

# Transcranial magnetic stimulation: an alternative physical treatment in depression

Veronica O'Keane

*Ir J Psych Med* 2001; 18(3): 79-81

There are still a very limited number of physical therapies available for those suffering from depression, in spite of the rapid developments in pharmacological treatments. Electroconvulsive therapy (ECT) has the highest rate of response of any form of antidepressant therapy but is generally used only in those patients failing to respond to pharmacotherapy, except in specific and very limited situations where it is recommended as a primary therapy. Stereotactic subcaudate tractotomy (SST), the standard neurosurgical procedure employed in the UK for resistant depression, is only indicated when patients are suffering from severe, disabling depressive illness; and have failed to respond to all other treatments. Physical therapies are generally framed in this context, i.e. as treatments for those suffering from intractable depression. Novel physical therapies will inevitably be compared to ECT as the standard physical treatment. The categorisation and comparison of new physical therapies with ECT may not be the appropriate way to proceed with evaluating the usefulness of such treatments. Transcranial magnetic stimulation (TMS) is a new technology for non-invasively stimulating the brain and may be an example of a treatment option that needs to be re-evaluated outside the context of resistant depression.

## Transcranial magnetic stimulation (TMS): mechanism of action

TMS has been used as a tool for mapping brain function for over a decade. TMS involves placing an electromagnetic, insulated coil on the scalp and rapidly changing the currents in the coil so that magnetic fields are generated. These magnetic fields induce currents in neurones to a depth of about 2cm from the coil surface; thus altering neuron function, probably by depolarisation.<sup>1</sup> Different TMS frequencies result in different physiological effects: electrophysiological studies have shown that 1-Hz rTMS of the primary motor area can produce a local decrease in excitability, whereas higher frequencies are associated with facilitation of motor cortical excitability.<sup>2,3</sup> The effects obtained from TMS also depend on the interstimulus intervals (ISIs), as different neuronal circuits are recruited by differing ISIs.<sup>4</sup> For example, intracortical inhibitory circuits are activated at ISIs of 1-4ms and facilitatory circuits at ISIs of 8-12ms.<sup>5</sup>

## Effects of TMS

Stimulation of selective cortical areas results in specific motor, sensory, cognitive and behavioural effects.<sup>6</sup> Left temporal cortex stimulation can block speech production,

and stimulation over the occipital cortex can induce visual disturbance.<sup>7,8</sup> Stimulation over the left dorsolateral prefrontal cortex can inhibit working memory.<sup>9</sup> Motor evoked potentials (MEP) in peripheral muscle results from stimulation of the motor cortex and this effect has been used to investigate hemispheric differences in motor cortical excitability in depression.<sup>10</sup> This group compared MEPs rising from cortical stimulation on the right and left cerebral hemispheres in depressed and control groups and found that depressed patients showed lower excitability on the left and greater excitability on the right, compared to controls. This finding is in keeping with neuroimaging studies suggesting that depressed individuals have a relative reduction in left dorsolateral prefrontal activity.<sup>11,12</sup> TMS has been used as an investigative tool in several neurological disorders including Parkinson's Disease, associated with reduced motor cortical inhibition at ISIs of less than 5ms, and cerebellar degeneration, associated with reduced cortical facilitation.<sup>13,14</sup>

## TMS as an antidepressant therapy

The use of TMS as a potential therapeutic tool derived from the observation that subjects experienced changes in affect during TMS over dominant frontal regions.<sup>15</sup> Initial studies had equivocal results but with the development of rapid rate magnetic stimulators, using frequencies of up to 20Hz, and targeting the left dorsolateral prefrontal cortex (LDLPFC), more robust results were obtained.<sup>16,17,20</sup> TMS is administered following determination of the patient's individual motor threshold by evaluating the minimal stimulation over the motor cortex that will produce an MEP. This measurement is an index of cortical excitability and determines the stimulation for treatment (usually 80%-90% of motor threshold). A 'mapping' procedure identifies the LDLPFC: this site is located on the cortex by observing MEP or movement of the abductor pollicis brevis on the contralateral side. The LDLPFC is located 5cm anterior to the optimal site of stimulation of this muscle.

