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Transcranial magnetic stimulation in depression

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Neurologists have employed transcranial magnetic stimulation (TMS) as an investigative tool for more than a decade, but as its potential effects on mood have become apparent, interest has grown in its use in the treatment and assessment of psychiatric conditions, such as major depression.

The underlying principle of TMS is focal electromagnetic induction (remember Faraday's Law?) with an insulated coil conducting an electric current placed on the surface of the scalp. By changing the current through the coil, magnetic fields are generated which pass easily through electric insulators, such as skin and bone. Stimulator machines now generate up to 2 Tesla (magnetic field strength) and activate neurons to a depth of around 2 cm from the coil surface (Rudiak & Marg, 1994). Within the cortex, electrical currents flow because of electrical field gradients, induced by the rapidly changing magnetic field. These currents have the capacity to interrupt and facilitate neuron function, probably by depolarisation.

A variety of motor, sensory and cognitive effects have been described after stimulating cortical areas (Wassermann, 1997). Stimulation over the motor area results in an observable muscle movement and motor evoked potential (MEP). Stimulation over the left temporal cortex can block speech production (Pascual-Leone *et al*, 1991), over the occipital cortex it can induce visual disturbances (Amassian *et al*, 1989), and over the left dorsolateral prefrontal cortex, it can inhibit working memory (Pascual-Leone & Hallett, 1994). In this way, TMS has been used to 'map' cortical function and establish the integrity of corticospinal pathways. In addition to its use as an investigative tool, potential therapeutic applications have been considered for specific neurological symptoms. Different TMS frequencies appear to have opposite physiological effects. For example, lower frequencies (less than 1 Hz) are inhibitory, higher frequencies activating (Chen *et al*, 1997). Low-frequency TMS may be useful in inhibiting (quenching) overactive epileptogenic areas (Weiss *et al*, 1995; Chen *et al*, 1997). Higher-frequency TMS applied over the motor cortex can result in improved reaction time for specific motor tasks in patients with Parkinson's disease (Pascual-Leone *et al*, 1994).

During earlier studies of language localisation, researchers noticed that subjects experienced changes in affect during TMS over dominant frontal regions. This led to the hypothesis that TMS may have clinically useful antidepressant effects. Initially, low-frequency TMS was used in patients with depression with inconclusive results. With the development of rapid-rate magnetic stimulators and using frequencies of up to 20 Hz, apparently more robust results were produced by treating major depression with stimulation over the left dorsolateral prefrontal cortex (DLPFC; Pascual-Leone *et al*, 1996; George *et al*, 1997). Without exception, trials of TMS in depression have used small or highly selected groups of patients, have employed no, or doubtful, placebo conditions and have used a variety of stimulus applications, so that the jury on treatment efficacy is still out. Its intuitive theoretical appeal, first positive open trial results and an increasing 'user' awareness and demand for information or even treatment, make it important for the psychiatrist to have some basic information on the procedure.

WHAT DOES TMS INVOLVE?

The subject is typically seated, fully conscious, and able to cooperate with the procedure. A specially designed cap is worn to enable marking of the coil position on the surface of the head. Electrodes over the first dorsal interosseus or abductor pollicis brevis muscle transmit MEP signals to a digital recording and display device. Concurrent electroencephalographic (EEG) monitoring is suggested by some authors to enable monitoring for ictal phenomena during a TMS session, but continuous monitoring of electromyographs (EMG) may be just as useful in detecting cortico-cortical spread of activation which may be the prelude to ictal activity.

The initial stage of a TMS procedure is called 'mapping'. This involves moving the coil position over the motor cortex and recording the EMG until the optimum site of stimulation of the contralateral target muscle is found. Most coils are either single flat loop or in the shape of a 'figure of eight'. The latter gives a more discrete focus of stimulation. Determination of the patient's motor threshold follows the mapping procedure. This is the lowest stimulation strength over the motor cortex to produce a movement or EMG response from the target hand muscle. The individual's motor threshold is important as a measure of cortical excitability and a calibration for the stimulus strength during treatment. For treatment protocols, the next stage is marking the treatment position of the coil on the scalp. A variety of sites have been investigated, although it has been suggested that the left DLPFC may be associated with the greatest antidepressant response (Pascual-Leone *et al*, 1996; George *et al*, 1997). The site for the left DLPFC is conventionally located by measuring 5 cm anterior to the optimal site for abductor pollicis brevis stimulation.

Treatment parameters are currently the focus of investigation into the efficacy and safety of TMS in depression. These parameters include stimulus strength relative to motor threshold, total number of stimuli, frequency of stimulation, duration of stimulus trains and inter-train intervals. An example of a treatment regimen could be five daily sessions at 100% of motor threshold, using 10 Hz, five-second trains, repeated 20 times with an inter-train interval of 60 seconds, that is, 1000 stimuli daily.

HOW SAFE IS TMS?

TMS is considered a safe procedure if used within guidelines for maximum safe combinations of stimulus frequency, intensity and duration (Pascual-Leone & Wassermann, 1996), and inter-train interval (Wassermann *et al*, 1996*a*).

