

Clinical use of brain stimulation in psychiatry – a motivated review

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Summary

The combination of different treatment modalities has advanced psychiatric therapy, particularly for chronic or treatment-resistant psychiatric conditions. While the field has successfully integrated psychotherapy approaches, pharmacotherapy and rehabilitation, a novel group of brain stimulation techniques could offer new options augmenting classical psychiatric treatment. This review summarises basic principles of transcranial magnetic stimulation, transcranial direct current stimulation, electroconvulsive therapy and deep brain stimulation. Brain stimulation allows for targeted transient modulation of cortical network activity. Electroconvulsive therapy is already a standard treatment in chronic depression. Evidence suggests that noninvasive brain stimulation may be successfully combined with pharmacotherapy and psychotherapy in treatment resistant affective disorders or schizophrenia. In very severe cases, deep brain stimulation may help to relieve chronic depression or obsessive compulsive disorder. The application of brain stimulation in psychiatry is constantly evolving. The new methods hold potential for the field of psychiatry, including new treatment modalities to offer for patients and novel skills to acquire for psychiatrists.

Keywords: transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation, electroconvulsive therapy, treatment resistance

Introduction

Brain stimulation is a widely used popular term for any intervention involving the application of electric or magnetic fields on the central nervous system. The application aims at deliberately altering brain physiology in order to either investigate neural function or treat disorders. The earliest use of brain stimulation dates back to the ancient Greek, when headaches, seizures, pain or depression were treated by exposing patients to electric fish [1].

Modern psychiatry relies on the integration of various methods, including psychopharmacology, psychotherapy, experience-based interventions such as sports or arts, supportive employment or housing, and brain stimulation. Collectively, these efforts target the way our patients feel,

behave or interact with their environment. At the same time, or as a consequence, these distinct treatment measures alter brain function and structure. For example, most psychopharmacological agents interact with neurotransmission, stimulating the expression of further receptors or the formation of new synapses [2–4]. Thus, pharmacology alters cerebral function, metabolism and structure. Likewise, psychotherapeutic interventions may target cognitive control of maladaptive emotions, which alters brain function and connectivity in prefrontal-limbic circuits within weeks [5, 6]. And one of the hypotheses concerning exercise interventions is that it may stimulate neurogenesis, allowing beneficial neuroplastic changes, even though this has not been conclusively demonstrated in humans.

The obvious unique selling point of modern brain stimulation techniques, however, is the motivation. This motivation is derived from knowledge of brain pathophysiology in psychiatric disorders. Therefore, neurobiology informs modern brain stimulation in the type, timing and target location of the intervention. This selective review summarises the most common brain stimulation techniques and their therapeutic application in psychiatry, as well as potential future developments in the field.

Modern methods of brain stimulation

Electroconvulsive therapy (ECT) has the longest tradition of the modern brain stimulation techniques. Patients are given short-duration anaesthesia and muscle relaxation, and then a short, strong electric current is applied to the skull surface, passing through the brain tissue to induce a generalised seizure lasting 30–180 seconds. The effect of ECT relies on the quality of the seizure, the amount of current and the electrode placement [7]. Current theories on the mechanism of ECT are direct effects of generalised seizures on brainstem and prefrontal cortex, restoration of neuroendocrine function, or a combination of both that may even induce hippocampal neurogenesis [7]. ECT is typically administered in series of 12 sessions over 4–6 weeks, with outstanding efficacy. A wealth of data support the efficacy and safety of the method [8–13]. The major drawback is anaesthesia, which requires anaesthesiologists and puts the patient at the common anaesthesia risk. Nev-

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ertheless, ECT is a safe method, with transient side effects related to both the seizure and the anaesthesia, such as headaches, muscular pain, anterograde amnesia, or nausea. Recent research suggests that problematic amnesia is much less frequent than previously expected, particularly concerning autobiographical memory with unitemporal stimulation [14–16]. Likewise, brain imaging studies reported increased hippocampus sizes in patients receiving ECT [17], strongly arguing against previous common assumptions that ECT harms the brain.

