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BRAIN BYTES

Spreading activation: the origins of brain stimulation in psychiatry

Introduction

The first modern application of brain stimulation in psychiatry occurred in 1938 and involved using electricity to induce therapeutic seizures for what had been considered until then to be untreatable schizophrenia (1). While treatment-resistant mental illness remains the purview of brain stimulation, the last 70 years have seen considerable advancement in both the sophistication and variety of brain stimulation methodologies used (Fig. 1).

Electroconvulsive therapy

In the early 1930s the psychiatrist Ladislas Meduna began inducing therapeutic seizures to treat intractable cases of schizophrenia (1). Initially, these seizures were induced pharmacologically using camphor and later metrazol, yet the use of these drugs was painful and complicated by the induction of bradycardia and bouts of terror prior to the patient losing consciousness. In an effort to overcome this, electricity was subsequently investigated as an alternative method for seizure induction and thus electroconvulsive therapy (ECT) was developed. While the use of ECT waned in the 1950s and 1960s with the introduction of psychotropic medication, 20 years later, following the observation that a large proportion of patients do not respond to medication, ECT progressively regained popularity primarily for treatment-resistant depression as well as for schizophrenia (1). ECT continues to be widely used today but, despite its superior clinical efficacy, there remain a number of problems with this treatment, which include high relapse rates and considerable cognitive side-effects (2). The therapeutic successes of ECT have led to the development of alternative forms of brain stimulation which have been investigated for their efficacy and safety in the treatment of psychiatric illnesses.

Transcranial direct current stimulation

In the 1960s, a novel form of weak electrical brain stimulation, namely, transcranial direct current stimulation (tDCS), was investigated as a possible treatment for schizophrenia. These initial investigations of the therapeutic efficacy of tDCS were not promising, but they were limited by the relatively basic understanding of the mechanisms of action of tDCS at the time and subsequently the way in which it was applied was not conducive to successful neuromodulation (3). However, over the last 10 years, there has been a resurgence of research in tDCS. We now know that through the application of a very weak electrical current to the scalp, tDCS alters neuronal excitability by shifting membrane potentials; with anodal stimulation leading to hyperpolarisation and cathodal stimulation resulting in depolarisation (4). Currently, tDCS is showing some early promise in the treatment of depression, whereby anodal stimulation is being applied to the left dorsolateral prefrontal cortex (DLPFC) with an aim to increase neuronal excitation (5). tDCS also appears to have a possible role to play in the remediation of cognitive deficits commonly seen in depression, with evidence that it may enhance cognitive functioning over and above its effects on psychopathology (5). It may also have applications in a number of other conditions such as chronic pain (4).

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was first observed to induce mood changes in a number of studies conducted in the 1990s, and has subsequently become the most researched brain stimulation technique in psychiatry (5). TMS involves the use of an alternating magnetic field to induce a focal electrical field in the superficial cortex which leads to the firing of nerve cells. When applied repetitively [i.e. rTMS (repetitive transcranial magnetic stimulation)] the repeated firing of neurons leads to longer lasting changes in neuronal activity. High frequency stimulation acts to increase neuronal firing, whereas low frequency decreases it. TMS has been predominantly investigated in treatment-resistant depression and to a lesser extent schizophrenia and other disorders. The majority of TMS trials in depression have investigated the antidepressant effects of high frequency left sided stimulation to the DLPFC, and there have subsequently been numerous meta-analyses of this research with most of them showing TMS to have a significantly greater antidepressant effect when compared with sham over a two-week treatment period (5). The majority of these meta-analyses have shown moderate effect sizes that are more in line with the modest effects seen with pharmacotherapy as opposed as ECT (6). Over approximately the last 10 years, there has been a concerted effort to investigate ways in which TMS efficacy could be improved, with efforts largely focussing on varying stimulation parameters. For example, studies have investigated the use of neuronavigation in targeting DLPFC, low frequency right sided stimulation, bilateral

