

Reappraisal

Transcranial stimulation in depression†

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Summary

Transcranial direct current stimulation is coming of age with the large treatment study published in this issue. We review transcranial stimulation methods, their efficacy and the likely impact on National Health Service (NHS) practice. Their use in individuals who do not respond to or cannot tolerate medication should now

be explored in large controlled naturalistic studies in the NHS.

Declaration of interest

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Treatment-resistant depression presents a clinical challenge: the number of different neurostimulatory treatments that are currently developed attest to a pressing clinical problem without a straightforward solution. Electroconvulsive therapy (ECT) is the most effective treatment for life-threatening or treatment-resistant depression; however, despite widespread use, concerns about cognitive side-effects remain, and its historical legacy has left it with a serious image problem. The holy grail of treatment would be one that is as effective as ECT, but is better tolerated, minimally invasive (and ideally does not require general anaesthesia) and has no serious side-effects including negative effects on cognition. Some neurostimulatory therapies, such as vagal nerve stimulation and deep brain stimulation, are a long way from routine use given that they are both more invasive than ECT, with potentially serious side-effects.¹ They are currently not used within routine clinical settings and are at a relatively early experimental stage. In contrast, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) promise to be well-tolerated minimally invasive treatments for depression. We reassess the evidence for both therapies, and consider whether they can realistically cross over from the arena of research to that of routine clinical practice.

Transcranial magnetic stimulation

Transcranial magnetic stimulation is based on the principle of electromagnetic induction: an alternating current is passed through a metal coil, inducing a magnetic field. When the coil is positioned over an individual's scalp, this induces an electrical current in a specific region of the brain, leading to depolarisation of neurons. There are therefore a number of key variables that can affect treatment, for example, coil design, coil location, stimulation intensity and frequency. Most commonly in the treatment of depression, coils are applied to the left dorsolateral prefrontal cortex, using stimulation intensity of 80–120% and high-stimulation frequency (5–20 Hz). Treatment effectiveness will also be affected by frequency, number and duration of sessions.

A meta-analysis based on 31 randomised trials of TMS with a sham control (1996–2008) included a cumulative total of 815 participants receiving active TMS and 716 sham TMS.² This showed a significant effect on symptom change in favour of TMS (Hedges' $g = 0.64$, 95% CI 0.50–0.79); the number needed to treat was 4 (95% CI 3–6). This significant but moderate effect size concurs with a second contemporary meta-analysis.³ However, such results need to be interpreted with caution due

to heterogeneity of results, presumably arising from a lack of consensus about the optimum mode of treatment delivery (coil location, stimulus frequency, etc.) that makes comparison of studies more difficult and places an additional translation barrier on its clinical use.

These difficulties have been overcome to some degree in the more recent, larger studies. For example, a 2007 multisite randomised double-blind study compared active and sham TMS over the left dorsolateral prefrontal cortex in 301 patients.⁴ Treatment was given for 20 sessions (10 Hz, 120% motor threshold, 3000 pulses per session). Active TMS was not effective after 4 weeks, as measured by the primary outcome measure, the change in mean symptom score on the Montgomery-Åsberg Depression Rating Scale (MADRS, $P = 0.06$). However, the effect size of MADRS group differences after 4 weeks' treatment (Hedges' g) was 0.26 (95% CI 0.03–0.49). In a second trial similar parameters were used, but with only 15 daily treatments.⁵ The authors found that in 199 participants with unipolar depressive disorder there were significantly more individuals whose depression was in remission after active treatment (14.1% active TMS *v.* 5.1% sham; $P = 0.02$) with an effect size (Hedges' g) at 3 weeks of 0.47 (95% CI 0.17–0.78).

After successful acute treatment with TMS, a 24-week follow-up study showed that the therapeutic effects of TMS are durable, and that it can be used to preclude impending relapse.⁶ Factors that increase the likelihood of a good antidepressant response to TMS include a shorter duration of current illness and an absence of comorbid anxiety disorder; worse outcomes are seen in those who failed to respond to more than one adequate trial of antidepressant medication during the current episode.⁷

Transcranial magnetic stimulation is generally well tolerated with minimal side-effects.⁸ The most commonly reported side-effects are scalp irritation or pain. There is a risk of seizure induction, and it is of interest to note that this side-effect has been exploited in the development of magnetic seizure therapy.⁹ Preliminary work suggests that TMS has a superior cognitive profile compared with ECT, leading to improvement in certain cognitive functions such as autobiographic, working memory and executive functioning.¹⁰ Case reports have shown that TMS can induce mania, particularly in those with bipolar disorder, but in general this is uncommon and other studies of TMS do not appear to have induced mania in those with bipolar disorder.