During transcranial direct current stimulation (tDCS), a low current is applied via two electrodes on the skin. The neurophysiological effects are found in the underlying cortex and depend on electrical stimulation parameters such as electrode placement, and current magnitude, duration and polarisation. The effects also depend on the cortical area to be stimulated, such as orientation of the gyrus, cortical thickness and the targeted neurones. Anodal stimulation is thought to facilitate neural activity, whereas cathodal stimulation is believed to inhibit neural activity; however, the effects strongly depend on the location [18]. Furthermore, distant effects on deeper brain structures are also observed, which may be directly induced by stimulating a cortico-subcortical network or follow as a consequence of altered cortical activity. Depending on the duration of stimulation, tDCS may exert online effects (only during the ongoing stimulation) or offline effects (outlasting the stimulation). tDCS is currently being tested as treatment for various neuropsychiatric conditions including depression, schizophrenia, substance abuse, pain and movement disorders. tDCS is a safe method with few side effects including mild headaches, local skin irritation, or sensory discomfort [18]. Anecdotal reports of hypomania with tDCS in combination with antidepressant drugs raised concerns that have not been substantiated by meta-analyses [18–20]. The treatment requires daily sessions of 10–30 minutes. Easy application and the relatively low cost of the devices led some authors to suggest trained tDCS use by the patients themselves at home.

Transcranial magnetic stimulation (TMS) exerts its effects locally in the cerebral cortex. A coil is placed on the skull that elicits short, intense magnetic pulses that pass through the skin and skull to induce an electric field within the first centimetres of cerebral cortex. The electric field depolarises axons and thus modulates brain network activity [21]. In clinical applications, TMS is repetitively administered, in series of several hundred short pulses per session, which has significant offline effects. Daily administration of such repetitive TMS (rTMS) will temporarily alter brain activity for days and weeks. Depending on the frequency and intensity of the pulses, local brain activity may be facilitated or inhibited. The most common protocols use low-frequency rTMS or continuous theta burst stimulation (cTBS) to inhibit brain activity, whereas high-frequency rTMS or intermittent theta burst stimulation (iTBS) may facilitate neural activity in the target area [22]. Compared with tDCS, the effect of rTMS on the cortex is much more localised and requires exact positioning of the coil; however, stimulation effects are not limited to the brain surface. The therapeutic use of rTMS has been developed since the late 1980s. Typically, rTMS is administered in series of 10–15 daily sessions over 2–3 weeks. In general, rTMS is considered

to be a safe method. Rarely (in fewer than 1 in 1000 patients) seizures may occur. Patients should wear ear plugs against the audible clicking sounds of the coil. Headaches, dizziness and sensory discomfort on the skin underneath the coil may occur as transient side effects of rTMS [23]. In addition, as with tDCS treatment, rare cases of switches to hypomania have been reported [21]. The TMS machines can be operated by any trained medical person.

Deep brain stimulation (DBS) includes the placement of thin electrodes in specific cerebral structures, such as nuclei of basal ganglia, and subsequent electrical stimulation driven by a pacemaker-like stimulation device implanted underneath the skin on the upper trunk. The high-frequency, targeted electrical stimulation aims at disrupting the spontaneous activity of dysfunctional brain circuitry. First developed to treat medication-resistant disabling movement disorders, such as Parkinson's disease, DBS is currently being tested as end-of-the-line treatment of psychiatric disorders with suspected dysfunction of brain circuits. The extensive preparation and the need of close collaboration between neurosurgery and psychiatry limit this method to highly specialised centres.

Treatment resistance

Despite a large number of pharmacological treatment options and psychotherapeutic interventions, a considerable proportion of patients do not achieve an adequate treatment response, even though remission is the primary treatment aim. For example, treatment resistance has been described in up to 30% of patients with major depressive disorder, bipolar disorder, schizophrenia, or obsessive compulsive disorder. Resistance is usually defined as failure to respond to at least two treatment trials of adequate dose and duration. Treatment resistance has many causes and is often associated with illness chronicity, increased symptom load, poor quality of life and poor social functioning, all of which contribute to an increased burden of disease on patients and families. For many psychiatric disorders, treatment resistance may be overcome with optimised or intensified treatment. Typically, patients are offered a combination of specific psychotherapy techniques with pharmacological augmentation. In some instances, such as major depression, ECT as a brain stimulation technique is already included in the treatment algorithm [24, 25].

Brain stimulation offers new treatment options that can be combined with existing traditional measures. Thus, brain stimulation helps to extend and optimise treatment algorithms in psychiatry.

Meta-analyses have demonstrated the superior effect of ECT over pharmacotherapy in acute major depressive disorder [8]. Most importantly, real ECT is much more effective than sham ECT. As remission is the main goal of depression treatment, ECT should be applied more frequently: 48% of patients with treatment resistance and as many as 69% of patients without treatment resistance achieve remission with ECT [26]. Higher age and psychotic features are predictors of a better ECT response in depression [27]. Unfortunately, Swiss patients with depression are less likely to be offered this effective treatment method than patients in other countries across Europe and the world.

