings following treatment reported by Pascual-Leone et al. (1996b). Mood effects were seen by George et al. (1996), only in a more sensitive subjective mood rating scale. Three subsequent attempts to replicate these effects on sad and happy moods have failed (Hajak et al., 1998; Nedjat and Folkerts, 1999; Mosimann et al., 2000), but recent work with low-frequency TMS suggests there may be positive effects on anxiety ratings in normal volunteers (Schutter et al., 2001). Animal experiments showing antidepressant-like actions of TMS in some rodent behavioral models of depression, as well as neurotransmitter system changes akin to many of the effects of ECS, provided more convincing suggestions that TMS may be clinically beneficial in depression (see review by Lisanby and Belmaker, 2000).

3.1.3. Trials in depressed patients

The initial studies of TMS in depression employed single-pulse stimulators, triggered at frequencies less than 0.3 Hz (Höflich et al., 1993; Grisaru et al., 1994; Kolbinger et al., 1995). These groups all used large circular coils positioned over the vertex, thereby stimulating a large ring of frontal and parietal areas bilaterally. In an open randomized trial, 2 weeks of single-pulse TMS was reported to augment the speed of response to antidepressant medication (Conca et al., 1996). While these studies were not blinded, they highlight the potential role of low-frequency stimulation and the more powerful and less focal round coil. Indeed, recent work has suggested that 1 Hz rTMS with a round coil may be of some value in depression (Klein et al., 1999a). One

possible advantage is that these coils may more closely approximate the coil-to-brain ratio (Weissman et al., 1992) achieved in animal studies of depression.

In the first study of the antidepressant effects of rTMS, George et al. (1995) administered 5 daily rTMS sessions to the left DLPFC of 6 medication-resistant depressed patients. Two patients in this open study experienced substantial improvement and Hamilton Rating Scale for Depression (HRSD) scores dropped by 26%. Subsequent open and blinded studies of rTMS to the left DLPFC followed, but results have varied. In a large open study, Figiel et al. (1998) found that 42% of the 56 patients responded to 5 daily rTMS sessions. Response rates were lower in the elderly. Extending the treatment to 2 weeks in another open trial, Triggs et al. (1999) reported a 41% drop in HRSD, although final mean HRSD remained greater than 20, which was the threshold criterion for study entry. Some open studies have not found antidepressant activity of rTMS (Schouten et al., 1999).

In blinded controlled trials of rTMS in depression, effect sizes have varied. Using a multiple crossover, within-subject design, Pascual-Leone et al. (1996c) reported that 5 daily rTMS treatments to the left DLPFC had marked antidepressant effects in 11 of 17 medication-resistant psychotically depressed patients, whereas stimulation of the right DLPFC or other areas was ineffective. Antidepressant effects began to relapse within 1–2 weeks after stopping rTMS. Extending the treatment to 2 weeks, George et al. (1997) found only modest antidepressant efficacy of rTMS to the left DLPFC in a within-subject crossover sham-controlled study of 12 depressed patients. Using the same stimulation settings in a parallel design ($n = 20$), Berman et al. (2000) found an antidepressant response that was statistically different from sham, but was still only of modest clinical impact. Both the George et al. (1997) and Berman et al. (2000) studies used a low stimulation intensity of 80% of the MEP threshold. Higher intensity stimulation may have been more effective (as later reported by George et al., 2000, see below); however, Loo et al. (1999) used 110% of the MEP threshold and found no differences between active and sham rTMS (26% drop in HRSD in both groups).