Some individuals experience mild discomfort on the scalp due to muscular

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contraction secondary to superficial nerve stimulation. Such local pain or headache usually responds promptly to simple analgesia. Coils produce a clicking sound on discharge. A permanent shift in hearing threshold was reported in one study using rabbits (Counter *et al*, 1990) although this has not been replicated in humans (Pascual-Leone *et al*, 1992). The use of ear plugs is recommended to avoid discomfort or a temporary threshold shift.

No harmful effects on cognitive, endocrine or neurophysiological function (EEG), have been reported (Chokroverty *et al*, 1995; Wassermann *et al*, 1996*b*) but further work in this area is needed. A histopathological study (Gates *et al*, 1992) looked at tissue from subjects who had received TMS for speech localisation prior to temporal lobectomy for intractable epilepsy. No related evidence of neural tissue pathology was found.

TMS has caused seizures in humans. All subjects made a full recovery with no long-term change in EEG or cognition. There are no reports that TMS can cause or worsen epilepsy. Seizures have occurred with single intense stimulation, or multiple stimuli with short inter-train intervals (Pascual-Leone *et al*, 1993). Safety guidelines were suggested after studies of MEP in normal individuals. Stimulation over the motor cortex tends to produce uniform MEPs in hand muscles. Increasing the intensity and frequency of TMS produces a spread of MEPs to adjacent and proximal muscles and also a rhythmic series of MEPs after stimulation has stopped. The former is an example of cortico-cortical spread of stimulation, the latter an 'after-discharge' equivalent seen on EMG. These findings were used to develop a 'trade-off matrix' defining safe combinations of frequency, intensity and duration (Pascual-Leone *et al*, 1993). These guidelines have been further revised to minimise seizure risk (Wassermann, 1997). Despite an increase in the number of studies taking place, no further seizures have been reported to date.

WHAT EFFECTS DOES TMS HAVE IN DEPRESSION?

Mood elevation after TMS was first reported in normal volunteers by Bickford *et al* (1987). Preliminary trials on depressed patients (Höflich *et al*, 1993; Grisaru *et al*, 1994) employed low-frequency stimulation (compared with later trials), few subjects and did not have control conditions. However TMS was well tolerated and the authors suggested further studies on larger groups of patients to evaluate therapeutic efficacy.

Kolbinger *et al* (1995) administered TMS in a parallel-design semi-blind pilot study of 15 patients with DSM–III–R (American Psychiatric Association, 1987) major depression. Ten female and five male in-patients were divided into three groups; a sham-treatment group, and treatment groups with stimuli above and below motor threshold. Twelve remained on antidepressant medication that was unchanged for two weeks prior to treatment. TMS was given with a flat coil over the vertex each morning for five days.

Patients received 250 stimuli at 0.25–0.5 Hz. Mean Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) scores decreased from 23.6 to 20.0 and 20.6 to 13.6 in the above- and below-threshold treatment groups, respectively, over the five days. No improvement was shown in the (*post hoc*) control group.

Later in 1995, George *et al* (1995) achieved significant antidepressant effects when targeting the left prefrontal cortex. Six patients with medication-resistant disorders, one unipolar, five bipolar type II, were evaluated in an open trial. Two patients, one of whom responded, were on a blinded mood stabiliser (carbamazepine) that was held constant. Stimulation was at 80% of motor threshold for at least five consecutive days, or as long as they were improving according to HDRS and clinical judgement. The group improved on the whole, with mean HDRS scores falling from 23.8 to 17.5. Two patients showed slight improvement and two others showed a robust decrease in their symptoms with one patient achieving clinical remission and euthymia for the first time in three years. Although limited in numbers and not blind, the authors found the results encouraging, considering that the patients' disorders were of a treatment-resistant nature.

The first double-blind, randomised and controlled trial (Pascual-Leone *et al*, 1996) showed significant and beneficial effects of TMS. Seventeen patients with drug-resistant, DSM–III–R psychotic subtype depression were evaluated. All had a history of at least three depressive episodes and nine had received electroconvulsive therapy (ECT) to which they responded. Five conditions were compared; sham (coil angulated away from the cortex) or real stimulation over the left DLPFC; sham or real stimulation over the right DLPFC; and real stimulation over the vertex. Each patient received five courses over five months. A TMS course consisted of 2000 stimuli per day, delivered at 10 Hz, at 90% of motor threshold for five consecutive days at the beginning of each month. The patients were then monitored weekly until the completion of the trial. Over five months the natural history of such patients could include modest spontaneous improvements. The order of different TMS conditions was randomised and counterbalanced across patients. The possible carry-over effect of the cross-over design was controlled by expressing rating scale scores as percentages of scores from the previous week. Analysis of variance of HDRS and Beck Depression Inventory (BDI; Beck & Beamesderfer, 1974) scores showed significant reductions from real left DLPFC stimulation compared with other scalp positions. The HDRS score fell from 25.2 to 13.8 after real left DLPFC stimulation. Six patients showed no improvement from treatment over this area and in those that did, the beneficial effects reduced over 14 days. The study is remarkable for retaining the cooperation of 17 patients with psychosis over five months; this provokes questions about the representativeness of patients.