## Clinical trials

The first study to employ targeted TMS examined responses in six patients with treatment-resistant major depressive disorder (MDD).<sup>18</sup> Two patients showed a slight, and two a marked, improvement. The results, although modest, were encouraging. Figiel *et al*<sup>19</sup> examined the anti-depressant efficacy of TMS in 56 refractory patients in an open trial, as measured by a 60% reduction in HDRS with a final post-treatment score of 16 or less, and found a 42% response rate. Subsequent clinical trials of rTMS can broadly be divided into those in resistant depression, comparative trials with ECT and those in mild-moderate depression. Only placebo-controlled, or sham, studies will be reviewed.

Veronica O'Keane, MB PhD MRCPsych FRCPI, Psychiatric Unit, Beaumont Hospital, Dublin 9, Ireland.

SUBMITTED: JUNE 19, 2001. ACCEPTED: AUGUST 21, 2001.

The first double-blind, randomised and controlled trial compared responses to sham and real TMS over the right and left DLPFC and vertex in 17 patients with drug-resistant, psychotic depression.<sup>20</sup> Left DLPFC stimulation resulted in significant reduction in some depression scores compared to other treatments. Berman *et al*<sup>21</sup> assigned treatment-resistant patients to an active (n = 10) or sham (n = 10) course of rTMS. A two week course of active rTMS resulted in statistically significant, but clinically modest reductions in depression scores, compared to sham. Padberg *et al*<sup>22</sup> compared fast frequency, slow frequency and sham rTMS in a group of 18 patients with pharmacotherapy-resistant MDD. Although HDRS scores fell by 18%, the authors concluded that rTMS did not show any clinically meaningful antidepressant efficacy. The most recent study compared real to sham rTMS in 40 patients with drug-resistant depression.<sup>23</sup> Real, but not sham rTMS, was associated with a significant decrease in HDRS, but only 12 patients decreased more than 50%. They concluded that rTMS targeting the LDLPFC was associated with antidepressant efficacy but that the size effect was small. One study found no difference between sham and real rTMS in 18 patients suffering from refractory depression.<sup>24</sup> There were no apparent methodological differences between this study and others to explain the differing findings.

George *et al*<sup>17</sup> compared sham to active LDLPFC TMS in out-patients with depression and found only a modest reduction in Hamilton Depression Rating Scores (HDRS). A subsequent study by this group<sup>25</sup> examined the efficacy of TMS, without concurrent antidepressant use, in 30 out-patients with MDD. Compared to sham, active TMS produced significantly greater reductions in HDRS but response rates were only 45% in the active group. A study from Russia compared real to sham rTMS, in combination with psychotherapy, in 29 patients with 'neurotic depression'.<sup>26</sup> HDRS fell from a mean of 22.9 to 8.6 in the treatment group and was significantly lower than the drop in scores in the sham group.

Studies comparing ECT to rTMS have employed differing designs. One protocol, employed in two studies, compares ECT to rTMS in a head-to-head design. One of these studies found superiority for ECT in some measures but found no overall differences between the two groups, as measured by rates of remission and drop in HDRS.<sup>27</sup> Another study randomly allocated 40 patients to either ECT or rTMS and found ECT to be superior in delusional depression but there were no differences in outcome between the two treatment groups in MDD without psychosis.<sup>28</sup> Another design examined the efficacy of alternating ECT with rTMS treatments vs ECT alone.<sup>29</sup> Combination therapy was as effective as ECT alone and not associated with as many subjective side-effects.

### Safety and tolerability of rTMS

TMS is considered a safe treatment if used within guidelines for maximum safe combination of stimulus frequency, intensity, ISI and duration.<sup>16</sup> A study of 22 patients who had brain volumetric analysis performed using MRI, prior to and following rTMS, found that there were no observed structural changes as a result of treatment.<sup>30</sup> The most frequent unwanted side effects are mild scalp discomfort due to muscular contraction, and noise. The use of ear plugs is recommended for this reason. Auditory threshold was examined in 18 subjects who received up to six weeks

exposure to rMRS and two patients showed mild high frequency hearing loss after several weeks.<sup>31</sup>

Neuropsychological function has been tested formally in several studies of rTMS and has been found: to improve globally following treatment, probably as a result of practice effects (as the improvement was also found in the sham group);<sup>31</sup> to selectively improve memory function only;<sup>32</sup> and to have no adverse effects on neuropsychological performance.<sup>33</sup>