Recently, investigators have begun examining the role of stimulation frequency and results suggest that lower frequencies may be worth exploring. Klein et al. (1999a) demonstrated in a sham-controlled trial ($n = 71$) that 1 Hz rTMS to the right DLPFC was more effective than sham (47% response rate to active compared with 17% response rate to sham). It is not known whether 1 Hz rTMS to the left hemisphere would have been similarly effective. However, work on the rTMS treatment of acute mania suggests that right hemisphere treatment may be more effective in that condition (Grisaru et al., 1998). Padberg et al. (1999) randomized 18 patients to single pulse (very low frequency) TMS, 10 Hz, or sham rTMS delivered to the left DLPFC. Although patients received only 250 pulses per day for 5 days, a mild antidepressant effect was seen with single-pulse TMS. In a sham-controlled trial in which patients were randomly assigned to receive an equivalent number of pulses at 5 or 20 Hz over 2 weeks ($n = 20$), George et al. (2000) recently reported a 45% response rate to active rTMS with no patients responding to sham. There were more responders in the 5 Hz than in the 20 Hz group, but this difference was not statistically significant. While the sample size may have been inadequate to detect a small difference between the groups, the suggestion that lower frequencies may work as well as, or even better than, higher frequencies has important implications for safety since lower frequencies have lower risk of seizure. A correlational analysis of treatment response and cerebral metabolic rate on 18-fluorodeoxyglucose positron emission tomography (Kimbrell et al., 1999) suggests that patients with decreased metabolism may respond better to relatively high frequency stimulation (10 or 20 Hz), whereas those with baseline hypermetabolism respond better to 1 Hz stimulation. This would be in keeping with the effects of rTMS on the excitability of the motor cortex and the rationale for the treatment. However, the effects of rTMS on mood examined in this study were not statistically significant on their own and the correlational data must be interpreted with caution.

3.1.4. Comparisons with electroconvulsive therapy (ECT)

rTMS has occasionally been suggested as a replacement for ECT, perhaps due to the fact that both treatments utilize transcranial brain stimulation. However, based on the presumably localized action of (subconvulsive) rTMS on cortical circuits and the requirement for a generalized seizure in ECT, there is no basis for drawing meaningful mechanistic parallels at present. Moreover, in view of the limited effectiveness of rTMS in some hands and the generally well-recognized strong antidepressant action of ECT, clinical comparisons seem somewhat premature. Two published studies have compared the efficacy of these two treatments directly. In an open study of 40 patients, Grunhaus et al. (2000) reported that rTMS and ECT had equal efficacy in a non-psychotic subgroup, while ECT was superior in patients with psychotic depression. Aside from the initial report of Pascual-Leone et al. (1996c), others have also found rTMS to be less effective in psychotic depression (Epstein et al., 1998; Figiel et al., 1998). In another open study of 32 patients using a similar design, Pridmore et al. (2000) found that fixed dose, right unilateral ECT had an overall advantage in changing the HRSD, but that patients receiving rTMS and ECT had the same remission rate (69%). A trial using optimal ECT methods in which raters are kept rigorously blind to the treatment condition would help resolve the issue of the relative effectiveness of rTMS and ECT. At this point, it is not possible to recommend rTMS clinically instead of ECT.

3.1.5. Therapeutic seizure induction with TMS

With the efficacy of conventional rTMS remaining an open issue, another approach being pursued involves using rTMS at convulsive levels as a more targeted form of ECT. Although research shows that the efficacy and side effects of ECT are highly dependent upon the path of the current passed through the brain (Sackeim et al., 1993, 2000a,b), present ECT procedures provide limited control over the location and extent of stimulation. Eddy current stimulation with TMS, on the other hand, may offer greater control over the spatial extent and intensity of the stimulation, thereby producing seizures with optimal location and magnitude (Sackeim, 1994). Targeting seizures to focal cortical areas, such as regions of the prefrontal cortex, may reduce the side effects of convulsive treatment. Magnetic seizure therapy (MST) has now been tested in monkeys and recently 11 patients with depression have been treated (Lisanby et al., 2001b,c,d). Additional work is needed to evaluate the clinical efficacy of this approach and to determine if it has significant advantages over ECT.

