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EDITORIAL

Focal brain stimulation with repetitive transcranial magnetic stimulation (rTMS): implications for the neural circuitry of depression[1]

BRAIN STIMULATION IN THE TREATMENT OF MAJOR DEPRESSION

Repetitive transcranial magnetic stimulation (rTMS) is an experimental medical procedure that is currently under investigation for its potential therapeutic value in major depression and other psychiatric and neurological disorders (Wassermann & Lisanby, 2001). The idea of using brain stimulation to treat depression dates back to the origins of ECT, and includes more recently developed techniques such as deep brain stimulation and vagus nerve stimulation. The value of brain stimulation in psychiatry is still most clearly seen in the, as yet, unparalleled efficacy of ECT in treating severe depression (American Psychiatric Association, 2001). While ECT is the most effective and most rapidly acting treatment for depression, it also causes a variable degree of undesirable cognitive side effects that limit its clinical utility and prevent many patients who could benefit from receiving this often life-saving treatment (McElhiney *et al*. 1995; Lisanby *et al*. 2000*b*). The search for an effective somatic treatment for medication resistant depression with fewer cognitive side effects than ECT has motivated much of the work with rTMS in psychiatry.

Attempts to reduce the side effects of ECT date back to the early years of use of convulsive therapy, and have primarily focused on targeting the stimulation to focal brain regions. The idea of improving the focality of ECT to enhance efficacy and reduce side effects was originally proposed over 55 years ago (Heath & Norman, 1946): they stimulated discrete cortical sites using small electrodes and found in an open uncontrolled study that the sites of focal stimulation differed in their efficacy, acute cognitive side effects, autonomic response and degree of generalization to the motor cortex. There is now substantial evidence from double-blind randomized clinical trials that the means of seizure initiation (including variations in the placement of the stimulating electrodes and the electrical dosage administered above the threshold for inducing seizure) exerts a significant impact on the efficacy and side effects of ECT (Sackeim *et al*. 1993, 2000; McCall *et al*. 2000).

Modern procedures to spatially target ECT have used asymmetric bilateral (Swartz, 1994) and bifrontal (Bailine *et al*. 2000) electrode placements in an attempt to focus the current and seizure induction in the prefrontal cortex to maximize efficacy while limiting spread to temporal cortex to minimize cognitive side effects. Letemendia *et al*. (1993) reported that bifrontal (BF) ECT was superior to the traditional bilateral (BL) placement and resulted in less severe cognitive effects. Bailine *et al*. (2000) compared BF and BL ECT (both given at 1·5 times seizure threshold) and found that the two treatments were equal in efficacy, but that BF ECT exerted a modest cognitive benefit as measured by the mini-mental status exam (MMSE). Future studies, that use more sensitive cognitive measures, will be needed to confirm this finding. Other studies have failed to replicate the advantages of BF ECT. Heikman *et al*. (2002) reported that high dose right unilateral (RUL) ECT was superior to BF ECT in antidepressant efficacy. Further work is needed to clarify the efficacy/side-effect profile of BF relative to other electrode placements. With all of these modifications, there remains some degree of cognitive side effects thought to result from the induced seizure and also aspects of the electrical stimulus used to induce the seizure. A challenge shared by all strategies to optimize electrode placement with ECT is the impedance of the scalp and skull that shunts the bulk

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of the electrical stimulus away from the brain, resulting in stimulation of widespread cortical and subcortical regions (Hayes, 1950; Rush & Driscoll, 1968). Non-invasive stimulation of the brain using transcranial magnetic stimulation has been proposed as a means of overcoming this limitation.

FOCAL SUBCONVULSIVE BRAIN STIMULATION WITH rTMS: IS A SEIZURE NECESSARY?

Unlike electricity, magnetic fields pass through tissue without impedance (Barker *et al.* 1985). The electrical field induced by magnetic stimulation is relatively more focal than that induced by ECT and only penetrates about 2 cm below the scalp, so its direct effects are confined to superficial cortex (Epstein, 1990; Lisanby *et al.* 1998*a*, *b*). Thus, magnetic stimulation offers more precise control over current paths in neural tissue than the transcranial application of electricity. As a non-invasive tool for stimulating functional neuronal circuits, rTMS offers the promise of tailoring a focal treatment to what is known about the neural systems underlying depression. The therapeutic value of subconvulsive levels of rTMS is under active examination (George *et al.* 1999; Lisanby & Sackeim, 2000). In tandem with studies on subconvulsive rTMS, convulsive doses of rTMS (termed magnetic seizure therapy (MST)) are also being explored as a more focal means of performing convulsive therapy that is not constrained by issues of tissue impedance (Lisanby *et al.* 2001*b*, *c*, *d*, 2002; Lisanby, 2002). Initial clinical trials with MST suggest that it has fewer cognitive side effects than conventional ECT, presumable due to its greater focality and control over dosing (Lisanby *et al.* 2001*c*, 2003).