A meta-analysis of six trials demonstrated the efficacy of tDCS for acute depression as an add-on treatment in achieving treatment response (34%) or remission (23%) [28]. Most of the studies were performed in first-episode depression, and shorter duration of depression predicted good response to tDCS. A more recent meta-analysis including more trials confirmed this effect [29]. Thus, tDCS is not as effective in the treatment of depression as ECT or rTMS (see below). tDCS has also been tested in small studies in obsessive compulsive disorder or schizophrenia. Much more work is still needed to determine, whether tDCS may become an effective, low-cost and safe at-home treatment option for psychiatric patients.

The effect of rTMS on depression has long been documented. Several stimulation protocols are reported as effective treatment for depression. A recent meta-analysis of treatment trials with different stimulation protocols identified four protocols that are effective in achieving response; two protocols were able to achieve remission [30]: high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) or bilateral rTMS (high-frequency over left DLPFC and low-frequency over right DLPFC). In addition, the novel facilitatory intermittent theta burst stimulation (iTBS) protocols at 50 Hz were found to achieve response too [30]. Importantly, one adequately powered trial in treatment-resistant depression reported noninferiority of two facilitatory stimulation protocols – 10 Hz rTMS and iTBS. This finding is very relevant because although both treatments are effective, high-frequency rTMS took 37 minutes daily, whereas iTBS is delivered within 3 minutes daily, saving relevant time during the therapy [31]. In sum, some TMS protocols have proven effectiveness in treating depression. The search now is for optimised protocols with superior efficacy. Another question is whether maintenance TMS would be beneficial or whether effects could be boosted by administration of TMS at specific time points. Even though rTMS in depression is effective in both acute and chronic cases, the efficacy is considered to be lower than that of ECT [21, 23]. On the other hand, the effort to deliver rTMS is much lower than that of ECT.

In addition to depression, rTMS has also been effectively applied in schizophrenia patients with auditory verbal hallucinations. Voice-hearing patients seem to benefit from inhibitory stimulation over the parieto-temporal junction, close to the primary auditory cortex. This region is hyperactive during the perception of voices [32] and down-regulation of the neural activity by inhibitory rTMS is closely linked to improvement of auditory verbal hallucinations [33]. Thus, rTMS is able to directly alter aberrant brain activity associated with disturbing schizophrenia symptoms. Other treatment targets in schizophrenia are still at the experimental stage, but negative symptoms or psychomotor slowing might also be ameliorated by targeted rTMS [34].

In patients with severe treatment resistance, who failed to respond even to adequate ECT series, deep brain stimulation of structures of the human reward system has been tested. Most of the reported trials or case series placed stimulation electrodes in the nucleus accumbens, lateral habenula, anterior limb of the internal capsule, or the subgenual cingulate cortex. All of these structures are located along a fibre tract, the superolateral medial forebrain bundle (sl-MFB), which has also been suggested as a target

region [35, 36]. The evidence is still scarce, owing to the limited availability, costs and specialisation required. Nonetheless, approximately 150 cases receiving DBS for depression have been reported. DBS for depression requires constant stimulation and the effects may start very early after the fine-tuning of the stimulator, whereas some patients benefit from stimulation after several weeks. Critically, the setting of the optimal stimulation parameters is an individualised procedure that may take 3 or more months. Some studies reported that patients may start to benefit from DBS after 1 year. About 50–70% of this very chronic, treatment resistant population may achieve treatment response with add-on DBS therapy [35, 37]. Most patients require continuation of pharmacotherapy and psychotherapy. Despite challenges in adjusting the postoperative therapy to fluctuations in mood and hedonic tone, the patients who have received DBS for treatment-resistant depression in Bern are continuing to benefit from the procedure as compared with the situation prior to neurosurgery. DBS has also been tested in treatment-resistant obsessive compulsive disorder. The few reported trials targeted the nucleus accumbens or the subthalamic nucleus, with treatment response in approximately half of the patients [38]. One recent study demonstrated that personality traits were unchanged by DBS, strongly arguing against a typical pre-conception [39]. Overall, DBS may become a reasonable option for severe treatment-resistant patients. However, target location, selection of optimal patients and stimulation protocols still require more scientific exploration. Today, only highly specialised centres with established interdisciplinary collaboration already offer this option to a selected group of severely ill patients.

