Transcranial magnetic stimulation (TMS) as therapy for depression and other disorders

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Objective: An overview of the progress and prospects of transcranial magnetic stimulation (TMS) as a psychiatric therapy for depression.

Method: Published and unpublished studies of the usefulness of TMS as a therapy for depression were assessed, and characterised in terms of a consistent measure of dosage. Additional information was obtained through correspondence, personal meetings and visits to facilities.

Results: TMS, a means for inducing small regional currents in the brain, has been used in clinical neurology for some time, and can be used on conscious subjects with minimal side-effects. Early researchers noticed transient mood effects on people receiving TMS, which prompted several inconclusive investigations of its effects on depressed patients. More recently, knowledge of functional abnormalities associated with depression has led to trials using repetitive TMS (rTMS) to stimulate underactive left prefrontal regions, an approach which has produced short-term benefits for some subjects. The higher dosage delivered by high-frequency rTMS appears to produce greater benefits; scope exists for more conclusive studies based on extended treatment periods.

Conclusions: rTMS is a promising technology: the reviewed evidence indicates that it may be useful in the treatment of depression, and perhaps other disorders which are associated with regional hypometabolism. Should rTMS prove an effective, non-invasive, drug-free treatment for depression, a range of disorders could be similarly treatable.

Introduction: The basis of magnetic stimulation

Electromagnetism, the production of magnetic fields by moving electrical charges, is a phenomenon familiar from high-school physics. Its counterpart, the induction of electric currents by varying magnetic fields, is only slightly less familiar.

Changing magnetic fields are easily produced by varying an electric current; the primary coil of a transformer is a good example. A secondary current induced by a changing field runs at right angles to it – parallel but opposite to the primary current – at a level determined by the rate of change in the field, and the electrical properties of the secondary medium. Magnetic fields pass easily through insulators like bone, so that a current induced inside the skull by an electromagnet can be restricted to a small area. This possibility contrasts with the global stimulation delivered by electroconvulsive therapy (ECT), whose side-effects arise largely from the difficulty of delivering current within the skull from cutaneous electrodes. The technique of inducing small cortical currents using a pulsed electromagnet is called transcranial magnetic stimulation (TMS).

TMS is implemented by passing a time-varying electric current through a coil held close to the head. The resultant magnetic field passes through the skull and induces a small secondary current in the cortex, which probably leads to depolarisation of cortical neurons at appropriate levels [1]. The coil shape dictates the characteristics of the magnetic field, which influences the distribution of the secondary current. A widely distributed cortical current is produced by a flat coil; tighter focus can be achieved with a coil wound in a figure-of-eight pattern [2]. Stimulation typically reaches the outermost white matter underlying the cortex, though it may be possible to stimulate deep structures by using other coil designs [3].

Aside from proximity to the coil and the type of tissue involved, the secondary current depends on the rate of change of the primary current, which is limited by the components used in a given stimulator. The time required to accumulate the necessary charge limited the stimulation rate of early machines to under 1 Hz; more recent high-frequency repetitive TMS (rTMS) machines have better power supply systems which allow rates up to 50 Hz, producing qualitative differences in the effects which can be obtained.

Stimulating various cortical regions, or using TMS pulses to interrupt normal processing, have produced a wide variety of sensory and cognitive effects, listed in Table

1. It is thought, but not known, that TMS and rTMS produce such effects by depolarising cortical neurons via induced currents.

Insert Table 1 about here.

Judging an effective TMS level for individuals is somewhat arbitrary – the threshold to produce observable motor reactions can be gauged quite simply, but it is unclear whether this level is directly relevant to stimulation of other regions, whose physical situation and cytoarchitectonics may be unlike those of the motor cortex. Nonetheless, the motor threshold (T_m) is the generally accepted reference level for most TMS. It is defined as the minimum stimulus intensity which produces five potentials greater than 50 μV in the contralateral abductor pollicis brevis muscle, from ten pulses at the optimal scalp location [6].

