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Newer Neuromodulation Techniques for Psychiatric Disorders: A 2023 Update

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Abstract

There are several challenges exist in the management of psychiatric disorders. Many of these factors are related to psycho-social circumstances. Despite being diagnosed accurately and receiving adequate treatment, several patients with psychiatric disorders remain nonresponsive to treatment, commonly called a state of treatment resistance. Though pharmacological management and psychotherapy are well-established treatment modalities in the management of psychiatric disorders, several patients show inadequate responses requiring treatments using neuromodulation. Sometimes, the nature of psychiatric illness also determines the preference of going for neuromodulation. For example, managing a patient with acute suicidal behavior or catatonia may be better and rapidly treated with electroconvulsive therapy (ECT). Recent decade has witnesses several newer spectra of neuromodulation techniques using a range of stimuli (electrical, magnetic, sonic, photic, thermal, etc) to neuromodulation for the management of several neuropsychiatric disorders. This review highlights the newer neuromodulation techniques and their potential roles in managing psychiatric disorders with research evidence.

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Introduction

Conventional neuromodulation techniques for Psychiatric disorders

Since the introduction of path-breaking electroconvulsive therapy (ECT), a little short of a century ago, the field of neuromodulation has shown tremendous growth and now has been broadly classified into noninvasive and invasive neuromodulation. A brief update on the advances of conventional neuromodulation techniques is being given below.[1-5]

Electroconvulsive therapy (ECT)

Despite the advances in the field of neuromodulation, no other techniques have been able to take the place of ECT, which remains the treatment of choice for life-threatening conditions like catatonia, food refusal and severe depression with active suicidality till date.[6] However, over time, there has been improvements in the technique of ECT in terms of better efficacy and tolerability. Direct or unmodified ECT has become part of history with the Mental Health care Act introduced in 2017. Newer brief pulse ECT machines are found to be more efficacious and ultra-brief pulses cause minimal cognitive deficits and are recommended to be selected depending on the patient's clinical profile. Further, right unilateral frontal ECT is being recommended again to reduce cognitive side effects.[7]

Repetitive transcranial magnetic stimulation *(rTMS)*

The stigma surrounding ECT, which infamously is referred to as shock therapy by public has impelled the introduction of rTMS in psychiatry. Maximum evidence for the use of rTMS has been for treatment-resistant depression as adjunctive treatment [8]. Additionally, it is also indicated in migraine prophylaxis[9]. Intermittent Theta burst stimulation (iTBS) which has been approved for use in depressive disorders, has the advantage of reduced duration of individual sessions and is cost-effective [10]. Recently deep TMS has been introduced and is indicated as adjunctive treatment in treatment-resistant obsessive-compulsive disorder (OCD). Deep TMS has the advantage of penetrating the deeper structures of brain, overcoming the shortcomings of the conventional rTMS. Further deep TMS is indicated in tobacco anti-craving as well as anxiety comorbid with major depressive disorder (MDD) [11].

Transcranial direct current stimulation (tDCS)

One of the barriers to accepting ECT or rTMS has been the need for repetitive sessions delivered only in institutional set ups. tDCS has given the hope and direction for a domiciliary approach to neuromodulation [12]r. Being a portable device, tDCS has maximum evidence in the treatment of depressive disorders, followed by treatment-resistant cases of schizophrenia and OCD [13]. Research is underway for it's use in cognitive disorders.[14]

Vagal nerve stimulation

Vagal nerve stimulation(VNS) is a promising add on invasive and approved neuromodulation strategy in treatment of refractory depression [15]. Preliminary data on efficacy has also been reported in other psychiatric conditions like schizophrenia, Alzheimer's disease and OCD. New noninvasive VNS devices are being evaluated in stress-related disorders but conclusive evidence is lacking.[16]

Deep brain stimulation (DBS)

Deep brain stimulation is a favorable invasive neuromodulation technique, especially when depression or OCD are treatment resistant and intractable.[17] However, recent recommendations of the neuromodulation society and the Indian Society for Stereotactic and functional neurosurgery (ISSFN) must be followed before implementing the procedure. This group recommendation has specified three conditions: treatment-refractory depression, OCD and Tourette syndrome.[18]

Newer neuromodulation techniques for Psychiatric disorders

Over the past decade various neuromodulation techniques have been used for the treatment of psychiatric disorders. The commonly used conventional neuromodulation techniques cannot completely manage the psychiatric disorders; hence, there is a perceived need to find a cost-effective, safe and highly efficacious neuromodulation facility that will enhance the outcome of care in psychiatric disorders. The newer neuromodulation techniques with relevance to psychiatric disorder management are discussed here.