3.1.6. Conclusions concerning rTMS in the treatment of depression

In conclusion, the key findings in depression have not been systematically replicated and effect sizes have often been small and variable. Sources of variability across studies include differences in stimulation parameter settings, concomitant medications, and patient sample characteristics. In addition, simple and economical methods for precise and reliable coil placement are needed, as this factor is likely important for effectiveness (Kozel et al., 2000). In much of this work, the magnitude of antidepressant effects, while often statistically significant, has been below the threshold of clinical usefulness (Berman et al., 2000), and has not lived up to expectations raised by encouraging results in animal studies. The disparity between the human and animal studies on depression may relate to the differences in amount and site of stimulation between humans and rodents (see Section 4). Furthermore, the persistence of antidepressant effects beyond the 1–2 week treatment period has rarely been examined. Initial evidence suggests that the beneficial effects may be transitory, making the development of maintenance strategies important if rTMS is to move to the clinic. Establishing whether non-convulsive rTMS has antidepressant properties aside from its clinical usefulness is of theoretical importance, since positive data support the notion that focally targeted manipulations of cortical function can result in mood improvement. Nonetheless, as a clinical antidepressant intervention, the future of rTMS is far from certain. More work and larger studies are needed to establish its efficacy, optimal treatment paradigm, and appropriate patient population.

3.2. Obsessive-compulsive disorder (OCD)

A single study (Greenberg et al., 1997) of rTMS treatment in 12 OCD patients, using 20 Hz rTMS at 80% of the MEP threshold, found significantly decreased compulsive urges for 8 h after right lateral prefrontal rTMS accompanied by shorter-lasting mood improvement. Stimulation of the left lateral prefrontal midoccipital areas produced no significant effects on compulsions, obsessions, or mood. While the lateral prefrontal areas are not specifically implicated in the pathogenesis of OCD (Rauch et al., 2001) and the areas most affected in functional imaging studies (Rauch et al., 1994; Breiter and Rauch, 1996), the orbitofrontal and anterior cingulate cortices may not be directly accessible to transcranial stimulation, transsynaptic effects on distant frontal areas are theoretically possible (Cummings, 1995).

3.3. Schizophrenia

rTMS delivered to the right prefrontal cortex with a round coil at 1 Hz in two 60 s trains and a fixed intensity of 1 T was tried as a treatment in 10 (9 medicated) schizophrenic patients for 10 days, along with 14 patients with major depression (Feinsod et al., 1998). While the depressed patients appeared to experience mood improvement and the schizophrenic patients had some decrease in their degree of anxiety and restlessness, there was no effect on core psychotic symptoms in the schizophrenics. In a follow-up study of 31 schizophrenic patients by the same research group, the same treatment regimen produced no differences in outcome relative to sham stimulation (Klein et al., 1999b), despite the strong evidence for prefrontal dysfunction in schizophrenia. The use of higher frequency prefrontal rTMS has not been reported in schizophrenia and might be more effective.

rTMS has been used more successfully to reduce auditory hallucinations in schizophrenia by attempting to reduce excitability in cortical speech processing circuits. In a blinded, sham-controlled study based on localization data from functional neuroimaging, Hoffman et al. (2000) delivered 1 Hz rTMS at 80% of the MEP threshold to the left temporoparietal cortex in 12 patients with schizophrenia and chronic daily auditory hallucinations. rTMS, particularly longer periods of treatment, reduced auditory hallucinations in most patients that were statistically significant for the group and significantly greater than after sham. This effect lasted for weeks in some individuals. Importantly, anticonvulsant drugs appeared to attenuate the therapeutic effect, suggesting that excitation of cortical neurons or synapses by the stimulating current was part of the mechanism.

4. Motor disorders

4.1. Parkinson's disease

Trials of rTMS as a potential therapeutic agent in PD began with Pascual-Leone et al. (1994b) who observed

that 5 Hz rTMS at 90% of the resting MEP threshold, delivered to the motor cortex opposite the performing hand in 6 patients, significantly speeded performance on the Grooved Pegboard Test, a widely used test of psychomotor speed (Lezak, 1995) with which PD patients have great difficulty. Faster task performance with rTMS was particularly apparent when the patients were in the unmedicated and clinically 'off' state; no such benefit was seen in healthy controls.

