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Neuromodulation: Tools to Investigate and Manage Neuropsychiatric Disorders

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Abstract

Neuromodulation is the technique used to maintain neuroregulation and homeostasis in the body through neural signals with electrical or magnetic modes of stimuli. The brain has the capacity to undergo neuronal plasticity, which can be positive or negative according to the surrounding environment. Neuromodulation could be either invasive or non-invasive depending on the requirements. Invasive techniques such as spinal cord stimulation, deep brain stimulation, trigeminal nerve stimulation, peripheral nerve stimulation, cervical nerve stimulation, etc., which works by surgically placing electrodes inside the neural tissue. On the other hand, non-invasive neuromodulation or brain stimulation (NIBS) which is much safer, accessible, and less side effects or limitations and involve techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial Random noise stimulation (tRNS), transcutaneous auricular vagus nerve stimulation (taVNS). These techniques are widely used for the treatment of neurological and psychological disorders with fair results observed in various clinical conditions. These NIBS techniques have the advantage of lower cost, applicability at home, and can be combined with training or rehabilitation. In this review, we will discuss neuromodulation techniques in brief, and neurological and psychiatric disorders in which these modalities can be considered as management with expert supervision, and the future direction of neuromodulation.

Keywords: Neuromodulation; Brain Stimulation; Psychological Disorders

Abbreviations: TMS: Transcranial Magnetic Stimulation; TDCS: Transcranial Direct Current Stimulation; TACS: Transcranial Alternating Current Stimulation; TRNS: Transcranial Random Noise Stimulation; TAVNS: Transcutaneous Auricular Vagus Nerve Stimulation; DBD: Deep Brain Stimulation; OSA: Obstructive Sleep Apnea; RTMS: Repetitive Transcranial Magnetic Stimulation; MDD: Major Depressive Disorder; MEPS: Motor Evoked Potential; TBS: Theta Burst Stimulation; DLPFC: Dorsolateral Prefrontal Cortex.

Neuromodulation Principles, Types and Utility

Neuromodulation is the modality of applying stimulation technology by altering the neuronal and synaptic properties with electrical or magnetic stimulation to specific neurological sites in the body. Since electrical stimulation was growing along with drug infusion as an application for the treatment of pain. These methods made it possible to develop very powerful therapeutic approaches such as Neuromodulation. The era of neuromodulation began in the early 1960s with the use of deep brain stimulation. So, Neurosurgeon C. Norman Shealy implanted the first neuro-modulatory device in 1967 called these device as 'dorsal column stimulators', but it had many complications. Then in, 1974, lesser invasive electrodes had been implanted outside the sub-arachnoid space enabling the stimulation without side effects like spinal cord compression and leakage of cerebrospinal fluid [1].

Principle of Neuromodulation

A mature human brain is capable of long-lasting changes in neural pathways due to changes in behaviors, previous experiences, physiological demands, or environmental pressures which is collectively known as Neuroplasticity. It can be synaptic (strengthening or weakening of synaptic connections in response to increase or decrease their activity) or non-synaptic involves functional modification of ion channels in the neuronal axon, dendrites and cell body results in the neuronal axon, dendrites, and cell body results in modification of intrinsic excitability of the neuron [2].

Neuromodulation, whether electrical or magnetic, starts the body's natural response by stimulating nerve cell activity through the process in which a neuron uses one or more chemicals to regulate a diverse population of neurons. Neuromodulators bind to metabotropic, G-protein coupled receptors to initiate a second messenger signaling that induces a long-lasting signal. Main neuromodulators include dopamine, serotonin, acetylcholine, histamine, norepinephrine, and nitric oxide [1].

By knowing this, neuromodulation is indicating:

- Neural system can undergo neuroplastic changes, either it can be physiologically altered outcomes or pathological outcomes.
- Many neuromodulator approaches can induce neuroplasticity by altering neural activity and can be used for the reversal of maladaptive neuroplastic changes or to facilitate adaptive neuroplasticity.
- Neuromodulation can be positive neuroplastic changes or reversal of maladaptive ones with functional improvement [2].