Transcranial alternating current stimulation (tACS)

Transcranial alternating current stimulation (tACS) is a form of transcranial electrical stimulation (tES) that uses low-intensity alternating electric current on the scalp to modulate the neuronal activity of the underlying cortex.[19] The pathological oscillatory activity of the neurons are reported in psychiatric disorders. tACS alters the membrane potential of the neurons by modulating the oscillatory frequency of the neurons, bringing them to the frequency of the induced electric current.[20] Accumulating evidence suggests that [20]:

- tACS at alpha frequency over the dorsolateral prefrontal cortex improves depression.
- tACS at gamma frequency improves memory in patients with Alzheimer's disease.

Evidence suggest that tACS is more beneficial than tDCS in causing cognitive improvement.[20] tACS has been used in the treatment of depression, schizophrenia, and cognitive impairments in Alzheimer's disease.[20] Even in healthy individuals, tACS was found to improve cognition.[20] In elderly individuals, tDCS improves associative memory performance.[21] As per the existing evidence, there is no serious or long-term side effects and further safety investigations are required.

Transcranial random noise stimulation (tRNS)

Transcranial random noise stimulation (tRNS) is a newer neuromodulation technique. Here, low-voltage electric current passes through the brain at random frequencies.[22] The frequency band used in tRNS ranges between 0.1 Hz to 640 Hz. Frequencies between 0.1Hz to 100Hz are low-frequency, whereas frequency between 100 to 640 Hz is called high-frequency.[22,23] The effects of tRNS often last for an hour following application for 10 minutes [23]. Though evidence suggests that high-frequency tRNS produces neuronal excitability more effectively, the therapeutic efficacy depends on the width of the selected frequency.[22] Research supports that when a frequency with 100–700Hz is given, it produces more cortical excitability than a frequency of 100-400Hz and 400–700Hz given.[22] Longer application of tRNS, either through a single prolonged administration or multiple short applications, is known to enhance neuroplasticity.[24]

tRNS produces more intense cortical excitability than tDCS.[25] High-frequency tRNS has been used in various research and found to enhance visual attention, facial perception, facial emotion recognition, arithmetic skills & calculation, pain modulation, mood regulation (effective in depression), improving the negative symptoms of schizophrenia, reducing tinnitus and cognitive enhancement.[22,26] A randomized controlled trial that evaluated the role of tRNS in the management of depression found that tRNS is not superior to its sham counterpart in the treatment of depression.[27]

Micro transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) uses magnetic stimulation, which is applied to scalp and on reaching the cortical surface, it gets converted to an electrical stimulus and produces focal neuromodulation. However, the major limitation with TMS being the device is large and capable of doing superficial cortical neuromodulation (due to limited permeability). Recently, researchers are working on implanting micro-magnet in the targeted neuronal tissue to do neuromodulation.[28] Evidence suggests that the spatial orientation of the micro-TMS coil with respect to the neurons is largely responsible for producing a variety of neural responses.[28] The micro-TMS is in early stage of development and holds promise for precise person-centered neuromodulation for various neuropsychiatric disorders.[29]

Magnetic seizure therapy

Magnetic seizure therapy (MST) uses high-frequency magnetic stimulus to produce convulsion, which has a similar mechanism like ECT.[30] MST also requires general anesthesia and skeletal muscle relaxant for carrying out the procedure. The cognitive side effects produced by MST is significantly lower than ECT [30]. MST using various frequencies of magnetic pulses were tried in research for the treatment of major depressive episode, and it was found that patients receiving high-frequency MST (100Hz), had highest remission rate.[31] In another interesting study, it was found that MST effectively reduces suicidal behavior (remission rate from suicide by approximately 48%) and this effect was elicited [32]. Low to moderate-frequency MST is associated with higher reduction of suicidality compared to those receiving high-frequency.[32] MST is also found to be as effective as ECT in reducing the symptom severity of schizophrenia [33]. MST has minimal neurocognitive sequel. Patients receiving MST, often have intact memory functioning and their reorientation is achieved early following the procedure.[34]

Optogenetics

Optogenetics is a newer intervention modality that uses optical and genetic methods to manipulate the cell level for behavioral modification.[35,36] The precision of intervention in optogenetics goes to cell and genetic level.[37] The photosensitive neurons of the brain and retina are often the targets in optogenetic intervention. Photic (optic) stimuli produce several changes in these neurons, subsequently altering the functional connectivity by modulating sleep, arousal, behavior, mood regulation, reward processing, and fear.[37] There are possible roles of optogenetic interventions in schizophrenia, depression, anxiety disorders and substance use disorder.[37,38]

