DOI: 10.14744/DAJPNS.2024.00258
Dusunen Adam J Psychiatr Neurol Sci
2024;37:175-178

GUEST EDITORIAL

Paradigm shift in psychiatric treatments: Brain stimulation

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Psychiatric disorders are prevalent and debilitating despite advances in medicine (1). The burden of psychiatric disorders largely stems from treatment resistance and recurrent cases. Pharmacological agents and psychotherapy used to be the first-line treatment options. However, new strategies are needed for treatment-resistant cases. Electroconvulsive therapy (ECT) was one of the earliest treatment modalities in psychiatry, but its side effects limit its use. However, a variety of other brain stimulation methods have emerged, offering alternatives to current psychiatric treatments. Transcranial electrical stimulation, transcranial magnetic stimulation, vagus nerve stimulation, and deep brain stimulation are among the most prominent methods for treating psychiatric disorders.

Transcranial electrical stimulation (tES) encompasses transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). Transcranial direct current stimulation modulates neuronal excitability in the targeted brain region mainly through polarization effects (Fig. 1a). A closed loop current (1-4 milliAmperes) flows from the anode to the cathode electrode, penetrating the intervening brain tissue (2). The anodal site increases the resting membrane potential of neurons, enhancing cortical excitability, while the cathodal site decreases the resting membrane potential, causing hyperpolarization. Transcranial direct current stimulation promotes plasticity, neurotransmitter release, gene expression changes, regional blood flow alterations, and modulates glial cells. The outcomes of tDCS are influenced by several key factors, including polarity, intensity, duration, electrode placement, and individual differences.

Transcranial alternating current stimulation influences brain activity by applying weak alternating currents at specific frequencies that resonate with the brain's natural oscillatory activity. Transcranial alternating current stimulation entrains cerebral networks with a particular rhythm, and this entrainment (or synchronization) is proposed to enhance or suppress specific brain rhythms depending on the frequency and phase of the current (Fig. 1b) (3). Electrode locations, duration, and intensity of stimulation influence the outcomes, but frequency and phase are the most important determinants in tACS. Transcranial random noise stimulation is a non-invasive brain stimulation technique that applies a weak electrical current with randomly varying frequencies to the scalp (Fig. 1c). The exact mechanism of action of tRNS is not fully understood, but random fluctuations in neuronal activity have been shown to enhance neural performance in various experiments (3). Both tACS and tRNS are suggested to work through the phenomenon of stochastic resonance, which may help detect and process weak signals by making neurons more responsive to incoming stimuli and enhancing neural plasticity and network-level synchronization capabilities (3).

Transcranial magnetic stimulation (TMS) operates based on the principles of electromagnetic induction

How to cite this article: Atagun MI. Paradigm shift in psychiatric treatments: Brain stimulation. Dusunen Adam J Psychiatr Neurol Sci 2024;37:175-178.

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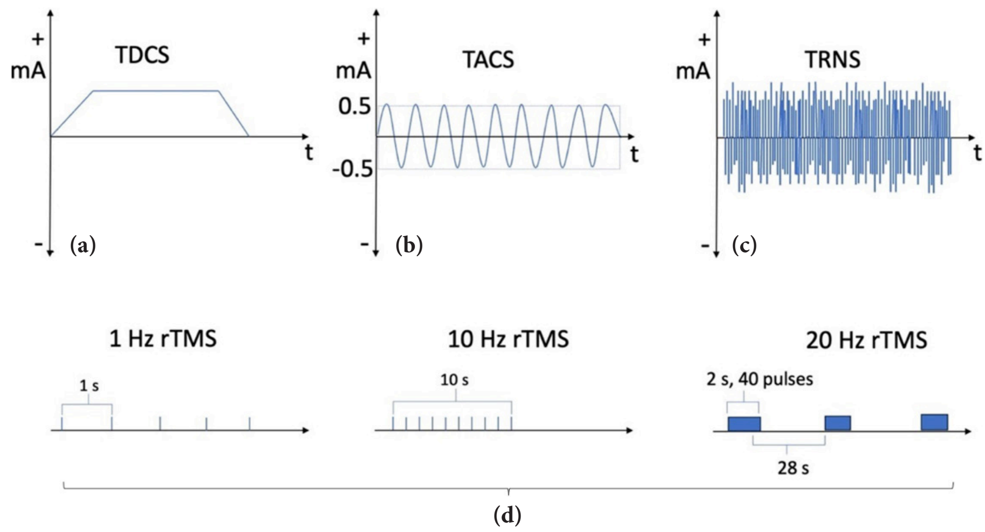

Figure 1. Transcranial electrical stimulation (tES) and transcranial magnetic stimulation strategies (TMS). The first row, from left to right **(a–c)**, shows transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). The second row **(d)**, from left to right, illustrates 1, 10, and 20 Hz TMS stimulation strategies.

and neuronal excitability. A TMS device consists of a capacitor and a coil of wire through which a rapid, high-intensity electrical current is passed. This current generates a strong, time-varying magnetic field around the coil. When the coil is positioned near the scalp, the magnetic field penetrates the skull and induces an electrical current in the underlying brain tissue, altering neuronal activity by either increasing or decreasing excitability. Transcranial magnetic stimulation can also influence network dynamics by exciting neurons, inducing plasticity, changing blood flow, enhancing neurotransmitter release, and promoting the production of neuropeptides (4). The effects of TMS depend on several factors, including the intensity, frequency, and duration of the stimulation, as well as the specific brain region targeted. Modern TMS devices incorporate various coil designs to target specific brain regions with greater precision. The shape and size of the TMS coil determine the focality of the stimulation. Transcranial magnetic stimulation is a non-invasive technique, considered safe, with mild and transient side effects. It does not require any surgical procedures or the implantation of electrodes.