Although a seizure is necessary for antidepressant effects with ECT (Gottesfeld *et al.* 1944; Hargrove *et al.* 1953; Ulett *et al.* 1956) it was not known whether that would also be the case for rTMS. Recent research has shown that, with ECT, merely inducing a seizure is not sufficient for antidepressant efficacy. Studies indicate that the electrical dosage administered in excess of the threshold for eliciting a seizure with ECT exerts a profound impact on the efficacy and side effects of ECT (Sackeim *et al.* 1993, 2000; McCall *et al.* 2000). It is also true, however, that high dose forms of ECT induce seizures that differ from low dose ECT in their ictal and post-ictal characteristics (Nobler *et al.* 1993, 2000; Luber *et al.* 2000). With ECT, it is not possible to disentangle the electricity fully from the characteristics of the induced seizure, unless one blocks the seizure induction pharmacologically. In a rodent model, McGarvey *et al.* 1993, administered an anticonvulsant medication prior to electroconvulsive shock (ECS) and demonstrated that the dosage of the electrical stimulus was responsible for certain ECS-induced neurochemical changes. Another method to study the differential contributions of the current and the seizure is through the use of MST, which induces seizures with an electrical field, this is more focal than ECT (Lisanby *et al.* 1998*a*, *b*; Lisanby, 2002).

If the electrical current induced by ECT does indeed contribute to its efficacy, but is not sufficient in the absence of a seizure to constitute effective antidepressant treatment, why would one expect subconvulsive rTMS to work any better than subconvulsive ECT? The difference may lie in the distinct physical properties of these two forms of brain stimulation. ECT must overcome the impedance of the scalp and skull to reach the brain. These tissues shunt the bulk of the electricity away from the cortex. It is not clear how much of the subconvulsive electrical stimulus delivered with ECT actually reaches the target cortical structures. Tissue impedance has no impact upon the efficiency of stimulation with magnetic fields. Subconvulsive ECT and rTMS also differ substantially in their dosing schedules. Subconvulsive ECT consists of a single brief electrical stimulus given under anesthesia three times a week, while subconvulsive rTMS consists of multiple trains of stimulation, often 20 or more, given without the interference of anesthesia in daily treatment sessions repeated five times per week for several weeks. Animals studies have shown that subconvulsive rTMS is able to achieve some of the same neurochemical and anticonvulsant effects of ECS, but without the seizure (Belmaker *et al.* 2000; Lisanby & Belmaker, 2000; Lisanby *et al.* 2000*a*). These studies provide support for the possibility that subconvulsive rTMS might be capable of modulating brain activity in a way that subconvulsive ECT cannot. While these animals studies are suggestive, the gold standard by which the clinical value of subconvulsive rTMS must be judged is the randomized clinical trial.

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CLINICAL EFFICACY OF SUBCONVULSIVE rTMS IN DEPRESSION: WHAT IS AND IS NOT YET KNOWN

Studies in depressed populations have consistently shown that rTMS has virtually no cognitive side effects, but its clinical utility as an antidepressant treatment remains uncertain. Recent meta-analyses of the controlled trials on the antidepressant efficacy of active rTMS compared with sham suggest that rTMS has a statistically significant effect on depressive symptoms (Burt *et al.* 2002; Martin *et al.* 2002). Burt *et al.* (2002) reported an overall effect size of 0·62. The magnitude of the clinical improvement across studies was modest, with an average 29% drop in depressive symptoms with active rTMS compared with 7% improvement with sham. While numerous studies have demonstrated that rTMS results in a greater degree of improvement than sham treatment, the number of patients who showed substantial benefit was often modest (Berman *et al.* 2000; Garcia-Toro *et al.* 2001*a*) and some studies were negative (Loo *et al.* 1999*a*; Garcia-Toro *et al.* 2001*b*; Lisanby *et al.* 2001*a*; Manes *et al.* 2001; Martin *et al.* 2002; Mosimann *et al.* 2002). As is the case with some modes of ECT, it is likely that the efficacy of subconvulsive rTMS will depend in part upon the parameters of stimulation. More work is needed to determine the most effective parameter combination and the patient population most likely to benefit. Indeed, the best responses with rTMS have been seen in patients referred for ECT (Grunhaus *et al.* 2000; Janicak *et al.* 2002). While the studies comparing rTMS with ECT subjects were not double-blind, there is a suggestion that patient selection may explain some of the heterogeneity in response rates to both active and sham rTMS across studies.