### Mechanism of action of rTMS in depression

The pathophysiology of depression may include hypoactivity in the left prefrontal cortex, as demonstrated by neuroimaging studies.<sup>11</sup> One mechanism of action of rTMS in depression may be to increase activity in the DLPFC brain region. Several studies have tested this hypothesis, using diverse research strategies. Catafau *et al*<sup>34</sup> examined regional cerebral blood flow (rCBF) in seven patients with MDD before and following treatment with rTMS. They found that treatment induced a significant increase in rCBF in the left prefrontal cortex but no relationship could be established between increases in rCBF and clinical response. Another single photon emission computed tomography (SPECT) study examined brain blood flow changes in 22 depressed adults following a two week course of standard rTMS therapy.<sup>35</sup> At medication-free baseline blood flow in the bilateral medial temporal lobes, left prefrontal cortex and caudate declined with increasing depression severity. This negative correlation disappeared following treatment. Responders showed increased inferior frontal lobe activity compared to non-responders prior to treatment and this difference increased further following treatment.

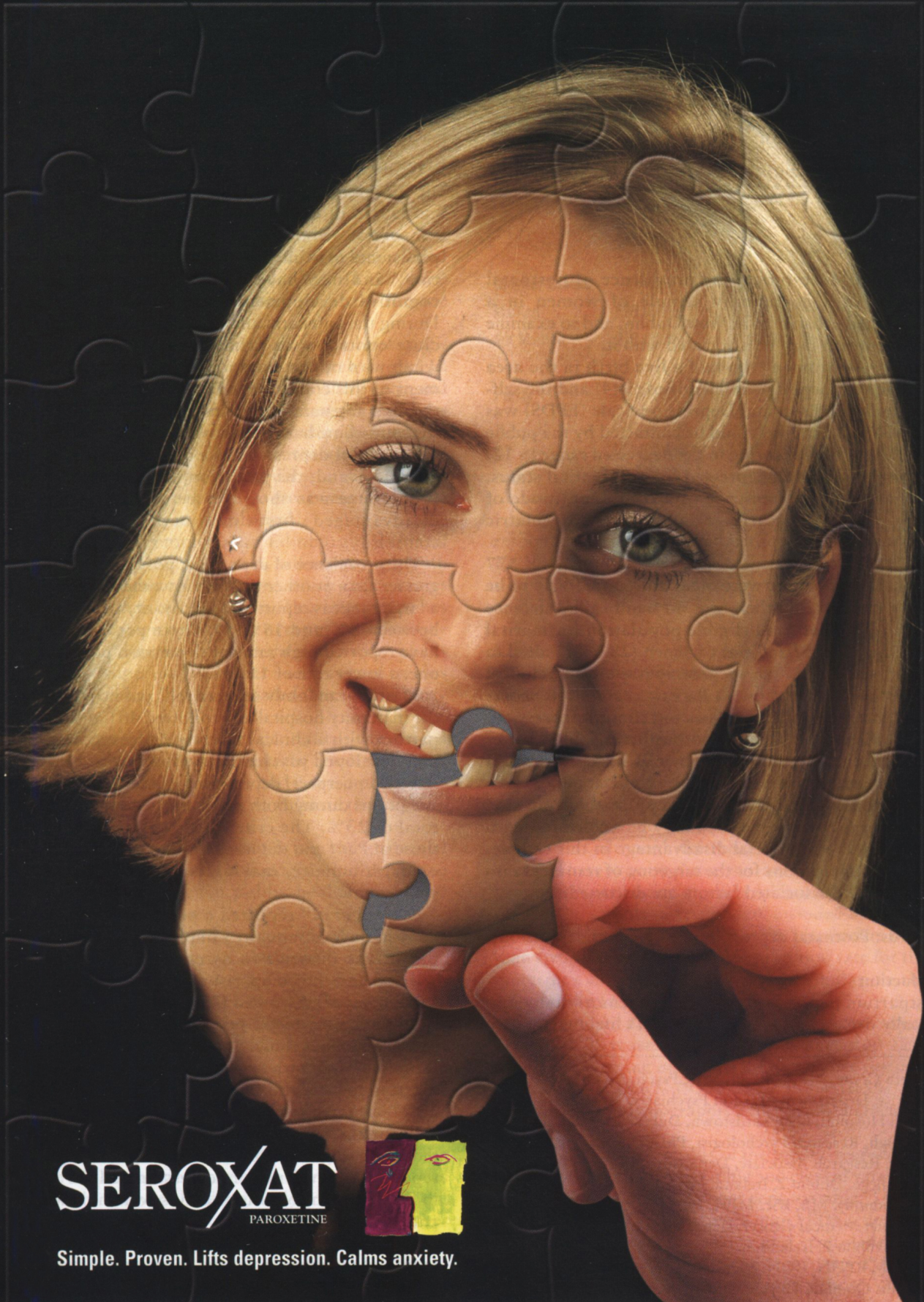
A neuroimaging study using positron emission tomography (PET) has examined rCBF in 10 patients using high and low frequency rTMS.<sup>36</sup> High frequency rTMS resulted in increased rCBF in bilateral frontal, limbic and paralimbic regions, whereas low frequency rTMS produced more circumscribed decreases. Taken together, these results suggest that rTMS affects prefrontal and paralimbic activity, but the relationship between this effect and treatment response is not clear.