Another aspect of TMS' effect on cortex is the directional specificity of stimulation [20]. Generally, midline moderate-level stimulation, with coil currents running in one direction only during the pulses (and at low levels in the other direction between pulses), stimulates the motor cortex on one hemisphere more effectively than the other; this asymmetry reverses when current direction is reversed. These effects are probably caused by cell morphology differentiating the degree of depolarisation produced by currents in different directions [20]. Clearly, the interaction of magnetic stimuli and the brain is incompletely understood, and consists of more than circular currents induced in tissue and fluid.

Background: cellular perspectives on mental illness

Psychiatric disorders are increasingly described in terms of dysfunctions at the cellular or molecular level [21]; treatment entails alteration of the structure, physiology and long-term behaviour of neurons. Traditionally, psychiatrists have used techniques including psychotherapy, pharmaceuticals, light therapy and ECT to indirectly alter patterns of gene expression [22-24] in achieving this end. rTMS offers another avenue for non-invasively influencing the activity of cortical regions, which may make it clinically useful.

The brain's interconnectivity implies that local problems produce widespread effects, a principle evident in depression [25], obsessive-compulsive disorder [26,27] and schizophrenia [28]. Austin and Mitchell [29] recently emphasised the prefrontal (particularly left prefrontal) and basal ganglia dysfunction observed in depression, and Bench *et al*. [30] have reported that the associated left prefrontal hypoperfusion returns to

normal with remission. This is related to recent studies using rTMS to change mood by stimulating dorsolateral prefrontal regions. Pascual-Leone and coworkers [18] observed slight self-rating effects which differed according to rTMS location; further, more significant findings have indicated that mood control is lateralised, and that the effect of rTMS is identifiably changed during depression [31,32], raising the possibility of testing for the disorder. Given such an anatomical correlate, using rTMS to focally hyperperfuse cortex [33] is a plausible treatment for depression, or any disorder associated with regional underactivity.

rTMS versus ECT

ECT has been an effective and valuable clinical tool for almost sixty years. This paper is not intended as a criticism of ECT, but the negative aspects of convulsion, risky and expensive anæsthesia, associated memory disturbance and ECT's considerable stigma are side-effects worthy of consideration. By contrast, TMS gives electrical stimulation without anæsthesia or convulsion, and avoids these drawbacks without posing obvious additional hazards. The stimulation provided is qualitatively different to that of ECT, but the results of preliminary studies suggest that there are also essential similarities.

Early studies of TMS present an inconsistent picture with regard to treatment parameters. Accordingly, a recent conference planned a systematic evaluation of parameter combinations, using an international consortium of research teams.

Early studies

TMS was first linked to affect by Bickford and colleagues' observation that "… several of our normal subjects have noted mood elevation." [34] Six years later, Höflich *et al*. [35] were the first to publish a study of psychiatric rTMS: two "drug-resistant major depressed psychotic patients" received ten rTMS sessions followed by ten ECT sessions. Low frequency rTMS, delivered using a 14 cm flat coil over the vertex, was grouped in ten sets of twenty-five (0.3 Hz, 0.75-1.5 T / 105-130% T_m) with intervening one-minute breaks; the coil was flipped between sets to give equal stimulation in each direction. Two sets of five daily sessions were separated by two days without treatment.

Treatment produced no clear improvement in these two cases. One patient's Hamilton Depression Rating Scale (HDRS) score decreased 21% after rTMS, and a further 31% after ECT. The other showed no response to rTMS, but a rapid 56% improvement

followed ECT. The authors considered that this moderate response, and possible rTMS priming for ECT, suggested further study.

Grisaru and coworkers [36] treated ten schizophrenic and ten depressed individuals with TMS. Patients were administered the HDRS and the Brief Psychiatric Rating Scale (BPRS) before and after sixty pulses (2 T) were delivered to the motor cortex in an hour; no other parameters were reported. Schizophrenic patients received no overall benefit: one showed slight improvement, another was worse and the others remained the same. Among the depressed individuals, five were unchanged, one was worse, but four were mildly better. TMS, delivered very slowly over a single treatment session, failed to provide any clear benefit in this study. However, the antidepressant effects of other treatments depend on chronic administration, and different rates of rTMS produce markedly different cortical effects [37]. A single session of very low frequency stimulation, delivered to an arbitrary site, was not an adequate evaluation of rTMS treatment for depression in general.