Bright augmentation

The most complex issue when planning psychiatric treatment is choosing the right combination of methods. As mentioned above, for some disorders there are already indications of which medicines or psychotherapy techniques are ideally combined. Most brain stimulation techniques are currently administered as add-on treatment while pharmacotherapy or psychotherapy interventions are continued. However, particularly in the field of noninvasive brain stimulation, there may be optimal time points at which to administer stimulation. Given that it may either temporarily facilitate brain activity or inhibit unwanted brain activity, brain stimulation could be used to enhance the effects of psychotherapy, for example by fostering learning or extinction processes. Three potential combinations have been proposed [40]: sequential administration, in which brain stimulation is given prior to psychotherapy; simultaneous administration during the entire psychotherapy session; or interactive administration, in which brain stimulation is administered exclusively during specific processes within the psychotherapy session, for instance to facilitate procedural learning. First studies have demonstrated beneficial effects of sequential rTMS immediately before cognitive behavioural therapy sessions in patients with posttraumatic stress disorder [41] or of simultaneous tDCS during cognitive control training in major depression [42]. As the field is generating more knowledge on brain stimulation effects, bright augmentation strategies may become the standard in psychiatric treatment algorithms.

Monotherapy

Even though not part of our current practice, brain stimulation could also be administered as monotherapy to treat mild to moderate depression. This option might be particularly relevant for patients who are reluctant to accept psychotherapy or pharmacotherapy. One randomised double-blind trial of 245 patients with major depression (75% recurrent) tested the effects of 15 daily plus 7 weekly tDCS sessions of 2 mA and 30 minutes vs escitalopram 10–20 mg vs placebo over 10 weeks. Escitalopram was superior to both tDCS and placebo in reducing depression severity; however, tDCS also was superior to placebo [43]. This finding puts tDCS treatment in an intermediate position between placebo and an antidepressant drug as depression monotherapy.

Early rTMS studies tested real rTMS as monotherapy for acute depression and demonstrated efficacy of left DLPFC high frequency rTMS over sham [44, 45]. There are no studies directly comparing rTMS with antidepressant monotherapy in the acute phase. Thus, no evidence supports the use of rTMS monotherapy over antidepressants or psychotherapy at this time. This evaluation might change as more trials are conducted. For instance, one study compared antidepressant drug plus rTMS vs rTMS alone vs drug alone in patients who had achieved remission with antidepressants. Results of this single-blind trial suggest that rTMS alone or in combination is superior to antidepressant drugs alone in preventing depressive relapse [46].

Finally, in some special conditions such as perinatal depression, tDCS or TMS could be interesting treatment options. One small study suggested that right DLPFC low frequency rTMS may be beneficial in treating depression in pregnant women [47]. No such studies have been published for the use of tDCS.

Chances for psychiatry

The introduction of novel brain stimulation techniques to psychiatry brings several advantages for the field. Our current understanding of brain network function and the link to psychiatric symptoms or suffering is still in its infancy. Targeted brain stimulation requires knowledge on the pathobiology of psychiatric conditions. Psychiatric therapy will integrate not only learning, neurotransmitters and interpersonal behaviour, but also brain network physiology. This will foster further interest in our field. Most importantly, application of brain stimulation in clinical care offers new treatment options to patients with a severe burden of disease and a chronic course. In addition, noninvasive techniques such as TMS and tDCS may be delivered in the future to patients at every stage of their disorder. All brain stimulation is readily combined with current treatment options in psychiatry including pharmacotherapy or psychotherapy. TMS and tDCS may also be a great alternative for patients who are reluctant to take medicines. The methods are safe and some already have proven effectiveness. With the rapid developments ahead, noninvasive techniques will soon have wider availability. What we need now are more randomised controlled trials on the different protocols and indications, specific continuing medical education programmes covering brain stimulation techniques, more published standards and guidelines, and reimburse-

ment from the health insurance companies. This would allow brain stimulation to be offered to a large variety of psychiatric patients in many settings. Finally, the use of brain stimulation techniques requires new skills for psychiatrists. For example, psychiatrists need to identify potential candidates for these novel treatments, inform patients about potential options, select the appropriate stimulation target and protocol, and integrate brain stimulation wisely into the general therapeutic concept. Clinical psychiatry is already starting to embrace brain stimulation techniques, as the Canadian guidelines to treat depression now list rTMS as first-line treatment in patients who have failed to respond to at least one antidepressant drug, with A-level evidence [25]. With increasing application in clinical practice, research will also focus more on the link between symptoms and brain network dynamics.

Conclusion

Novel brain stimulation techniques are an exciting addition to the psychiatric toolbox. These methods are readily combined with existing treatments, providing new options for chronic treatment-refractory patients as well as offering alternatives to existing therapies. Currently, the field needs more clinical research to establish the best brain stimulation protocols for specific conditions. Furthermore, targeted education of psychiatrists is necessary so the broad range of practitioners will be able to offer noninvasive brain stimulation. Finally, economic incentives are required to implement brain stimulation in clinical practice. In summary, novel brain stimulation techniques have much potential for psychiatry.

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