Rat studies have inevitably examined changes in brain serotonin (5HT) function consequent to rTMS. One study found that rTMS reduced the sensitivity of 5HT<sub>1A</sub> autoreceptors: a finding also demonstrated following antidepressant treatments.<sup>37</sup> Another study has found that rTMS in 'high-anxiety' rats attenuates behavioural and neuroendocrine (cortisol) stress responses.<sup>38</sup> Comparable studies in humans are lacking.

### Conclusions

Neuropsychopharmacological treatments for depression continue to advance but the area of physical somatic interventions has lagged behind. TMS therapy undoubtedly has antidepressant actions, as evidenced by the above studies. It has the advantage of not requiring anaesthesia, not inducing seizure and has no apparent cognitive side effects. Preliminary data from rTMS and PET studies reveal differential effects of rTMS frequency on regional cerebral neural activity in depressed patients. That rTMS may be more efficacious in severe depression, compared to mild/moderate depression, may be because rTMS is targeting a specific brain dysfunction present only in more 'biologically' defined depressions. These findings are also

# You made her life more complete...



## SEROXAT

PAROXETINE



Simple. Proven. Lifts depression. Calms anxiety.

**PRESCRIBING INFORMATION** Presentation: 'Seroxat' Tablets, PA 49/50/1-2, each containing either 20 mg or 30 mg paroxetine as the hydrochloride and 'Seroxat' Liquid, PA 49/50/3, containing 20 mg/10ml paroxetine as the hydrochloride. **Uses:** Treatment of symptoms of depressive illness of all types including depression accompanied by anxiety. Prevention of relapse and also recurrence of further depressive episodes. Treatment of symptoms and prevention of relapse of obsessive compulsive disorder (OCD). Treatment of symptoms and prevention of panic disorder with or without agoraphobia. **Dosage:** Adults: Depression: 20 mg daily and if necessary increase dose by 10 mg increments to a maximum of 50 mg according to response. Obsessive compulsive disorder and panic disorder: 40 mg daily. Start on 20 mg and increase weekly in 10 mg increments to a maximum of 60 mg daily according to response. Possible worsening of panic symptoms during early treatment of panic disorder is generally recognised, thus low initial starting dose is recommended. Dosage should be reviewed and adjusted if necessary within two to three weeks of initiation of therapy and thereafter as judged clinically appropriate. Continue treatment for a sufficient period, which may be several months for depression and for OCD and may be even longer (9 months) for panic disorder. Abrupt discontinuation should be avoided. **Elderly:** 20 mg daily increasing by increments of 10 mg up to 40 mg daily according to response. **Children:** Not recommended. Severe renal impairment (creatinine clearance <30 ml/min) or severe hepatic impairment: 20 mg daily. Restrict incremental dosage if required to lower end of range. **Contra-indications:** Hypersensitivity to paroxetine and related drugs; use with MAO inhibitors; unstable epilepsy or convulsant disorders; severe renal failure. **Precautions:** History of mania. Cardiac conditions, use with ECT: caution. Caution in patients with controlled epilepsy (monitor carefully). Stop treatment if seizures develop. Caution patients about driving and operating machinery. **Drug interactions:** Do not use with or within two weeks after stopping MAO inhibitors; leave a two-week gap between stopping 'Seroxat' and before starting MAO inhibitor treatment. Possibility of interaction with tryptophan. Great caution with warfarin and other oral anticoagulants. Consider using lower doses if given with drug metabolising enzyme inhibitors; adjust 'Seroxat' dosage if necessary when given with drug metabolising enzyme inducers. Combination with other highly bound protein drugs may alter plasma levels of either. Alcohol is not advised. Caution with other CNS active drugs. Keep dosage of concomitant benzodiazepines low. Use concurrent lithium administration with caution and monitor lithium levels. **Pregnancy and lactation:** Use in pregnancy only if essential and avoid during