In 1995 the same group published a three-part study [38] comparing subconvulsive rTMS with electroconvulsive shock (ECS, a rodent model of ECT). Rat and mouse subjects received rTMS (25 Hz, 2 s, 2.3 T) to the whole brain. In rodents, prior treatment with chronic ECS enhances behavioural stereotypy induced by apomorphine; in this study, chronic daily rTMS produced similar effects, though acute stimulation did not.

Secondly, the team used the Porsolt swim test, measuring a subject's periods of immobility in a water bath, as an analogue of 'despair'. The duration of immobility was most reduced by prior ECS, but two prior rTMS treatments also significantly reduced the time when compared with sham treatments. Thirdly, a single rTMS session raised seizure thresholds for subsequent electrical stimulation just as ECS does, a phenomenon believed to be related to the antidepressant properties of ECT.

Though limited, these parallels between rTMS and ECS in rats suggest corresponding similarity between rTMS and ECT in humans. Whether the qualities shared by rTMS and ECT are those which make treatment effective remains to be seen. Both are means for creating electric currents in the cortex, though significantly it appears that rTMS is incapable of inducing a seizure in rodents or non-human primates [39].

Small-animal models of human TMS are also flawed by the fact that the effective depth for magnetic stimulation reaches the whole brain in small animals, whereas only the outer cortex is stimulated in human TMS [3]. In this respect, rodent rTMS resembles ECS more than human rTMS does ECT, though the absence of seizure is important.

Evaluating rTMS in the treatment of depression

The study of TMS / rTMS in the treatment of depression has progressed rapidly in the last few years, with early experiments giving way to more systematic evaluations. Kolbinger and colleagues [40] reported a parallel-design, semi-blind pilot study of TMS in DSM-IIIR major depression. Fifteen patients were divided into a placæbo (sham treatment) group and two treatment groups (above and below T_m). TMS was administered through a 14 cm flat coil at the vertex (0.25 - 0.5 Hz; 250 stimuli), each morning for five consecutive days. Coil orientation (and hence field direction) was changed every twenty-five stimuli; it is not known whether there were breaks between trains.

HDRS ratings were not significantly changed in either treatment group, and the control group remained unchanged. On a self-rating scale, there was no change in the suprathreshold and control groups, but a strong trend toward improvement in the subthreshold group. The authors characterised TMS as "practically without any side-effects," and noted that no seizures were induced. Their results were largely inconclusive, though the self-rating trend suggested that this treatment could improve patients' mind-states. In the absence of sham treatment, this trend is indistinguishable from placebo response. Furthermore, there is no reason to suppose that stimulation at the vertex would affect the symptoms of depression.

Later the same year, George and coworkers [41] reported a trial of rTMS with six medication-resistant unipolar and bipolar depressed patients. Noting that hypoperfusion of the left prefrontal cortex accompanies depression [3,42], they stimulated that region (80% T_m, 20 Hz, 2s / min for 20 min) for at least five consecutive days. Patients remained in treatment while they were improving according to clinical assessment and the HDRS, though there was no provision for extending the treatment in the hope of consolidating its benefits, if any.

rTMS to the left prefrontal region was well tolerated and apparently safe. For the group as a whole there was an improvement in symptoms: two patients were unchanged, two improved slightly, and two showed robust improvement. Of the latter, one showed complete remission whereas the other had some residual symptoms. While this study was not blind, such results with highly medication-resistant patients are promising. The authors recognised the need to investigate stimulation parameters for treating depression; their own stimulation was restricted to 80% of motor threshold in order to obtain ethical and FDA clearance [George MS: personal communication]. At such levels it seems less likely that

frontal neuron depolarisation or other cortical effects are occurring, which may have compromised the clinical benefits observed.