Parameters of stimulation that have been explored in relation to the efficacy of rTMS include intensity of the magnetic field, pulse frequency, duration of the pulse trains, number of pulses per day and number of weeks of stimulation. Less is known about the ideal cortical location to guide the placement of the stimulating coil. Early studies employed large round coils that possess a non-focal field, while more recent studies have utilized more focal figure-8 coils, making the selection of stimulating site all the more important. It is possible that the therapeutic value of rTMS has been underestimated by the failure to identify the optimal site of stimulation. The action of rTMS has been found to be comparable to that of ECS in animal models of depression, but it is important to realize that these rodent studies utilize non-focal coils that result in stimulation of the entire brain. A return to non-focal stimulation in clinical trials, or a systematic search for the optimal site of stimulation may help to optimize the utility of subconvulsive rTMS. Bilateral rTMS represents a step in the direction of reduced focality in an effort to enhance the efficacy of rTMS.

AN ATTEMPT TO INCREASE THE EFFICACY OF rTMS: SIMULTANEOUS BILATERAL rTMS

Loo *et al.* (1999*b*) after failing to find a significant antidepressant benefit of left unilateral prefrontal cortex rTMS in a sham-controlled trial, went on to develop simultaneous BL rTMS of the right and left prefrontal cortices as a means of potentially boosting the efficacy of this treatment. It is widely accepted that BL ECT is more effective that RUL ECT when given at doses close to the seizure threshold (American Psychiatric Association, 2001). If rTMS and ECT share commonalities in their modes of action, one might predict that BL rTMS would be more effective than unilateral rTMS.

Loo *et al.* (2003) (in this issue pp. 33–40) achieved simultaneous BL rTMS by using two focal figure-8 coils positioned over the left and right prefrontal cortex. A separate magnetic stimulator powered each coil. The stimulators were simultaneously triggered using the same high frequency parameters of stimulation. The non-focal round coil, used in early work with rTMS, also simultaneously stimulates bilateral frontal regions. But, BL rTMS as performed by Loo *et al.* differs from stimulation with a round coil in several ways. The non-focal round coil stimulates bilateral posterior frontal and parietal regions in addition to anterior frontal regions. Thus, stimulation with a round coil at intensities in excess of the threshold for eliciting a motor twitch (motor threshold) would elicit motor contractions in the arms with each pulse. On the other hand, prefrontal stimulation, even at intensities that

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moderately exceed the motor threshold, does not elicit movement. Aside from issues of patient comfort, this fact is relevant because the motor cortex is the cortical region with the lowest seizure threshold. Thus, creating a form of BL stimulation that avoided the motor cortex could have advantages in terms of the safety margin and tolerability of the treatment (Wassermann, 1998).

Another difference between BL stimulation with a round coil and BL stimulation with two focal coils has to do with the direction of the induced electric field. The round coil induces current that flows in opposite directions in the two hemispheres (lateral-to-medial in one prefrontal cortex and medial-to-lateral in the other), while the method of Loo *et al.* induces current in the medial-to-lateral direction in both prefrontal cortices. There is a preferential direction of current flow for stimulating the motor and visual cortices (Meyer *et al.* 1991; Kammer *et al.* 2001*a*). If the same is true of the prefrontal cortex, then the round coil might only effectively stimulate one hemisphere. If the direction of current flow chosen by Loo *et al.* for simultaneous BL rTMS were the optimal direction for prefrontal cortex, then their method could preferentially stimulate both hemispheres. Likewise, if Loo *et al.* have not chosen the optimal direction for prefrontal cortex, their method may be sub-optimal for effectively stimulating either hemisphere. The optimal direction for stimulation of the prefrontal cortex to produce therapeutic benefit is not known, and represents another parameter that would be important to study in subsequent work. Of note, the direction of induced current is not standardized across manufacturers of rTMS devices and coils (Kammer *et al.* 2001*b*), so this represents yet another source of variation in clinical response rates across centres.