More recently, George *et al* (1997) completed a double-blind study of 12 outpatients with depression (11 unipolar, one bipolar II disorder). Nine were drug-free while three remained on a stable dose of antidepressant on which they had only had a partial response after 10 weeks. They were given, in random order, two weeks of active treatment over the left DLPFC, and two weeks of sham treatment. Stimulation consisted of 20 trains at 20 Hz for two seconds over 20 minutes. Intensity was set at 80% of motor threshold. Again the treatment was well tolerated, with all subjects completing the study. There was a statistically significant decrease in HDRS scores of the group from a mean entry score of 28.5 to 23.25 points during the active phase of treatment. However, only four individuals achieved a modest reduction in HDRS by at least 25%. HDRS scores increased by a mean of 3.33 points during the sham/placebo phase, the effect of TMS was not sustained.

The largest published study to date (Figiel *et al*, 1998) reports the treatment of 56 patients with treatment-refractory disorders in an open trial and with a 42%

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response rate, defined by a 60% reduction in HDRS with a final post-treatment score of 16 or less, together with a moderately to markedly improved rating on the Clinical Global Rating Scale (Figiel *et al*, 1998). The treatment protocol consisted of five sessions of 10 trains at 10 Hz for five seconds, to the left DLPFC at 110% of motor threshold. Six patients failed to complete the course; two because of pain during the procedure, one from a recurrence of pre-existing motor tics, another because of right arm muscular contractions and two more for reasons unrelated to TMS treatment. Six patients remained on psychotropic medication which they had received for several months without improvement and which remained constant during TMS.

Despite its limitations, the published research suggests a beneficial effect on depressive symptoms with few side-effects. As with all novel forms of antidepressant therapy a significant period of time is required for evaluation of safety and efficacy. There is a need systematically to investigate the different parameters that constitute a TMS treatment course. If the antidepressant effect is specific, it will depend on such factors as coil placement, stimulus number, intensity, frequency, duration and inter-train length. This work is currently underway, with at least 17 centres worldwide researching the application of TMS in psychiatric disorders. Information is disseminated rapidly between groups with the aid of a list server on the Internet.

As with ECT, it is difficult to find a suitable placebo condition for TMS. Angled coil position has been described and to some extent validated using neuroimaging studies (George *et al*, 1998). There is, however, preliminary evidence that sham repetitive TMS, performed with certain angulations of the coil, may result in measurable voltage induced in the brain, as measured by intracortical multicontact electrodes in the rhesus monkey (S. H. Lisanby & H. A. Sackheim, personal communication, 1998; Lisanby *et al*, 1998). This could, of course, have unpredictable effects on relative efficacy.

In contradiction to the initial impression, a recent preliminary report by Padberg *et al* (1998) suggests that rapid (10 Hz) and slow (0.3 Hz) stimulation are equally effective in reducing depressive symptoms in medication-resistant depression. Preliminary reports (George *et al*, 1998) also suggest that a higher stimulation strength and a greater total number of daily stimuli are associated with more favourable antidepressant responses. However, the dose–response curve may not be linear. Optimum stimulus parameters for lateralised suppression of speech, for example, appear to require a frequency and stimulus numbers lower than those previously used (Epstein *et al*, 1996) suggesting an inverted U-shaped dose–response curve. Moreover, psychiatric disorders may require specific parameters to excite or inhibit specific cortical functions. Even the most positive studies have shown a reappearance of symptoms over two weeks after treatment. It will be important, therefore, to consider requirements for maintenance treatment.

Finally, if TMS has antidepressant action, what are its possible roles in the treatment of depression? Because of practical and cost considerations, first-line therapies are likely to remain a combination of medication and psychological therapies. It is possible that TMS may be useful as an adjunct or alternative, should drug therapy fail. Recent preliminary evidence supports TMS as effective 'add on therapy' to standard antidepressant medication (Conca *et al*, 1996), similar to strategies such as lithium augmentation.

Some authors have suggested that TMS may replace ECT (Zyss, 1994). However, recent work, limited as yet by small numbers, suggests TMS is only as effective as ECT in non-delusional major depression (L. Grunhaus, personal communication, 1998), thus favouring ECT in these very ill patients. Nevertheless, TMS may occupy a niche in a variety of specific clinical situations, for example where anaesthesia is risky, in patients who are unable to tolerate the adverse effects of medication, or in those with prior evidence of cognitive deficits. Further developments in our understanding of TMS mechanisms of action could define stimulation paradigms also effective in delusional depression.

The research to date suggests that TMS has the potential to become part of the investigative and therapeutic repertoire in psychiatry, and it certainly justifies further systematic enquiry. The pathophysiology of depression and of other psychiatric disorders is increasingly conceptualised in terms of a dysfunction of neuronal circuits (Drevets & Raichle, 1992) and of neurons at a cellular and molecular level (Duman *et al*, 1997). TMS, as a non-invasive tool, is well placed to explore these mechanisms in psychiatric disease, and may have a role to play in clinical treatments of the future.

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