Types of Neuromodulation

There are two major types of neuromodulations: invasive and non-invasive brain stimulation (NIBS). Invasive neuro-modulation methods require surgical implantation of an electrode according to the specific site of pathogenesis. Typically, an invasive system consists of delivering electric current including an epidural, subdural, or parenchymal electrode via percutaneous leads, an open surgical exposure to the target (paddle or grid electrodes), or stereotactic implants for the central nervous system [1].

The invasive system works by delivery of a constant train of stimulation- 'feed-forward stimulation'. To cite an example, during epileptic seizures, the device would get activated and deliver a desynchronizing pulse to the cortical area. This type of method would likely become more prevalent as physi such as Spinal-cord stimulation- In chronic pain, this reversible, non-pharmacological therapy delivers mild electrical pulses to the spinal cord. Stimulation is in the range of 20-200 Hz range. It is used in post-laminectomy syndrome, peripheral neuropathy, peripheral vascular disease, and angina [1].

Other mode of invasive stimulation is Deep Brain Stimulation (DBS) which requires a neuro-surgical procedure for the placement of a neurostimulator, which in turn sends electrical impulses, through implanted electrodes to specific targets. To cite an example in Parkinson's disease, DBS targets the sub-thalamic areas, globus pallidus interna, and in essential tremor ventral intermedia nucleus of the thalamus. DBS is also given for dystonia, OCD, depression, and pain [3-5].

Other types of Invasive electrical methods are

- Vagus nerve stimulation- It is an invasive neurostimulation technique, in which a pulse generator is implanted below the clavicle, and lead is wrapped around the vagus nerve in the carotid sheath. It is commonly used in epilepsy, autism spectrum disorder [6,7].
- functional electrical stimulation- It is a technique that uses low-energy electricity to generate body movements artificially, for individuals who are injured or paralyzed because of having an injury in the central nervous system. Movements are grasping, walking, bladder voiding & standing. Its use is in spinal cord injury, drop foot, stroke, multiple sclerosis, and cerebral palsy [8].
- Hypoglossal nerve stimulation is an option for those who have obstructive sleep apnea (OSA). It involves an implanted medical device that stimulates the hypoglossal nerve in a rhythmic synchronized way with the patient's breathing. The hypoglossal nerve supplies the genioglossus muscle which has decreased tone in OSA and to prevent tongue retraction while sleeping, the device is implanted in the eligible patient, and programming is done by a physician. The patient has a remote and the range is adjusted by the physician according to the patient's condition. The device sends a gentle pulse with the breathing to clear the airway [9-11].
- Sacral nerve stimulation- it involves implanting a small device under the skin which delivers electrical impulses

to the sacral nerves. It works via a small incision in the lower back a thin wire is attached to the sacral nerves. It is not suitable for everyone but it is considered a safe and effective treatment for bladder and bowel control problems such as urge incontinence and fecal incontinence [12].

Another type of neuromodulation is- Non-invasive electrical stimulation: It is also known as "Non-invasive brain stimulation" or "Transcranial electrical stimulation", is a few decades old method, approved by FDA used to treat many psychiatric conditions, including treatment-resistant depression. It includes the use of external electrodes to apply a current to the body. Methods include tDCS (transcranial direct current stimulation), TENS (transcutaneous electrical nerve stimulation), and ECT. There are non-invasive magnetic methods in which no invasive procedure is required to allow a magnetic field to enter the body. Magnetic pulses can penetrate quite easily the scalp and skull compared to electrical stimuli which get lots of resistance from these tissues [2].

Two techniques are highly used to induce changes in magnetic field strength and ionic currents in the body, which is: Repetitive transcranial magnetic stimulation (rTMS), Transcranial direct current stimulation (tDCS) mostly used and other modalities are also used which are described later.