Photobiomodulation

Transcranial Photobiomodulation more often uses near-infrared (NIR) light, which easily penetrates the head and reach the brain surface.[39] The therapeutic effect of this procedure is mediated by mitochondrial cytochrome C oxidase activation, though heat-gated ion channels also play a role.[39] Increased cerebral blood flow, and reduction of the inflammatory process facilitate neuronal repair and neuroprotection after Photobiomodulation.[39] There is a possible role of Photobiomodulation in the management of stress, depression, anxiety, and neurocognitive disorders.[39-42] Photobiomodulation reduces oxidative stress by reducing the production of reactive oxygen species and facilitating neuroplasticity.[41] Ceranoglu *et al*., (2022) has used Photobiomodulation in the treatment of autism spectrum disorder and found that there is a noticeable improvement in the core symptoms of autism following the intervention.[43]

Trigeminal nerve stimulation

Trigeminal nerve stimulation is a noninvasive neuromodulation technique that stimulates the peripheral cutaneous endings of the trigeminal nerve on the scalp, there by modulating the associated brain areas linked to trigeminal nerve nucleus.[44–46] Trigeminal nerve stimulation is safe, with no major side effects.[46] Existing evidence supports the potential role of trigeminal nerve stimulation in managing major depressive disorder, posttraumatic stress disorder, attention-deficit hyperactivity disorder (ADHD) and epilepsy.[44–48]

Transcutaneous vagus nerve stimulation

Transcutaneous vagus nerve stimulation is a newer noninvasive neuromodulation technique that stimulates the auricular branch of vagus through electrode placement by modulating the activity of associated brain areas.[48–51] Transcutaneous vagus nerve stimulation is a safe technique and has been successfully used in managing refractory (drug-resistant) epilepsy[50,52], depression[46], and migraine.[49] Adverse effects of transcutaneous vagus nerve stimulation are often mild to moderate and may be manifested as erythema & pain at the stimulation site, headache, nausea, vertigo, fatigue.[50–52]

Transcutaneous electrical cranial-auricular acupoint stimulation (TECAS)

Transcutaneous electrical cranial-auricular acupoint stimulation (TECAS) is a noninvasive electrical nerve stimulation recently introduced in managing depression.[53,54] TECAS enhances the connectivity between the default mode network (DMN), and right frontoparietal network (RFPN). It also increases the connectivity between default mode network (DMN), and dorsal attention network (DAN), which is responsible for its therapeutic effects.[53]

Ultrasound-mediated noninvasive brain stimulation

Transcranial ultrasound Ultrasound-based noninvasive brain stimulation (NIBS) is an innovative technique that shows promise for treating psychiatric disorders. It utilizes ultrasound waves to deliver precise stimulation to specific regions of the brain without requiring surgery.[55,56] Compared to traditional methods like deep brain stimulation (DBS), ultrasound-based NIBS has the potential to be safer and more effective.

Research has demonstrated the effectiveness of ultrasound-based NIBS in addressing various psychiatric disorders,[57,58] including depression, anxiety, and obsessive-compulsive disorder (OCD). A recent study revealed that ultrasound-based NIBS is equally effective as medication in treating depression, while causing fewer side effects. Furthermore, NIBS is being explored as a potential treatment option for schizophrenia and bipolar disorder.

Although still in its early stages of development, ultrasound-based NIBS could potentially transform the treatment landscape for psychiatric disorders. Further investigation could establish ultrasound-based NIBS as a safe and effective approach, significantly improving the lives of millions affected

Table 1: Newer neuromodulation techniques and current status of evidence

Modality of neuromodulation	*Target conditions*	*Evidence*
Transcranial alternate current stimulation (tACS)	• Depressive disorders • Chronic insomnia • Cognitive impairment • Schizophrenia	Promising results from small RCTs [68,69]
Transcranial random noise stimulation (tRNS)	• Mood regulation • Depressive disorders • Negative symptoms of schizophrenia • Cognitive impairment	Small RCTs with conflicting results [70],[27] Preliminary case studies
Micro transcranial magnetic stimulation	Ultra-focal brain stimulation	Ongoing studies in healthy volunteers[29]
Magnetic seizure therapy	• Major depressive episode • Suicidal behaviour • Schizophrenia	Positive findings from Systematic reviews of RCTs [71]
Optogenetic stimulation	• Possible roles of optogenetic interventions in schizophrenia, depression, anxiety disorders and substance use disorder	Preclinical studies in animal models [37,38]
Transcranial Photobiomodulation	• Autism spectrum disorder • Possible role in management of stress, depression, anxiety, neurocognitive disorders	Positive findings from proof of concept studies [43]
Trigeminal nerve stimulation	• Major depressive disorder • Attention deficit hyperkinetic disorder • Posttraumatic stress disorder • Epilepsy	Small Randomized control trials [72]
Transcutaneous vagal nerve stimulation	• Refractory epilepsy, depression and migraine	Promising Results from open-label trials [73]
Transcutaneous electrical cranial-auricular acupoint stimulation (TECAS)	• Mild to moderate depression	Positive findings from multicentric RCT [54]
Transcranial Ultrasound-based noninvasive brain stimulation (NIBS)	• Putative role in depression, anxiety and Obsessive-compulsive disorders	Animal Studies and studies on healthy human volunteers [74]

by these conditions.[58,59] Here are some of the advantages associated with ultrasound-based noninvasive brain stimulation for psychiatric disorders:

- Enhanced safety and effectiveness compared to traditional brain stimulation methods.
- Ability to target specific brain regions for treatment.
- Applicability in treating a range of psychiatric disorders.
- Potential to significantly improve the lives of many individuals.

However, several challenges must be addressed before ultrasound-based noninvasive brain stimulation can be widely implemented as a treatment for psychiatric disorders:[55]

- Further research is necessary to ascertain ultrasound-based NIBS's long-term safety and efficacy.
- NIBS devices and adequately trained personnel are unavailable due to its recent introduction.
- The cost of ultrasound-based NIBS might be prohibitive for some individuals.

Despite these obstacles, ultrasound-based noninvasive brain stimulation represents an encouraging new technology that could revolutionize psychiatric disorder treatment.[57] Continued research and development could establish ultrasound-based NIBS as a safe and effective approach, offering significant improvements to the lives of millions affected by these conditions.

Future directions

While several established forms of neuromodulation, such as electrical and magnetic stimulation, ongoing research and development efforts are exploring other modalities, here are some newer forms of neuromodulation:

- Thermal Neuromodulation: Thermal neuromodulation involves using temperature changes to modulate neural activity. It can be achieved through techniques like transcranial cooling or heating. These temperature alterations can influence brain function and have potential applications in pain management, psychiatric disorders, and neurorehabilitation. However, research in this area is still in its early stages, and further studies are needed to explore its efficacy and safety.[60,61]
- Chemical Neuromodulation: Chemical neuromodulation involves the use of chemical agents to modulate neural activity.[62] It can be achieved by delivering neurotransmitters, neuromodulators, or pharmacological agents to specific brain regions. Chemical neuromodulation techniques hold promise in treating various neurological and psychiatric disorders, but their development is still ongoing, and rigorous testing is required to ensure their effectiveness and safety.[62,63]
- Audio-Visual Entrainment (AVE): Audio-visual entrainment involves the presentation of synchronized audio and visual stimuli, typically through specialized devices like light and sound machines or goggles. The purpose is to induce specific brainwave patterns and promote desired states of consciousness, such as relaxation or focus [64,65]. AVE is often used in meditation, stress reduction, and cognitive enhancement practices. While it may have some beneficial effects, more research is needed to fully understand its mechanisms and effectiveness.
- Music Neuromodulation: Music has been found to profoundly impact the brain and can be considered a form of neuromodulation. The therapeutic use of music, known as music therapy, has shown potential in various clinical settings, including pain management, mood disorders, and rehabilitation. By carefully selecting and designing musical stimuli, it is possible to elicit specific emotional and cognitive responses, leading to changes in brain activity and behavior.[66,67]

It's important to note that while these newer forms of neuromodulation show promise, many of them are still in the experimental or research stages. The field of neuromodulation is rapidly evolving, and ongoing studies are necessary to fully understand their mechanisms of action, efficacy, and safety before they can be widely adopted in clinical practice. Table 1 below summarizes the evidence base of newer neuromodulation techniques.

Conclusion

In the past decade, there have been notable advancements in neuromodulation techniques, providing new and improved possibilities for patients struggling with various mental health disorders. Although these emerging techniques show great potential, conducting ongoing research, rigorous clinical trials, and long-term follow-up studies is important to establish their safety, effectiveness, and optimal usage. Moreover, ethical concerns and criteria for patient selection need to be carefully addressed to ensure responsible and fair utilization of these interventions.

To summarize, as of 2023, the field of neuromodulation for psychiatric disorders has made significant progress. Deep brain stimulation, transcranial magnetic stimulation, vagus nerve stimulation, and closed-loop systems have all seen advancements, offering hope for better treatment outcomes, symptom management, and improved quality of life for individuals with psychiatric conditions. As research and innovation continue, it is crucial to strike a balance between progress, safety, and ethical considerations to ensure the responsible implementation of these state-of-the-art therapies in clinical practice.

Author's contribution

1st Author: Conceptualization, literature search, manuscript writing, manuscript editing

2nd Author: Literature search, manuscript writing, manuscript editing.

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