In their attempt to replicate the effect of rTMS in 11 similar patients in the unmedicated state, Ghabra et al. (1999) found no beneficial effect on Grooved Pegboard Test performance during or after stimulation. In fact, in an appreciable number of patients, stimulation at 90% of the resting MEP threshold catastrophically disrupted movement, making the task impossible. This phenomenon has been observed by others and likened to cerebellar tremor (Topka et al., 1999). Decreasing the stimulation intensity removed the tremor, but did not improve task performance. In another study, Tergau et al. (1999a) administered the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS), a test of walking speed, and a simple motor reaction time task in 7 medicated patients with PD before and after 500 pulses of rTMS at 1, 5, 10, and 20 Hz delivered to the motor cortex on 4 different days. Neither beneficial nor adverse effects were seen.

One sham-controlled study in PD (Siebner et al., 1999a) appeared to show a potentially beneficial and specific effect on movement in PD. Here, pretreatment with 2250 pulses of TMS at 90% of the resting MEP threshold, delivered at 5 Hz in 5 trains of 30 s duration to the motor cortex contralateral to the performing hand, shortened movement time on a ballistic pointing task to a visual target. More specifically, rTMS treatment seemed to restore a smooth velocity profile to the movement. Pointing accuracy was unaffected and sham stimulation with the back edge of the coil placed in the midfrontal area and the surface angled 45° off the scalp had no effect. A potential weakness of this study is that it seems likely that the subjects would have been aware that the active stimulation was delivered at the site where MEPs were evoked during the threshold determination, whereas the sham was delivered elsewhere.

Others (Mally and Stone, 1999a,b; Shimamoto et al., 1999) have reported sustained improvements in movement-related measures with various regimens of repeated TMS pulses administered with round coils over periods of weeks to months in small groups of PD patients. These studies, while interesting, suffered from the use of unblinded designs or unrealistic sham control procedures, e.g. holding the coil away from the head, and therefore fall short of providing convincing evidence of a therapeutic effect of rTMS in PD. It is important to note that PD patients can show marked and sustained improvements on objective measures with placebo treatment even in rigorously controlled and blinded trials (Goetz et al., 2000).

Finally, Boylan et al. (2001) delivered 10 Hz rTMS at 150% of MEP threshold to a midsaggital area corresponding to the presumed location of the supplementary motor area (SMA) with a figure-of-8 coil in 8 PD patients. The patients were tested on a variety of motor tasks before, during, and after 50 pulse trains of 5 s duration. Rather than improving, the stimulation caused worsening (compared with sham) of spiral drawing and reaction time. These effects were statistically significant 30–45 min after stimulation and may have been present even 1 week later.

The rationales for rTMS trials in PD have involved either replacing or increasing cortical excitability to movement-related thalamocortical drive which is thought to be deficient in PD (DeLong, 1990) or more speculative notions about modulations of catecholamine metabolism based on rodent experiments (e.g. as proposed by Mally and Stone, 1999a,b). While perhaps more plausible, the first theory assumes that the biasing signals from the basal ganglia relayed by the thalamus act uniformly upon the motor cortex and that a treatment which increases cortical responsiveness or somehow replaces excitatory input will be therapeutic. However, evidence from single-cell recordings suggests that the output of the basal ganglia may have important temporal relations to movement and be quite selective with respect to its targets in the cortex, inhibiting unwanted motor programs as well as facilitating the intended movement (Mink, 1996). Viewed in this light, it is more difficult to envision rTMS modulation of cortical excitability as being helpful. On the other hand, similar criticisms could be made of other physiological interventions that have established benefits in PD, e.g. ablative lesions or disruptive stimulation of the globus pallidus and subthalamic nucleus.

4.2. Task-related dystonia (writer's cramp) and tic disorder

Physiological studies in task-related dystonia (e.g. writer's cramp) have suggested hyperexcitability of the motor cortex or a failure of intracortical inhibition due to overactive or distorted thalamocortical control (Hallett, 1998). Here, as in PD, investigators have perceived an opportunity to intervene with rTMS treatments intended to alter cortical excitability. However, the intention in focal dystonia has been to reduce unwanted cortical activation with low-frequency stimulation. Siebner et al. (1999b) applied 1 Hz rTMS at an intensity below the MEP threshold to the motor cortices of patients with writer's cramp and healthy controls. Twenty minutes after treatment, they found both reduced paired-pulse cortical excitability (Kujirai et al., 1993), prolonged cortical silent period, and an average decrease in writing pressure, one of the several mechanical parameters of writing that were measured. This was accompanied by transient clinical improvement in some subjects.