Investigative and Treatment Regimens

Neuromodulation- invasive or non-invasive, both have different applications and investigative systems in neurology and psychiatric conditions. Neuromodulation can be helpful in the diagnosis of upper motor diseases, spinal cord lesions, multiple sclerosis, and Parkinson's disease. It also helps to assess disease progression, with which prediction can be done to the response to therapy. Pre-surgically, we can be assured of targeting the areas which have to be protected during surgery. Invasive neuromodulation, such as deep brain stimulation (DBS) introduced by Benabid and colleagues in the year 1987. In Parkinson's disease, it influences abroad neural network to control the symptoms in Parkinson's disease. It shows the results in medication-resistant tremor dyskinesia impairing quality of life. It showed a better PDQ-39 (Parkinson's disease questionnaire) score than the medical therapy at 1 year follows up.

DBS on cervical dystonia showed better results after 12 months of stimulation in dystonia, especially focal dystonia. In Alzheimer's disease, DBS has shown improvement in showing cognitive decline at 6 & 12 months after stimulation. Laxton et al. conducted a phase 1 trial. DBS had been given at fornix in 6 patients with mild Alzheimer's disease. Glucose metabolism was increased in the temporal and cortical areas for 1 month and sustained till 1 year in affected areas shown in follow-up. In major depressive disorder (MDD), the sub-cingulate area is the most hyperactive. However, DBS has few studies on this. One study of 6 patients with treatment-resistant depression found a sustained remission of depression. One study in a cohort study of TRD of 20 patients who underwent DBS for 3-6 years shows a considerable improvement in social functioning and degree of involvement in work-related activity [13].

Vagus nerve stimulation, bipolar electrode around the vagus nerve. in the review of four clinical trials, (n=355) given VNS for 6-12 months, showed improvement in resistant depression sustained up to 2 years [13]. Trigeminal nerve stimulation, performed in 120 Hz frequency with pulse wave duration of 250 micro sec. & cycle of 30s. It specifically sends signals to the anterior cingulate cortex- mood, attention, communication, and emotional regulation [13].

Spinal cord stimulation, used a spinal cord stimulator which is implanted, mostly used after non-surgical pain treatment failed to provide pain relief. It consists of thin wires (the electrodes) which are placed between the spinal cord and vertebrae (the epidural space), and a pacemaker-like battery pack is placed under the skin, usually near the lower back or abdomen. Spinal cord stimulators allow patients to send electrical impulses using a remote control when they feel pain. It is used in conditions such as back pain (after surgery failed), post-surgical pain, and angina, injuries to the spinal cord, diabetic neuropathy, and pain after an amputation [14].

NIBS and Medical Disorders

Non-invasive neuromodulation or non-invasive brain stimulation (NIBS) is an advanced form of electrotherapy that is used in acute, chronic & post-operative pain. It is safe and effective and works on two principles:

- Our body has its healing capacity, so this ability to recover by stimulation on the areas of the brain for regulation of the autonomic nervous system and homeostasis could be promoted.
- It provides local effects- by stimulating skin, blood, and muscle vessels; generalized effects- effects on nervous and endocrine systems. The major goal of NIBS is to activate C- fibers maximally, so that, secretion of C-peptides neurotransmitters such as endorphins, and enkephalins should be more for analgesic effect. Most importantly, it promotes neuroplasticity. Eg. functional recovery after damage to the CNS or to prevent maladaptive neuroplastic changes in the brain. There are many types of non-invasive treatments that are given for therapeutic purposes and investigation purposes.

NIBS techniques (with their mechanism of plasticity, parameters of stimulation, and clinical applications):
Transcranial magnetic stimulation (TMS)- it is one of the useful techniques for the treatment of brain disorders and especially, and it is approved in treatment-resistant depression. TMS functions by passing a large (500-4000V) electrical current through a wire coil which can be a circular or 8-shaped coil (mostly used) to produce more focal stimulation of the two loops.

The apparatus consists of boosters, a control panel connected to a computer & stimulating coil which is made up of wire loops encased in insulated plastic & connected through a cable to one or more capacitors.

TMS works on Ampere's law- changing electric current in a wire coil induces a changing magnetic field perpendicular to the current flow in the coil. This generated magnetic field passes unimpeded through the scalp and skull and induces an electric current in the brain that flows in the opposite direction to the current in the coil (Faraday's law).