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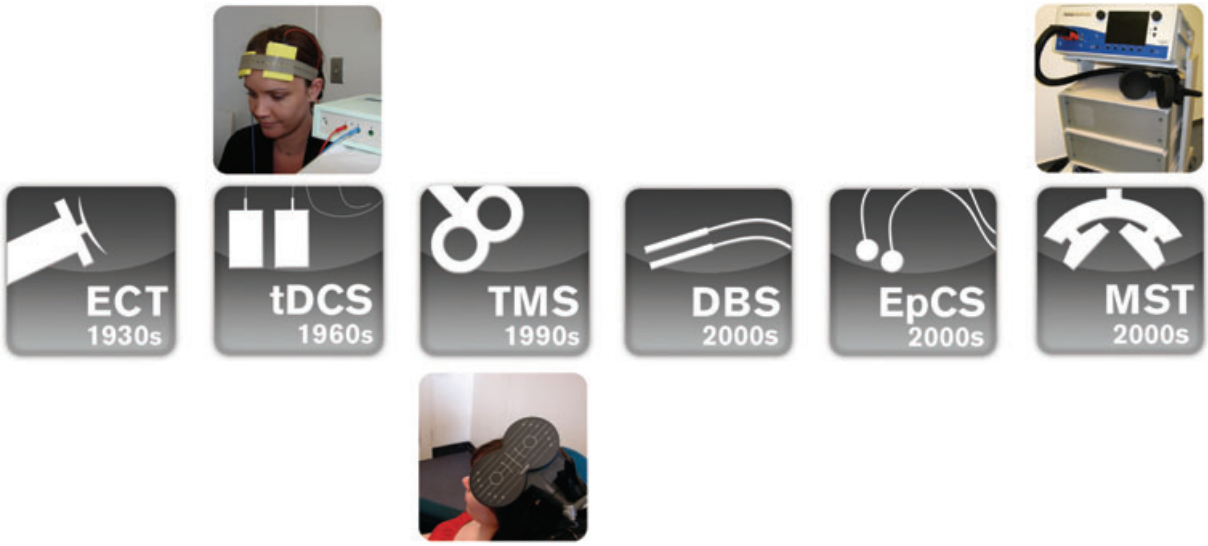

Fig. 1. Timeline of introduction of brain stimulation techniques into psychiatry. DBS, deep brain stimulation; ECT, electroconvulsive therapy; EpCS, epidural cortical stimulation; MST, magnetic seizure therapy; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

TMS and theta burst stimulation (7). The results of these investigations have been largely promising, although there is still much work to be carried out to optimise the delivery and efficacy of TMS. As patients with treatment resistant depression have continued to not always respond to novel interventions such as TMS other, more invasive, techniques have begun to be explored.

Deep brain stimulation

Deep brain stimulation (DBS), initially developed for neurological disorders, involves the implantation of electrodes into localised brain regions in order to alter both local and connected brain activity through ongoing high frequency stimulation (8). DBS for psychiatric indications, namely, obsessive compulsive disorder (OCD) and treatment refractory depression, began to be investigated in the mid-2000s. In OCD, stimulation has generally been targeted at the anterior limb of the internal capsule, whereas in depression, the two main sites are subgenual anterior cingulate cortex and ventral striatum/nucleus accumbens (5). Results for both indications have been promising; however, the amount of data to date is limited. In addition, the potential classification of DBS as psychosurgery has implications for its widespread use as there are varying legislative restrictions on the use of psychosurgery worldwide.

Epidural cortical stimulation

Epidural cortical stimulation (EpCS) is another neurological technique that has been applied to psychiatry, with initial investigations occurring in the late 2000s (5). EpCS involves the administration of direct weak electrical stimulation through implanted electrodes placed above the dura at the desired brain region (9). To date, the only psychiatric indication EpCS has been trialled in is depression and there have been less than 20 patients treated in published studies (5). Again, while results are positive and provide a clear impetus for further investigation of this technique, conclusions regarding antidepressant efficacy would be premature at this early stage.

Magnetic seizure therapy

One of the most recently developed brain stimulation techniques is magnetic seizure therapy (MST). MST uses very high frequency repetitive magnetic stimulation to induce a highly focal seizure. The focality of the seizure, which is restricted to the superficial regions of the cortex with no spread to deeper regions of the brain, is thought to be responsible for the superior cognitive profile seen following MST, when compared to ECT (10). Clinical trials using the most advanced MST equipment, capable of 100 Hz stimulation, began in 2008 and are being conducted at a number of centres worldwide (10). Early results with respect to antidepressant efficacy are promising and rigorous investigation of this technique will continue.

As described above, over the last 20 years there has been an explosion of research into the use of brain stimulation techniques in psychiatry. This research is providing both a growing understanding of the pathophysiology of mental illnesses and the development of a wider array of evidence-based therapies for patients to access. However, most of these techniques require the conduct of substantive rigorous multi-site trials to establish efficacy and for many, this needs to follow a better exploration of optimal stimulation techniques.

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