In tic disorder, where there is a similar increase in paired-pulse cortical excitability (Ziemann et al., 1997) and pathogenetic theories that posit aberrant control of the cortex by circuits through the basal ganglia (Hallett, 1993), preliminary data (Karp et al., 1997) suggest that 1 Hz rTMS of the

motor cortex and possibly the SMA may reduce the frequency of tics.

4.3. Epilepsy and related disorders

Investigators have attempted to use low-frequency rTMS to treat seizure disorders and other manifestations of cortical hyperirritability, based on its ability to reduce the excitability of the motor cortex. In an open trial in 9 medicated patients with frequent and intractable seizures, Tergau et al. (1999b) found that 5 days of 1000 pulses of 0.3 Hz rTMS delivered at 100% of the MEP threshold appeared to reduce self-rated seizure frequency that lasted for weeks. The authors mentioned the study of Weiss et al. (1995) where 1 Hz electrical stimulation of the amygdala could 'quench' kindled seizures in rats as a potential explanation for this effect. However, Weiss et al. (1998) subsequently were unable to replicate their study until they realized that it had been done with a malfunctioning stimulator that maintained a constant voltage difference between the electrodes. Thus, the quenching effect may require more than repetitive stimulation.

Recently, Menkes and Gruenthal (2000) reported a single patient with a cortical dysplasia which was the intended target of 0.5 Hz rTMS at 5% below the MEP threshold, delivered with a large round coil twice a week for 4 weeks. During the treatment period, both fewer seizures and fewer EEG spikes were observed. In cortical myoclonus, a disorder characterized by cortical hyperexcitability to efferent stimulation and spontaneous cortical discharges resulting in involuntary movements (Shibasaki, 2000), low-frequency rTMS has also been tried. Encouraged by pilot results (Wedegaertner et al., 1997), we have treated several cortical myoclonus patients with 10 days of 1 Hz rTMS over the motor cortex and occipital sham stimulation at just above the MEP threshold. However, no significant beneficial effects have been observed so far (E.M. Wassermann, unpublished results).

5. Conclusions and future directions

After a decade of speculation and experimentation, TMS has not yet yielded any treatments that effectively alleviate any disorder. Despite this fact, interest remains high, perhaps due to the intuitive appeal of the idea that non-invasive stimulation of potentially plastic neural circuits must have some application. Part of the reason for the failure to find provable therapeutic effects to date may concern the selection of disorders. For instance, while research has greatly deepened our understanding of the neurophysiological changes in depression, this understanding is still far from complete. The metabolic and blood flow changes manifest on functional brain imaging in depression are distributed (Davidson et al., 1999) and the selection of the DLPFC as the only target may have been premature. To take another example, PD is a relentlessly progressive process of death in a small and critical population of neurons for which even highly effective physiological interventions, such as disruptive stimulation of the subthalamic nucleus (Benabid et al., 2000), produce benefits that disappear almost immediately when the stimulation stops. A priori, intermittent treatment directed at the cortex does not seem likely to be helpful.

New areas of investigation, particularly the use of low-frequency TMS to depress activity in hyperexcitable neural circuits, for example in focal dystonia, epilepsy, and the auditory hallucinations of schizophrenia, appear stronger in their scientific basis, making the preliminary data suggesting therapeutic effects more plausible. This model of applying TMS based on specific, testable pathophysiological hypotheses and robust electrophysiological effects and targeting the intervention based on strong localizing data is likely to be the most fruitful approach for future clinical studies.

Aside from its potential clinical role, TMS remains a valuable probe of brain function that is unparalleled in its ability to alter cortical activity in awake behaving subjects. As an investigative tool, TMS has the potential to refine our knowledge of the neural circuitry underlying neuropsychiatric disorders. This added knowledge might go a long way toward developing new treatments (magnetic or otherwise) that are more precisely targeted to the specific cortical systems affected.

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