Neurostimulation techniques in the treatment of depression

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Abstract

Depression is a common and highly debilitating psychiatric disorder. The treatment for depression varies from talking therapies such as cognitive behavioural therapy to drug treatment and, in severe cases, the use of electroconvulsive therapy (ECT). Unfortunately ECT, despite its effectiveness and safety, remains unpopular among the public because of its negative portrayal in the media and historical stigma. In this short paper, we explore the non-invasive neurostimulation techniques of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), as well as an invasive technique known as deep brain stimulation (DBS). These neurostimulation techniques are being increasingly utilized in clinical practice, particularly rTMS. Although rTMS has received NICE approval, it is still seldom used in the public health sector. An increasing number of private clinics are offering rTMS to many patients who do not want to take medication, cannot tolerate medication or fail to respond to medication. DBS requires an initial surgical procedure and due to this invasive nature, it is seldom used outside of clinical research in depression. More research and a broader evidence base are needed before these neurostimulation treatments become much more widely used.

Introduction

The modern neurostimulation techniques for the treatment of depression have their roots in the 1950s for deep brain stimulation (DBS), 1960s -1970s for transcranial direct current stimulation (tDCS) and the mid 1980s for transcranial magnetic stimulation (TMS). TMS is attributed to Barker and colleagues who first successfully carried out this technique in Sheffield, UK in 1985. TMS was further developed in the 1990s as a therapeutic technique known as repetitive transcranial magnetic stimulation (rTMS) for treatment of psychiatric disorders, including depression (1, 2).

These neurostimulation techniques have been developed alongside increasing knowledge of brain circuitry, largely ascertained from a number of imaging techniques such as CT, MRI, fMRI and PET scanning. This is leading to furthering the understanding between differences in brain structure and the psychiatric symptomatologies which constitute individual disorders such as depression.

In this short paper we describe some of the neurostimulation techniques being utilised for the treatment of depression. The techniques, namely repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS) will be explored at the level expected for a general practitioner. These modalities will be reviewed from the viewpoint of indications, contraindications and inclusion in the NICE guidelines. A brief overview of the evidence and future considerations will be provided.

Transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS)

TMS is a method of neurostimulation which involves the application of rapidly alternating magnetic pulses with an insulated coil placed over the patient's scalp (2, 3). The magnetic pulses can be applied as a single burst (TMS), or repeated in set bursts (rTMS) which have varying effect on the polarisation of target neurons (3).

Methods utilizing MRI scans and EEG are used to localize the target superficial regions of the brain. The subsequent effects of TMS/rTMS through the brain depend upon a number of extrinsic and intrinsic factors. The former include motor threshold (MT), frequency of stimulation (measured in Hz), number of stimuli and the time period over which the stimulation is carried out. The intrinsic factors include anatom-

ical and functional connections within the brain.

In general, pulses with frequencies of below 5Hz lead to a decrease in neuronal excitability and cerebral blood flow, causing inhibitory effects on their target, whilst pulses with frequencies higher than 5Hz lead to an increase in neuronal excitability and cerebral blood flow, and hence an excitatory effect (4). Studies have shown that applying a repetitive burst of magnetic pulses generates an effect which outlasts the duration of treatment (4). In 1995 it was suggested from functional neuroimaging that depression and mood regulation were associated with hypofunction of the prefrontal cortex. It was hypothesized that rTMS applied to this specific area might restore function (5).

By 2001, as the evidence base grew, the potential of rTMS in the treatment of depression was investigated in a Cochrane review. Fourteen studies were covered, including 197 patients, showing a statistically significant difference between rTMS and sham only for a treatment period greater than two weeks for high frequency to the left dorsolateral prefrontal cortex (DLPFC), and low frequency to the right dorsolateral prefrontal cortex (6). This effect was not maintained two weeks after cessation of treatment. The authors concluded that rTMS showed promise in the treatment of depression but the small sample sizes of studies were preventing a more definitive answer from being obtained. Researchers persisted with rTMS for a number of reasons as unlike ECT, it is non-invasive and does not require anaesthesia (7-9). The efficacy of rTMS compared to ECT was recently assessed in a meta-analysis of 25 studies, which concluded that ECT is slightly superior or equivalent to rTMS, depending on the pre-treatment depression score (9). Accurately locating the left DLPFC is achieved simply with a single MRI scan in patients, after which co-ordinates are recorded. The technique of rTMS has maintained its reputation as a safe, tolerable treatment with minimal adverse effects and a low reported dropout rate (8-10). Adverse effects commonly include headaches, discomfort at the stimulation site and fatigue. A very low risk of seizures and worsening of depressive symptoms have been reported; however, the difference between real and sham rTMS groups is not statistically significant (8). No episodes of cognitive impairment have yet been reported. Current contraindications to rTMS treatment are ferromagnetic material inside the head/neck, patients with reduced seizure threshold from medication/conditions, significant heart disease, sleep deprivation and alcohol dependence (11, 12).

It is likely that the small number of meaningful studies also impacted the inclusion of rTMS into UK NICE guidelines in 2015. One of the first studies to change this was an open-label trial of rTMS in treatment-resistant major depressive disorder, funded by the American National Institute of Mental Health. With a sample size of 190, the study demonstrated increased remission rates with rTMS against sham treatment, given Monday to Friday for two weeks (14.1% and 5.1%, $p = 0.02$) (7). This was supported by subsequent meta-analyses, leading to the addition of rTMS as a strategy for treating depression in the UK (13). This was not quantified further in NICE guidelines; however, looking at previous recommendations it appears that psychological treatment should be attempted first, followed by biological treatment and then neurostimulation techniques. Despite evidence supporting rTMS treatment alone in depression it has not been shown to be superior to current medications. It is clear therefore that rTMS has an established role as adjuvant treatment, or in rare cases where medication is contraindicated (14). Some recent advances have been made by modification of pulse parameters, such as the use of theta burst stimulation (TBS) which has facilitated shorter treatment sessions and lower magnetic intensities (15).