Transcranial magnetic stimulation is a versatile tool with a wide range of applications in neuroscience research and clinical practice. Ongoing advancements in technology and a growing understanding of brain function continue to expand the potential of TMS for treating neurological and psychiatric disorders, as well as enhancing cognitive abilities. Below are the most commonly used protocols designed to target specific brain regions for different therapeutic or research objectives (5):

1. **Single-Pulse TMS (spTMS):** A single magnetic pulse is applied to the brain, inducing a brief current in the targeted area. Single-Pulse TMS is primarily used for mapping brain function and studying cortical excitability and connectivity.
2. **Paired-Pulse TMS (ppTMS):** This involves delivering two magnetic pulses in rapid succession, with varying inter-stimulus intervals. Paired-Pulse TMS is used to investigate intracortical inhibition and facilitation processes, providing insights into synaptic plasticity and cortical circuit function.
3. **Repetitive TMS (rTMS):** Repetitive TMS delivers trains of repetitive magnetic pulses at different frequencies, inducing longer-lasting changes in brain activity. Frequencies above 5 Hz are classified as high-frequency rTMS (HF-rTMS), which is typically associated with increased cortical excitability and is commonly used to treat psychiatric disorders. Low-frequency rTMS (LF-rTMS), on the other hand, employs frequencies below 1 Hz and is often associated with decreased cortical excitability (Fig. 1d). Low-frequency rTMS is being investigated for conditions such as epilepsy and chronic pain (5).
4. **Theta-Burst Stimulation (TBS):** Theta-Burst Stimulation delivers bursts of three pulses at 50 Hz, repeated at a theta frequency (5 Hz). Theta-

Table 1: Comparison of current brain stimulation methods in psychiatry

	ECT	TMS	TDCS	VNS	BLT	DBS
Efficacy	+++	++	++	++	+	++
Robustness	+++	++	+	++	+	+++
Resolution	+/-	+++	++	+	+	+++
Side effects	+++	+	+	++	+	++

ECT: Electroconvulsive therapy; TMS: Transcranial magnetic stimulation; TDCS: Transcranial direct current stimulation; VNS: Vagal nerve stimulation; BLT: Bright light therapy; DBS: Deep brain stimulation.

Burst Stimulation protocols include continuous TBS (cTBS), which typically decreases cortical excitability, and intermittent TBS (iTBS), which typically increases cortical excitability. Theta-Burst Stimulation is emerging as a faster and potentially more effective treatment for depression (6).

5. **Deep TMS (dTMS):** Deep TMS uses a specialized coil to reach deeper brain structures compared to conventional coils. It is used to treat conditions like obsessive-compulsive disorder (OCD) and major depressive disorder, which may involve deeper brain regions (7).

Many strategies are available for TMS by adjusting stimulation parameters, including frequency, intensity, duration, and inter-stimulus intervals, as well as target location, depending on the desired therapeutic or research outcomes. Additionally, TMS can be personalized based on individual differences and the pathogenesis of specific disorders. Combined with neurophysiological assessments, TMS offers promising avenues for further research into neural mechanisms and disease pathogenesis.

Vagus nerve stimulation (VNS) is typically implemented using an implanted pacemaker-like device that surrounds the vagus nerve, transmitting signals to the brain (8). The United States Food and Drug Administration (FDA) approved VNS for treatment-resistant epilepsy in 1997, major depressive disorder in 2005, and stroke rehabilitation in 2021 (9). Vagus nerve stimulation stimulates the release of neurotransmitters and neurotrophic factors, activates the hypothalamus and orbitofrontal cortex, increases blood flow to the amygdala and hippocampus, and promotes brain plasticity.

Deep brain stimulation (DBS) is a neurosurgical procedure involving the implantation of electrodes into specific brain regions to deliver electrical impulses that modulate neural activity. While DBS was initially developed for movement disorders such as Parkinson's disease, it is increasingly being explored and used for the treatment of various psychiatric disorders (10). Deep brain stimulation targets specific brain regions and networks based on personal evaluations of the patient. Treatment-resistant cases of obsessive-compulsive disorder, major depressive disorder, Tourette syndrome, and schizophrenia are potential candidates for DBS. However, its invasive nature, potential adverse effects, and long-term impacts limit its use. Advances in technology and neuroscience continue to offer potential for DBS in severe and treatment-resistant psychiatric cases (Table 1).

In conclusion, several neuromodulation therapies have emerged in the last two decades. This diversity of options has expanded psychiatric treatment possibilities, particularly for treatment-resistant cases. Future research is needed to better understand the mechanisms of action, side effects, clinical efficacy, and benefits for specific populations. One potential limitation in the field is that these interventional treatments are new to psychiatrists, and funding agencies are cautious. Despite these challenges, neuromodulation holds the potential to contribute to the future of neurological and psychiatric treatments.

Conflict of Interest: The author have no conflict of interest to declare.

Use of AI for Writing Assistance: Not used.

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