- Types of transcranial magnetic stimulation:
- Single Pulse TMS
- Paired Pulse TMS: l. Intracortical single coil
- Cortico- cortical (M1 + other region; two coils)
- Regular repetitive TMS:
  - rTMS- low-frequency(1Hz); inhibitory rTMS
  - high-frequency (>/5Hz); excitatory

- Pattern rTMS
  - Continuous theta-burst stimulation (cTBS); inhibitory
  - Intermittent theta-burst stimulation (iTBS); excitatory7

Basics of TMS

TMS is used to assess cortical excitability by different measurement methods to investigate changes associated with neurological & psychological disorders. It is having the ability to identify subtle deficits in brain inhibition & excitation [7].

The parameters which are used such as the amplitude of motor evoked potential (MEPs); resting or active motor thresholds (RMT/AMT: minimal intensity to generate small MEP of specific amplitude when the subject is at rest or active respectively), the silent periods (electromyographic activity following magnetic stimulation following magnetic generated MEP during the active contraction of the muscle of interest). Mapping of muscle representation in motor homunculus in the motor cortex. These all can be assessed by Single pulse TMS.

When the figure of an 8-shaped coil of TMS with low intensities is given on the M1 (primary cortex) area, it elicits I waves, arise from the trans-synaptic activation of cortico-spinal neurons and if given at higher intensities also evokes the D wave which represents direct stimulation of the corticospinal axon [15]. Clinical Applications of Single and Pulse TMS- In patients with PD, the resting motor threshold was found to be decreased in very rigid patients, and the Active motor threshold was increased in chronic bradykinetic patients. Also, for diagnostic purposes, TMS can be combined with fMRI which has great clinical potential to explore the network-related changes elicited by modulation of cortical excitability [7].

Repetitive TMS (rTMS)- It is described in 1993, as a treatment for drug-resistant depression. rTMS activates pyramidal neurons of layer V for the motor cortex. rTMS trigger the same set of synaptic connections multiple times.

rTMS showed that high frequency (>5Hz) increases cortical excitability, whereas low frequency (1Hz or lower). rTMS decreases cortical excitability. The physiological effects of a single effect of rTMS last around 30-60 min based on the protocol administered. These changes are likely caused by synaptic long-term potentiation or long-term depression since the effects of rTMS are blocked by the administration of drugs that interfere with N Methyl-D-aspartate (NMDA) receptors.

Clinical Applications

In depression, remission rates were higher with a longer duration of rTMS treatment & previous studies showed that at least 20-30 sessions are required. Along with the frequency of rTMS, no. of pulses is also important. In one study of tinnitus patients, those who received 6000 pulses did not improve but patients who received 12000 pulses reported a beneficial effect.

One protocol theta burst stimulation (TBS) involves magnetic pulses dispensed in bursts of three pulses at high frequency (50Hz) with an inter-burst interval of 200ms or 5Hz. High-frequency rTMS & theta- burst TMS of the left dorsolateral prefrontal cortex (DLPFC) have been approved by the United States Food & Drug Administration & Health Canada for the treatment of major resistant depression.

Other than this- rTMS can be given for neuropathic pain, post-traumatic brain injury-related headaches, schizophrenia, and obsessive-compulsive disorder.

Transcranial Direct Current Stimulation (tDCS)

It is a common NIBS method that stimulates the brain using an electrical current (1-2mA) through the electrodes placed on the scalp. Mechanism- there are two types of tDCS – Anodal tDCS (positive stimulation) increases cortical excitability likely depolarization of the resting membrane potential which increases neuronal excitability. On the other hand, Cathodal tDCS (negative stimulation) reduces cortical excitability, likely related to hyperpolarization of resting membrane potential [7].

Clinical Applications

Anodal tDCS over the DLPFC improves cognitive functions as well as emotional processes in patients with major depression. In patients with schizophrenia, auditory verbal hallucinations were reduced by tDCS relative to sham stimulation as indicated by positive and negative syndrome scales. Another study reported that 10 sessions of anodal tDCS over the cerebellar area improved symptoms for 3 months & modulated cerebellar-motor connectivity measured by cerebellar inhibition in patients with cerebellar ataxia [7].