Transcranial direct current stimulation (tDCS)

This is a relatively simple and cheap technique, which utilizes the same physiological target as rTMS. A current is passed through the dorsolateral prefrontal cortex via electrodes placed on the scalp, which primarily increases or decreases the depolarisation threshold, depending on the passing of current from the cathode or anode respectively (16, 17). Treatment durations are initially for 20 minutes per day, five days a week for 2 - 3 weeks (4, 18). A recent meta-analysis assessed all tDCS research in depression from its initiation in 2002 to late 2015 and reported mixed results (19). In a single trial investigating the acute treatment of depression, tDCS was more effective than sham treatment and fluoxetine 20mg, with similar results at 6 weeks (19, 20). The included meta-analyses failed to show a significant response rate, defined as an improvement in depression score of 50% or more. There was no increase in efficacy with more sessions or higher intensity (19). Another meta-analysis, including 289 patients, did show significant improvement with tDCS against sham for response (34% vs 19%) and remission (23.1% vs 12.7%), using similar param-

eters (21). A study into the safety of tDCS was performed on 77 healthy patients. They reported only mild tingling (75%), itchiness (30%), fatigue (35%) and headache (11.8%) with no significant difference against sham groups (21). It was concluded that tDCS had minimal adverse effects, as strongly supported by previous studies (19-22). Reports of induced manic episodes have been evident but rare (23).

All the studies appear to be limited by the lack of differentiation of treatment-resistant patients, for whom tDCS is less effective, and they did not control for the use of medication. This is important as tDCS achieves a long lasting effect through N-methyl-D-aspartate (NMDA) receptor upregulation, which has been shown to be affected by psychotropic medication. Notably, citalopram can enhance the effects of tDCS, while dopamine agonists reverse the excitatory effects and lorazepam delays and prolongs the effects (19). Conclusions from the meta-analyses are in line with current NICE recommendations that tDCS may be useful in the acute phase. There was uncertainty surrounding the treatment duration, number of treatments needed and electrode orientation due to the heterogeneity of current research.

Deep brain stimulation (DBS)

Some forms of DBS appear to have been carried out as early as 1950. DBS was first used systematically in 1987 for the treatment of movement disorders secondary to Parkinson disease (1, 24). DBS gained favour due to its efficacy in the treatment of resistant movement disorders and because it could replace ablative surgeries which carried higher adverse risks and whose effects were irreversible (1, 24). However, modern DBS techniques began much later, continuing to target Parkinson disease.

DBS is an invasive technique that requires initial input from a neurosurgeon. It involves insertion of electrodes into specific brain areas and stimulation with high-frequency pulses. These pulses can achieve an effect comparable to the ablation of the specific area. Looking forward, definitive research for DBS in depression is lacking, however multiple sites of action have been proposed. A systematic review by Moreshita et al. in 2014 identified a common set of targets for depression including the nucleus accumbens, ventral capsule/striatum (VS/VC), subcallosal cingulate white matter (Brodmann area 25), lateral habenula, inferior thalamic peduncle and median forebrain bundle (25). These sites have all been implicated in the regulation of mood or reward centres in the 'depression network'. Of these, the areas of VS/VC and SCC show the greatest promise with response rates of 71% and 29 - 58% respectively in small samples ($n < 20$) (25-27). However multi-centred, prospective RCT trials for each area failed to show statistical significance against sham at 16 week follow up and both were abandoned (28, 29). The adverse effects of DBS are more significant than rTMS or tDCS, because of the invasive initial surgical procedure and the requirement for general anaesthesia; they include bleeding, infection or complications of the anaesthesia (30). The stimulation itself has also been shown to induce manic episodes in a small subset of patients with co-morbid obsessive-compulsive disorder (26, 31). Researchers believe that modification of inclusion criteria, pulse frequency and site may produce better results, but there is currently no clear indication for DBS in the treatment of depression outside clinical trials.

Conclusion

There is an estimated 30% relapse rate for patients treated for depression with psychological, pharmacological and currently accepted brain stimulation techniques (4). There is also a subset of patients who cannot tolerate current treatment, due to adverse effects or ineligibility, for example due to pregnancy. There is therefore a continued effort to find alternative options for the treatment of depression in the hope that these patients can benefit. Three neurostimulation techniques which show promise as adjuncts or in isolation have been discussed. For rTMS, there is an abundance of high-quality research that supports its safety and efficacy as an adjuvant approach. This is reflected in its inclusion in the NICE guidelines. For tDCS and DBS, the research on efficacy is less clear. These techniques hold promise, but there is a lack of consensus on how the techniques should be used, and the patient inclusion criteria appear to be confounding results. As our understanding of the neuronal circuitry of depression improves, we can expect to see an improvement in efficacy.

Research is already focussing on refining these techniques, from the stimulation intensity to target sites and duration of treatment. There is currently no demonstrable significant negative effect of prolonged treatment. Longer exposures and longer follow up should contribute to the current knowledge base.

Larger and better-designed multicentre studies, with some standardisation of rTMS, tDCS and DBS protocols, are needed. Utilisation of some of these newer techniques, in combination with appropriate neuroimaging, should not only provide a better understanding of the precise neuronal targets for these techniques but should also help clinicians to determine where, when and which of these treatments will be most appropriate for the individual patient with depression.

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