Other groups have performed bilateral rTMS in a non-simultaneous, alternating fashion. Typically, the laterality of stimulation is alternated across days or between trains (Dragasevic *et al.* 2002). While some have used the same pulse frequency of stimulation on both hemispheres, others have used a high frequency on the left and low frequency on the right prefrontal cortex (Cohen *et al.* 2002). Altering the frequency of stimulation results in different patterns of effects on neurophysiological activity. Low frequencies have been found to have an inhibitory effect on motor cortex excitability (Chen *et al.* 1997; Muellbacher *et al.* 2000), while high frequencies have been found to be excitatory (Pascual-Leone *et al.* 1994; Wu *et al.* 2000). Responses to different frequencies of rTMS outside the motor cortex have been more variable, and may depend upon the basal level of activation in the site of stimulation (Kimbrell *et al.* 1999; Speer *et al.* 2000). Using a low frequency on the right and high frequency on the left prefrontal cortex has been theorized to shift the balance of activity between the right and left prefrontal cortices towards the left. Much of the work with unilateral rTMS has been predicated on the hypothesis that an imbalance in activity between the right and left prefrontal cortex underlies depression, and that relative hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) may be corrected through high frequency rTMS to the left DLPFC. One group has found that low frequency rTMS to the right DLPFC exerted benefits in depression in a sham-controlled trial (Klein *et al.* 1999). This has been interpreted as suggesting that low frequency rTMS exerts an inhibitory effect on the right DLPFC, and thereby achieves the same relative effect on the right/left balance of activity as that achieved by high frequency rTMS to the left DLPFC. However, the hypothesis that the mood effects of different frequencies of rTMS are hemisphere-dependent has not been directly tested.

Loo *et al.* (2003) report that simultaneous bilateral rTMS with high frequency stimulation was not effective in treating depression. If the effects on mood of different frequencies of rTMS are indeed hemisphere-dependent, and if altering the right/left ratio in prefrontal activity is critical to antidepressant response, then bilateral rTMS with a high frequency administered to both hemispheres would be expected to lack antidepressant properties. However, other possible explanations for their negative results should be entertained, such as inadequate sample size, too short a duration of treatment, suboptimal parameters of stimulation, patient population factors, etc. The fact that three of the patients experienced an adverse mood reaction during the stimulation (anxiety and sudden tearfulness) suggests that the stimulation was able to affect mood systems, albeit not in the desired direction. Indeed, mood symptoms were the most notable side effect of simultaneous bilateral rTMS. This form of stimulation was found to be otherwise safe and lacking in cognitive side effects.

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FUTURE DIRECTIONS

While Loo *et al*. failed to find antidepressant efficacy of simultaneous BL rTMS, it would be premature to abandon attempts to enhance the efficacy of rTMS. Further directions for optimizing efficacy include systematic evaluation of stimulus parameters, site of stimulation, duration of treatment, directionality of induced current, novel coil designs and convulsive levels of rTMS. Beyond its potential clinical applications, simultaneous rTMS to different cortical regions may be a useful tool in studying the neural circuitry underlying psychiatric illnesses. The finding that bilateral simultaneous rTMS lacked cognitive side effects was important to support future work with this new application of rTMS technology. It is possible that simultaneous stimulation with different frequencies (such as high frequency on the left combined with low frequency on the right prefrontal cortex) might have been more effective. As well, other coil locations may be worth exploring. The advent of rTMS made available a tool that could non-invasively modulate brain activity at the site of stimulation, and exert trans-synaptic effects in connected cortical regions. The ability to exert simultaneously such modulation at two sites within a connected network opens up new possibilities for experimental paradigms. For such an approach to be of maximal value, it would be of use to know what effect two-site rTMS has on functional brain activity. The availability of these new tools to modulate focally brain activity challenges the field to refine the functional circuitry (and individual variations therein) underlying the disorder in question so that available brain stimulation techniques may be applied to restore function. Using rTMS as a probe of brain function can complement functional neuroimaging to help clarify the circuitry to target.

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