Transcranial direct current stimulation

The success of trials of TMS in the treatment of major depression has contributed to a resurgence of interest in tDCS in the past decade. Transcranial direct current stimulation is a non-invasive

†See pp. 52–59, this issue.

and non-convulsive technique that delivers a low-amplitude (1–2 mA) direct current to the underlying cerebral cortex via sponge electrodes placed on the scalp. Depending on electrode polarity, tDCS will result in a modulation of cortical excitability and spontaneous neural activity.¹¹ In trials of tDCS for the treatment of major depression the anodal electrode is typically placed over the left dorsolateral prefrontal cortex. This shifts the resting membrane potential of underlying neurons towards depolarisation, enhancing cortical excitability and increasing the rate of neuronal firing. The cathodal electrode is usually placed over the contralateral supraorbital area or dorsolateral prefrontal cortex and appears to shift the resting membrane potential towards hyperpolarisation, reducing cortical excitability and decreasing the rate of neuronal firing. Such effects can outlast the duration of stimulation for up to 1 h.¹¹

A recent meta-analysis of randomised-controlled trials of tDCS for depression since 2000 found that active tDCS was significantly associated with a reduction of symptoms compared with sham tDCS (Hedges' *g* approximately 0.7, 95% CI approximately 0.2–1.2, *n* = 165) (details available from the authors on request). However, measures of heterogeneity were significant ($Q = 13.7$, *d.f.* = 6, $P = 0.03$). Methodological factors may account for the differences between studies; the optimal stimulus parameters (electrode placement, 2 mA rather than 1 mA stimulation strength) and protocol (higher frequency and longer duration of treatment sessions) for the treatment of depression are as yet unclear. Loo's most recent and the largest study to date, reported in this issue, recruited 64 participants with current depression with a score of ≥ 20 on the MADRS, who received active or sham anodal tDCS to the left prefrontal cortex (2 mA, 15–20-min sessions over 3 weeks).¹³ Concurrent antidepressant medications were continued at stable doses 4 weeks prior to study entry. Hedges' *g* after treatment was 0.52 (95% CI 0.01–1.03).¹²

Side-effects associated with tDCS are mild and include headache and skin irritation under the electrodes, although skin lesions have been reported in a 2 mA study.¹³ Generally, tDCS is not painful like TMS, and there have been no reported seizures. Also, as with TMS, case-reports have described induction of a transient hypomanic episode following tDCS. Adverse cognitive effects have not commonly been reported. Indeed, studies have reported that working memory significantly improved in the active tDCS group compared with the sham group.^{13,14} Contra-indications are epilepsy, metallic implants or severe eczema near electrodes, which may apply to all transcranial stimulation techniques.

Conclusion

Transcranial magnetic stimulation has been used for 15 years in the treatment of depression; it consistently produces small to medium effect sizes in people who are usually resistant to at least one type of medication. In this case, why has it not been introduced into clinical practice? The answer is: it has in the USA, Canada, Australia and some European countries. In the UK, a mixture of NHS rationing and systematic medical de-skilling of psychiatrists has so far left it the domain of private psychiatrists, neurologists and researchers. In fact, TMS requires some neurophysiological skills, such as localising the primary motor cortex and determining the motor threshold to calibrate stimulation strength, as well as the presence of a skilled operator on a daily basis. In view of this, tDCS may provide a cheaper and more practical alternative that requires expertise similar to

that necessary to administer ECT. Electrode positioning is standardised and stimulation strength follows protocol. The equipment needed for tDCS is easily transportable and can even be administered in the patient's own home. Assuming that it will pass scrutiny in large controlled naturalistic studies in the NHS, it may turn out to be the perfect future treatment in the community.

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