Transcranial Alternating Current Stimulation (tACS)

The technique which delivers oscillating currents to the brain. It is a variant of tDCS, that modulates the brain oscillating and cognitive functions to serve as a therapeutic tool in restoring cortical oscillations in neurological disorders [7].

Clinical Applications

tACS over M1 may improve cortical functions as identified by the improved cognition compared with sham or no stimulation. It can modulate impaired oscillatory patterns in PD leading to reduce tremor amplitude and also in resetting pathological oscillations in schizophrenia [16-21]. In OCD, tACS is given over 3 months to the orbitofrontal cortex to personalize the intrinsic beta gamma frequency to modulate reward learning and improve OCD behavior [14].

Transcranial Random Noise Stimulation (tRNS)

tRNS is a kind of tACS only where low-intensity alternating current is administered with randomized intensity & frequency. If tRNS is given for 10 minutes over the M1 with 1mA of the full spectrum of high frequency, transcranial random noise (hf-tRNS) elevated cortical excitability for 1-1.5h. In another study, it was observed that unilateral m1- tRNS enhanced motor learning. A study investigated the efficacy of tRNS over the left DLPFC on attention & NP in patients with multiple sclerosis and reported that N2-P2 amplitudes of pain-related evoked potentials and improved pain ratings [22].

Transcutaneous Auricular Vagus Nerve Stimulation (taVNS)

The Vagus which is 10th cranial nerve having major parasympathetic components and a mixed nerve having 80% sensory afferents and 20% motor efferents. It plays a key role in several body functions including swallowing, heart rate control, speech, respiratory, and gastric secretion. The vagus nerve can be invasive or invasive. taVNS is a relatively new method of non-invasive neural stimulation that targets the cutaneous receptive field of the auricular branch of the vagus nerve at the outer ear. A single-blind, sham-controlled study that assessed online (i.e., stimulation overlapping with the critical task) effects demonstrated that taVNS led to faster response selections during multiple tasks & helped by modulating the nor-adrenergic & GABA systems [22]. A study in patients with unilateral, non-pulsatile chronic tinnitus applied taVNS over 2 weeks found that taVNS can be used to improve tinnitus [23]. In a randomized, sham-controlled pilot study in patients with major depression, taVNS was administered for 15 minutes once or twice a day, 5 days/ week for 2 weeks [24].

Side Effects of Non-Invasive Neuromodulation [7]

All NIBS techniques have their limitations, but they are rare to cause any large health related issues.

- Generally minimal and skin irritation or redness are the most common side-effects (taVNS).
- Headache and fatigue followed by light, itching & burning sensation (tDCS).
- Nausea, discomfort & twitching over the motor cortex can lead to the perception of phosphenes or flashes in the subjects' visual field (tACS).
- Syncope is another potential side-effect of rTMS especially in patients with a high degree of anxiety, dehydration, or hypoglycemia (rTMS)
- Since rTMS can trigger epileptogenic activities, TMS is contraindicated in patients with history of epilepsy and metallic implants in the head & neck regions
- TMS most affects the cortical structures, difficult to target the specific sub-cortical regions.

Future Directions

Neuromodulation is a boon in the medical diagnostics and therapeutic field which has innovative strategies for treating brain disorders. In the upcoming 5-10 years, neuromodulation integrates with artificial intelligence, automatically adjusted by brain & external sensors, and controlled through cloud-based applications. The technological innovation in neuromodulation is of more targeted, safer, less invasive, better-tolerated treatments. On depression, there are new technologies such as closed-loop feedback-responsive DBS, multi-array DBS responsive feedback systems, directional & multi-lead DBS systems, and transcranial-focused ultrasound. Magnetic resonance imaging and electro-encephalogram (EEG) phenotypes inclusion can be used as biomarkers to predict treatment responses. It could also describe the neural circuit changes associated with effective treatment. A complementary study assessing potential EEG biomarkers of rTMS response is also ongoing. An exciting area is the combination of neuromodulation treatment with other modalities to improve outcomes, short-term & long-term. The advancement in this field provides an understanding of the neural circuitry of disorders of mood, thought & behaviors. Continuous progress in the development of new methods or combinations will ensure the future of neuromodulation with neuropsychiatric illness.

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