lactation. **Adverse reactions:** Most commonly nausea, somnolence, sweating, tremor, asthenia, dry mouth, insomnia, sexual dysfunction (impotence and abnormal ejaculation), hyperprolactinaemia/galactorrhoea, dizziness, constipation, diarrhoea, decreased appetite. Spontaneous reports of dizziness, headache, acute glaucoma, vomiting, diarrhoea, restlessness, hallucinations, hypomania, rash, blurred vision. Rarely mania has been reported. As with other SSRIs, symptoms suggestive of postural hypotension, hypotension, hypertension, tachycardia. Also other arrhythmias (rare). Extrapyramidal reactions, rarely hyponatraemia (possible SIADH), liver function abnormality. Abrupt discontinuation may cause dizziness, sensory disturbance, agitation or anxiety, nausea and sweating. **Product authorisation holder:** GlaxoSmithKline, Corrig Avenue, Dun Laoghaire, Co. Dublin. **Further information is available from this address.** Telephone: 01 204 3333. November 2007. Seroxat is a trade mark. © 2007 GlaxoSmithKline.

 GlaxoSmithKline

exciting because it lends further weight to the evidence implicating left prefrontal cortex dysfunction in depression. Repetitive TMS is not effective in psychotic depression, in contrast to ECT, and suggests that another brain area may be involved in processing the psychotic symptoms of depression.

TMS is not only a valuable treatment option but informs us about the nature of different depressive syndromes. Clearly, depression is a heterogeneous disorder, defined in terms of clinical syndromes rather than brain pathophysiology. That rTMS has not yet found a clinical niche may result from the limitations of our definitions of depression, rather than of the therapy itself. Therapies such as rTMS may enable us to move towards more biologically intelligent definitions of depressive syndromes.

#### References

1. Rudiak, Marg E. Finding the depth of magnetic brain stimulation: a re-evaluation. *Electroencephalography and Clinical Neurophysiology* 1994; 93: 358-71.
2. Chen R, Classen J, Gerloff C et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 1997; 48: 1398-403.
3. Wasserman EM, Wedegaertner RF, Ziemann U, George MS, Chen R. Crossed reduction of human motor excitability 1-Hz transcranial magnetic stimulation. *Neurosci Lett* 1998; 10: 141-4.
4. Pascual-Leone A, Tormos JM, Keenan PJ et al. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998; 15: 333-43.
5. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. *J of Psychol* 1996; 496: 873-81.
6. Wassermann EM. Repetitive transcranial magnetic stimulation: an introduction and overview. *CNS Spectrums* 1991; 2: 21-5.
7. Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology* 1991; 41: 697-702.
8. Amassian E, Cracco RQ, Maccabee PJ et al. Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalography Clin Neurophysiol* 1989; 4: 458-62.
9. Pascual-Leone A, Hallett M. Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. *Neuroreport* 1994; 5: 2517-20.
10. Maeda F, Keenan, JP, Pascual-Leone A. Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation. *B J Psych* 2000; 177: 169-73.
11. Baxter LR, Schwartz JM, Phelps ME et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 1989; 46: 243-50.
12. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation. Applications in neuropsychiatry. *Arch Gen Psychiatry* 1999; 56: 300-11.
13. Berardelli A, Rona S, Inghilleri M et al. Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. *Brain* 1997; 119: 71-7.
14. Liepert J, Wessel K, Schwenkreis P et al. Reduced intracortical facilitation in patients with cerebellar degeneration. *Acta Neurolog Scand*, 1998; 98: 318-23
15. Bickford RG, Guidi M, Fortesque P et al. Magnetic stimulation of human peripheral nerve and brain: response enhancement by combined magnetoelectrical technique. *Neurosurg* 1987; 20: 110-6.
16. Pascual-Leone A, Wassermann E.M. Repetitive transcranial magnetic stimulation: application and safety considerations. In *Advances in Occupational Medicine and Rehabilitation* (Nilsson J, Panizza M, Grandori F. eds). Pavia, Italy: Fondazione Salvatore Maugeri Edizione. 1996.
17. George MS, Wassermann EM, Kimbrell, TA et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in