George and colleages followed this pilot study with a double-blind trial using the same treatment programme for twelve depressed patients [43; George MS *et al*.: in preparation]. Half of the participants received two-week blocks of active rTMS followed by sham treatment, whereas the treatment order was reversed for the remainder. ANOVA of HDRS scores indicated a highly significant improvement for the group as a whole when given active rather than sham rTMS, but the benefits for individual participants were less apparent. A mild improvement (25% HDRS reduction) was obtained by only four patients, and indeed sham treatment had the same effect for two patients. The course over which the improvements were noticeable is not known; clearly, this study demonstrates statistically but not clinically significant effects of rTMS.

In 1996, Pascual-Leone and colleagues reported a study of seventeen patients whose major depression had resisted pharmacological treatment. These people were treated with rTMS, in its first published double-blind trial [44]. These patients had all suffered three or more major episodes, and had not been helped by medication, despite combined and high dosage trials; nine had previously required and responded to ECT. Daily rTMS consisted of twenty trains (10 Hz × 10 s, 90% T_m) separated by one-minute pauses; an 8-shaped coil was used to focus stimuli on various regions.

Five treatments were given: genuine or sham stimulation[1] of left dorsolateral prefrontal cortex (DPC), genuine or sham stimulation of right DPC, and stimulation at the vertex. The study sought to evaluate rTMS of the left DPC; other conditions were conducted as controls. Every month for five months, each patient received five consecutive days of one condition, and was monitored weekly thereafter with the HDRS and the Beck Depression Inventory (BDI). The order of conditions was randomised and counterbalanced across patients. All patients also received nimodipine (30 mg thrice daily) as a mood stabiliser.

Patients tolerated rTMS without complications; no seizures were induced, and seven patients reported occasional minor headaches. Analysis of variance of HDRS scores

[1] In this study, as for both of the George *et al*. studies, sham rTMS was administered by holding the coil at a 45° angle to the scalp. The discharge sound and the sensation in scalp muscles were very similar, but the magnetic field in the cortex was greatly reduced. Thus the patients were blind to the nature of stimulation; the raters did not observe the treatment session so that they were unaware whether active or sham stimulation had been adminstered.

showed significantly greater reduction from left frontal rTMS than the other conditions. BDI scores followed the same pattern, with high significance levels. The patients were asked to state which condition(s) were subjectively beneficial: nine nominated stimulation of left DPC, three picked rTMS to both left DPC and the vertex, two chose rTMS to both left and right DPC, and one responded to genuine and sham rTMS to left DPC. The beneficial effects of stimulation appeared to taper off over the next two weeks.

This study demonstrates that rTMS of left DPC (and perhaps other regions) had, for some patients, an unambiguous short-term antidepressant effect. It is likely that the higher stimulation level (90% rather than 80% of T_m) produced a stronger effect; nonetheless, the short-lived benefits obtained do not yet challenge the efficacy of current treatment methods (though drug therapy had been ineffectual for these patients).

A crucial aspect requiring attention is the issue of safety – if rTMS has serious health consequences or side-effects, its therapeutic benefits are irrelevant. To address this issue, it is useful to briefly summarise research into the safety or otherwise of TMS and rTMS.

Issues of patient safety and comfort

Hazards of rTMS

TMS is currently regarded as safe to use within sensible guidelines [39]. This judgement is based on studies spanning histology, physiology and neurology.

At the cellular level, most studies have detected no pathology in neural tissue exposed to TMS [45], though Matsumiya *et al*. [46] reported microvacuolar changes in the cortical neuropil of half the 24 animals they exposed to over 100 high-intensity stimuli. In humans, Gates *et al*. [45] found no histopathology evident in light microscopic examination of brain tissue, from two subjects who had received over 2000 stimuli in a speech lateralisation study, two and four weeks prior to anterotemporal lobectomy for epilepsy.

Chokroverty *et al*. [47] found no harmful short- or long-term effects on cognitive function, quantitative EEG or serum prolactin and cortisol levels in ten people given 35-50 TMS at 120-125% T_m. Eyre *et al*. [48] reported no change in the background EEG, cortical blood flow, blood pressure or heart rate of cats exposed to TMS (1.9 T; 0.2 Hz; 120-500 stimuli). These studies are representative of many others finding no harmful effects of TMS. A full review of safety issues for TMS treatment will shortly be available [39].

