Cambridge Textbook of Neuroscience for Psychiatrists

Chapter title: **Brain stimulation in psychiatry**

Name: Dr Camilla L Nord

Affiliation: MRC Cognition and Brain Sciences Unit, University of Cambridge

Email: camilla.nord@mrc-cbu.cam.ac.uk

Phone: 01223767481

Address: MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge, CB2 7EF

Brain stimulation in psychiatry

One of the best examples of translation from neuroscience to psychiatric treatment is brain stimulation, an array of techniques aimed at modulating the activity and/or plasticity of particular brain structures. Brain stimulation is not new: as far back as ancient Rome, the physician Scribonius Largus wrote of electrical stimulation to relieve migraine (although he employed a torpedo fish, a species of electric ray). Today, a number of invasive and non-invasive brain stimulation techniques show efficacy in treating psychiatric disorders. What these distinct approaches have in common is their ability to target specific neural regions more directly than traditional pharmacological or psychological approaches (see Figure 1). This capacity to influence the very circuits implicated in neuroscience studies has contributed to some transformative discoveries, but has faced key translational challenges, including response variability and inadequate placebos.

1. Non-invasive brain stimulation

There are two chief forms of non-invasive brain stimulation: **transcranial magnetic stimulation** (TMS) and **transcranial direct current stimulation** (tDCS). TMS uses brief, high-current pulses to induce a magnetic field, indirectly activating neurons, and causing an increase or decrease in brain activity in a localised target region[1]. There is substantial evidence that repetitive high-frequency TMS pulses over the left dorsolateral prefrontal cortex (L-DLPFC) are effective for major depressive disorder[2], purportedly by restoring activity in the L-DLPFC, a commonly-described source of aberrant activation in neuroimaging studies in depression (often, but not always, showing hypoactivation)[3]. More limited evidence suggests TMS might be helpful in other psychiatric conditions: targeting the ventromedial prefrontal cortex, for example, shows promise as a treatment for addiction disorders[4]. However, the precise mechanisms by which TMS might exert treatment effects in psychiatric disorders are still largely unknown.

tDCS is a mild electrical current that has a more diffuse effect than TMS (see Figure 1), evoking brain activation changes both locally and in anatomically connected but spatially distant regions[5]. At a neuronal level, anodal tDCS (using the positive electrode) increases the membrane potential of neurons towards depolarisation (rather than eliciting firing), and is thought to induce longer-term effects via synaptic plasticity. Many trials show moderately large effects of five or more L-DLPFC tDCS sessions on depression symptoms[6], but there have also been notable null results[7]. Laboratory studies in healthy populations report improvements in short-term memory and other cognitive measures during or immediately after tDCS delivery. These findings do not always replicate, but have nevertheless inspired a wealth of commercial ventures selling simple tDCS kits, and a dedicated public following among devotees of so-called ‘neurohacking’.

Both TMS and tDCS have a limited depth of penetrance, with biological effects rapidly falling off with increasing depth. As such, non-invasive brain stimulation is often restricted to targeting superficial neural structures. However, deep cortical and subcortical regions play a fundamental role in psychiatric disorders. Surgical brain simulation (and potentially some novel types of non-invasive brain stimulation), has the capacity to target these deeper structures.

2. How can we target deeper structures?

Perhaps the most famous form of brain stimulation, other than ECT, is **deep brain stimulation** (DBS). In open-label studies, DBS evokes profound short- and long-term improvements in patients with intractable depression[8] (electrodes typically target the

subgenual anterior cingulate cortex, ventral capsule, or nucleus accumbens). However, randomised controlled trials (RCTs) have been inconclusive, potentially due to the importance of peri-surgical effects of the stimulation and/or inadequate parameter optimisation. More recently, exploration of new targets such as the medial forebrain bundle has been coupled with more innovative trial designs – such as intraoperative exploration of the psychotropic effects of stimulation to guide electrode placement[9]. In patients with intractable obsessive-compulsive disorder (OCD), DBS of the ventral capsule and the anteromedial subthalamic nucleus are both effective in treating the symptoms of OCD[10]. A surgical approach like DBS is not intended to be a first-line treatment for any psychiatric disorder; however, DBS studies can also highlight novel targets which might be suitable for non-invasive brain stimulation.

In terms of non-invasive stimulation, a major hurdle is stimulating deeper structures with any degree of specificity, as stimulation necessarily passes through more superficial regions. Nevertheless, deep TMS can penetrate several centimetres below the skull, modulating deep prefrontal targets. In non-human primates, non-invasive ultrasound stimulation has recently been shown to modulate the amygdala and cingulate[11] (future work must establish the precise neurophysiological underpinnings and safety profile before translating this method to humans).

3. Challenges for the future of brain stimulation research

3.1 Placebo control

A major challenge across all forms of brain stimulation is adequate placebo control. This is a critical issue in DBS and TMS studies, which, respectively, have no or poor placebo stimulation options (ideally, the placebo would be some form of non-therapeutic stimulation indistinguishable from the intervention). Sham surgery, where an electrode is implanted but not stimulated, can be used as a control for DBS, and the lack of placebo stimulation does not typically prevent successful blinding in DBS studies. However, TMS produces an intense, albeit short-lived sensation: the lack of adequate placebo could certainly magnify the effects described in the literature. tDCS evokes milder sensations than TMS, and many tDCS studies show effective double-blind-controlled placebo stimulation, but at higher stimulation amplitudes people start to be able to differentiate between real and placebo stimulation.

3.2 Interindividual variability and mechanistic insight

As with all other psychiatric treatments, response to brain stimulation interventions varies substantially between individuals. A myriad of anatomical and physiological properties all contribute to this variability. Interindividual variability makes replication challenging, contributing to some of the inconsistencies in the brain stimulation literature. To address this, researchers have begun to add mechanistic measures, such as brain activation, to trials and studies. In patients with addiction disorders, TMS was found to specifically modulate cue reactivity (brain activation while viewing disorder-specific cues); this procedure could localise individually-specified target coordinates[4]. Mechanistic approaches might also identify responders and non-responders: in an RCT of tDCS combined with psychological therapy for depression, L-DLPFC activation measured with functional magnetic resonance imaging predicted later response to L-DLPFC tDCS[7].

The future of brain stimulation requires more refined ways to customise stimulation based on the particular disruptions found in an individual patient. This would require a degree of mechanistic insight into DBS, TMS, and tDCS that it is only possible to develop following carefully controlled experimental studies and innovatively-designed RCTs. Still, brain

stimulation offers remarkable potential to develop novel psychiatric treatments based on insights from neuroscience.

Outstanding questions

What are the long- and short-term neural changes evoked by each type of brain stimulation?

What is the optimal design for a DBS trial?

How can we adjust TMS, tDCS, and DBS parameters on an individual scale to improve patients' response to each intervention?

Could focused ultrasound or another form of non-invasive brain stimulation safely and selectively target deeper structures in psychiatric disorders?

Figure caption

Figure 1. The relative specificity and invasiveness of brain stimulation techniques compared to common depression treatments. CBT = cognitive behavioural therapy; SSRI = selective serotonin reuptake inhibitor; TMS = transcranial direct current stimulation; tDCS = transcranial direct current stimulation; ECT = electroconvulsive therapy; DBS = deep brain stimulation.

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