- patients with depression: A placebo-controlled crossover trial. *Am Journal of Psych* 1997; 154: 1752-6.
18. George, MS, Wassermann EM, Williams WA et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *NeuroRpor* 1995; 6: 1853-6.
19. Figiel GS, Epstein C, McDonald WM et al. The use of rapid rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *J Neuropsych Clin Neurosci* 1998; 10: 20-5.
20. Pascual-Leone A, Rubio B, Pallardo F et al. Rapid rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996; 348: 233-7.
21. Berman RM, Narasimhan M, Sanacora G et al. A randomised clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatr* 2000; 47: 332-7.
22. Padberg F, Zwanzger P, Thoma H et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999; 88: 163-71.
23. Garcia-Toro M, Mayol A, Arnillas H et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *J Affect Disord* 2001; 64: 271-5.
24. Loo C, Mitchell, P, Sachdev P et al. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J. Psychiatry* 1999; 156: 946-8.
25. George MS, Nahas Z, Molloy M et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biol Psychiatry* 2000; 48: 959-61.
26. Stikhina NI, Lyskov EB, Lomarev MP et al. Transcranial magnetic stimulation in neurotic depression. *Zh Nevrol Psikhiatr Im S S Korsakova* 1999; 99: 26-9.
27. Pridmore S, Bruno R, Turnier-Shea Y et al. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *Int J Neuropsychopharmacol* 2000; 2: 129-34.
28. Grunhaus L, Dannon PN, Schreiber S et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol Psychiatry* 2000; 47: 314-24.
29. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depress Anxiety* 2000; 12: 118-23.
30. Nahas Z, DeBrux C, Chandler V et al. Lack of significant changes on magnetic resonance imaging scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. *J. ECT* 2000; 16: 380-90.
31. Loo C, Sachdev P, Elsayed H et al. Effects of a 2-4 week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biol Psychiatry* 2001; 49: 615-23.
32. Little, J.T., Kimbrell, T.A., Wassermann, E.M. et al. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsych Neuropsychol Behav Neurol* 2000; 13: 119-124.
33. Triggs WJ, McCoy KJ, Greer R et al. Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition, and corticomotor threshold. *Biol Psychiatry* 1999; 45: 1440-6.
34. Catafau AM, Perez V, Gironell A et al. SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients. A pilot study. *Psychiatry Res* 2001; 106: 151-60.
35. Teneback CC, Nahas Z, Speer AM et al. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left frontal TMS. *J Neuropsychiatry Clin Neurosci* 1999; 11: 426-35.
36. Speer AM, Kimbrell TA, Wassermann EM et al. Opposite effects of high and low frequency rTMS in regional brain activity in depressed patients. *Biol Psychiatry* 2000; 48: 1133-11.
37. Gur E, Lerer B, Dremencov E et al. Chronic repetitive transcranial magnetic stimulation induces subsensitivity of presynaptic serotonergic autoreceptor activity in rat brain. *Neuroreport* 2000; 11: 2925-9.
38. Keck ME, Welt T, Post A et al. Neuroendocrine and behavioural effects of repetitive transcranial magnetic stimulation in a psychological animal model are suggestive of antidepressant-like effects. *Neuropsychopharmacology* 2001; 24: 337-49.

The Irish Journal of Psychological Medicine  
welcomes all correspondence by email

Email us at:

[psychological@medmedia.ie](mailto:psychological@medmedia.ie)