Side effects

Most TMS and rTMS side-effects are considered trivial, such as mild headache from direct stimulation of scalp muscles [49]. Counter *et al*. [50] reported a permanent threshold shift in animals due to the acoustic artefact of coil discharge from the Cadwell MES-10, although no deleterious effects occur if subjects' ears are protected [51]. Consequently, the use of ear-plugs has been recommended by some authors, although Pascual-Leone *et al*. [52] found no evidence of auditory deficits resulting from exposure to rTMS.

TMS can induce epileptiform activity in patients with epilepsy whose medication is reduced, prior to surgery [53,54]. However, no adverse sequelæ were observed, and Tassinari *et al*. [55] found no similar phenomena in drug-treated epileptic patients. Dhuna *et al*. [56] applied rTMS to eight patients being evaluated for epilepsy surgery, but were able to induce a partial seizure in only one subject. Jennum *et al*. [57] evaluated the epileptogenic effect of rTMS in epileptic patient waiting for surgery, and noted that sharp waves/spikes and low frequency potentials were actually reduced. No paroxysmal activity was provoked and no seizures developed, and they concluded that the rTMS used could not effectively induce paroxysmal activity. There are no accounts of TMS or rTMS causing or worsening epilepsy.

Pascual-Leone *et al*. [58] reported that single trains of rTMS could cause seizure in healthy individuals, and later published guidelines[2] for safe use [49]. However, two normal subjects had seizures after treated within these guidelines [59]; while the recommended maximum number of stimuli in a train was not exceeded, the interval between trains was one second or less. These incidents, and the outcomes of a recent conference[3] on the safety of TMS, have led to new guidelines for stimulation parameters and best-practice recommendations [39]. Minimum intertrain intervals are incorporated into the new recommendations, since there have been no reports of seizures when the interval is twenty seconds or more.

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[2] Subjects and investigators should wear hearing protection when the frequency of TMS used is 1 Hz or greater; rTMS should be conducted in settings where convulsions can be properly managed; rTMS may cause scalp burns at electrode sites, so precautions must be taken. The authors also provide guidelines about the maximum number of consecutive pulses which can be delivered before cortical excitability begins to spread – a precursor of ictal activity. Their recommendations are summarised graphically depending on intensity and frequency of stimulation, ranging from 2 stimuli (220% T_m; 25 Hz) to > 50 stimuli (110-150% T_m; 1-3 Hz) (Pascual-Leone *et al*., 1993).

[3] International Workshop on the Safety of TMS, Bethesda, Maryland, USA; June 1996.

Finally, TMS has been used in diagnostic medicine for over a decade without reports of adverse consequences in the literature. This absence is persuasive (though negative) evidence for its safety.

Current and future prospects

Recent editorials have noted the promise of rTMS as a psychiatric therapy, especially for depression [60,61]. Since then, the significant studies by George and team [41,43] and Pascual-Leone and coworkers [44] have strengthened that claim significantly.

Our short review of research into the use of rTMS for depression, outlined in Table 2, illustrates a progression from early, inconclusive experiments using TMS technology to recent, promising rTMS trials. It seems likely that studies currently in progress will provide the necessary data for a thorough evaluation of rTMS' potential as a therapeutic tool; at present, it is only possible to say that it shows promise.

Insert Table 2 about here.

The most positive studies of rTMS therapy have observed benefits lasting for two weeks after a week of treatment [44], and one remission after two weeks of treatment [41]. Such clinical benefits are not sufficient to justify a claim for rTMS as an effective new treatment for depression, but rectifying the deficits apparent in the treatment programmes used could improve outcomes. Most early studies chose arbitrary sites, and large coils produced diffuse stimulation. Of the three published studies which used focal stimulation of a region known to be affected in depression, two were restricted to low power and used short daily schedules [41,43], while the other ended treatment after a single week [44].

Clearly, an open-ended or longer term study involving a greater duration of rTMS treatment, at levels known to stimulate the cortex, would determine whether these factors are critical in treating depression with rTMS. Both major approaches in current use require two to three weeks before clear patient benefits [21], and it seems reasonable to expect that rTMS might require the same time to take effect.

Another factor may be the total daily amount of rTMS administered to a patient. Table 2 includes a column of calculated total daily doses given to subjects in each of the studies, expressed in units of the motor threshold (T_mU). This figure seems positively correlated with the degree of beneficial effects observed in each study, and in particular highlights the dosage difference between the two left-prefrontal studies by George *et al.* [41,43] and that of Pascual-Leone *et al.* [44]. The latter study used by far the greatest daily

T_mU dosage of those listed, and produced the most promising results. Daily motor unit dose may be a biologically relevant measure of the amount of rTMS given to a patient, which is useful for a technique with no defined dose such as the seizure threshold for ECT.

At present, ECT is a valuable therapeutic tool, albeit one that requires general anæsthesia, and one which is associated with seizure, headache and temporary memory disturbance. The stigma of seizure therapy will probably never be removed, and seriously limits its acceptance by patients. If rTMS is clinically useful, the removal of these adverse conditions represents a considerable improvement for patients. rTMS' spatial accuracy [2] and the fact that different parameters may excite or disrupt cortical activity [37] also suggest a wider repertoire of achievable effects.

This flexibility, and the growing literature on regional dysfunction in psychiatric disorders, imply that uses for rTMS will not be restricted to depression. Suggesting that rTMS may replace ECT for some patients is a conservative estimate of its value. It may also aid clinical situations in which ECT is not indicated, giving different but overlapping domains of clinical use. If upcoming studies indicate that rTMS can successfully produce remission for depressed patients, they will raise the possibility of using rTMS at different locations for other psychiatric disorders whose anatomical basis can be deduced. In any case, integrating rTMS into clinical approaches requires further assessment of the duration of benefits, and optimal treatment courses.

TMS is attracting attention and research interest around the world, with trials of psychiatric rTMS in progress in Spain, Israel and various centres in the US; studies are also planned in the UK, Japan, Australia and elsewhere. It seems likely that this treatment will be important to psychiatry: to reiterate George *et al*. [3], rTMS in the twenty-first century seems likely to be as significant as ECT has been in the twentieth century. The studies reviewed here hint at a range of potential benefits.

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Acknowledgment: *The authors are grateful to Dr Poul Jennum, Department of Clinical Neurophysiology, KAS Glostrup, Dantec Medical A/S, Skovlunde, Copenhagen, Denmark, and Dr Peter Kitchener, Department of Anatomy and Physiology, University of Tasmania, for their time and information.*

Table 1. Functions influenced by TMS / rTMS

		Parameters			
Function	**Paper(s)**	Rate	Intensity	Dur	Reps
Muscle control	Barker *et al*. [4]	0.3 Hz	max (2 T?)		
Tremor rate in Parkinson's disease	Pascual-Leone *et al*. [5]	0.2 Hz	50-200% T_m		300
Slowness in Parkinson's disease	Pascual-Leone *et al*. [6]	5 Hz	90% T_m		
Suppression of visual perception	Amassian *et al*. [7]	(pulse)	2-2.2 T		
Suppression of stereo vision	Takayama & Sugishita [8]	20 Hz	100% T_m	1 s	
Visual extinction	Pascual-Leone *et al*. [9]	25 Hz	115% T_m	0.2 s	
Disrupting vis. motion perception	Beckers & Zeki [10]	(pulse)	1.4 T		
Volition in motor programming	Ammon & Gandevia [11]	(pulse)	50-80% max		
Errors in saccade sequences	Müri *et al*. [12]	(pulse)	80-90% max		
Errors in verbal memory	Pascual-Leone & Hallett [13]	25 Hz	90% T_m		
Errors in procedural learning	Pascual-Leone *et al*. [14]	10 Hz	100% T_m		
Arrest of speech	Pascual-Leone *et al*. [15]	8/16 Hz	80% max	10 s	
	Jennum *et al*. [16]	30 Hz	116% T_m	1 s	
Errors in verbal comprehension	Claus *et al*. [17]	50 Hz	1 T	0.5 s	
Lateralised control of mood	Pascual-Leone *et al*. [18]	10 Hz	110% T_m	5 s	10
Reduction of reaction time	Pascual-Leone *et al*. [19]	(pulse)	± T_m		