REVIEW ARTICLE

An Overview of Noninvasive Brain Stimulation: Basic Principles and Clinical Applications

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ABSTRACT: The brain has the innate ability to undergo neuronal plasticity, which refers to changes in its structure and functions in response to continued changes in the environment. Although these concepts are well established in animal slice preparation models, their application to a large number of human subjects could only be achieved using noninvasive brain stimulation (NIBS) techniques. In this review, we discuss the mechanisms of plasticity induction using NIBS techniques including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), random noise stimulation (RNS), transcranial ultrasound stimulation (TUS), vagus nerve stimulation (VNS), and galvanic vestibular stimulation (GVS). We briefly introduce these techniques, explain the stimulation parameters and potential clinical implications. Although their mechanisms are different, all these NIBS techniques can be used to induce plasticity at the systems level, to examine the neurophysiology of brain circuits and have potential therapeutic use in psychiatric and neurological disorders. TMS is the most established technique for the treatment of brain disorders, and repetitive TMS is an approved treatment for medication-resistant depression. Although the data on the clinical utility of the other modes of stimulation are more limited, the electrical stimulation techniques (tDCS, tACS, RNS, VNS, GVS) have the advantage of lower cost, portability, applicability at home, and can readily be combined with training or rehabilitation. Further research is needed to expand the clinical utility of NIBS and test the combination of different modes of NIBS to optimize neuromodulation induced clinical benefits.

RÉSUMÉ : Aperçu de la stimulation cérébrale non effractive : principes de base et applications cliniques. Le cerveau est doté d'une plasticité neuronale innée, c'est-à-dire qu'il a la capacité de modifier sa structure ou ses fonctions en réaction aux changements continus qui se produisent dans l'environnement. Les concepts de la plasticité sont pratique courante dans les modèles de préparation de coupes de tissu animal, mais leur application à un grand nombre de sujets humains ne pourrait se réaliser qu'à l'aide de techniques de stimulation cérébrale non effractive (SCNE). Le présent article de synthèse portera ainsi sur les mécanismes d'induction de la plasticité par des techniques de SCNE, notamment la stimulation magnétique transcrânienne (SMT), la stimulation transcrânienne à courant continu (STCC), la stimulation transcrânienne à courant alternatif (STCA), la stimulation par bruit aléatoire (SBA), la stimulation transcrânienne par ultrasons (STU), la stimulation du nerf vague (SNV) et la stimulation vestibulaire galvanique (SVG). Après une brève introduction suivront des explications sur les paramètres de stimulation de ces techniques et leur potentiel d'application clinique. Bien que leurs mécanismes d'action soient différents, ces techniques de SCNE peuvent toutes induire une forme de plasticité au niveau des systèmes et permettre l'étude de la neurophysiologie des circuits dans le cerveau, en plus d'offrir un potentiel thérapeutique en psychiatrie et en neurologie. La SMT est la technique la plus utilisée dans le traitement des troubles cérébraux, et la SMT répétitive est une intervention approuvée dans le traitement de la dépression résistante aux médicaments. Il existe peu de données sur l'utilité clinique des autres modes de stimulation, mais les techniques de stimulation électrique (STCC, STCA, SBA, SNV, SVG) présentent différents avantages, dont un faible coût, la portabilité, l'applicabilité à domicile et la facilité d'utilisation associée à de la formation ou de la réadaptation. Aussi faudrait-il poursuivre la recherche pour élargir le champ d'application clinique de la SCNE et examiner différentes associations de mode de SCNE en vue de l'optimisation des bienfaits cliniques de la neuromodulation.

Keywords: Noninvasive brain stimulation (NIBS), Metaplasticity, Plasticity, Transcranial direct current stimulation (tDCS), Transcranial alternating current stimulation (tACS), Transcranial magnetic stimulation (TMS), Random noise stimulation (RNS), Transcranial ultrasound stimulation (TUS), Vagus nerve stimulation (VNS), Galvanic vestibular stimulation (GVS)

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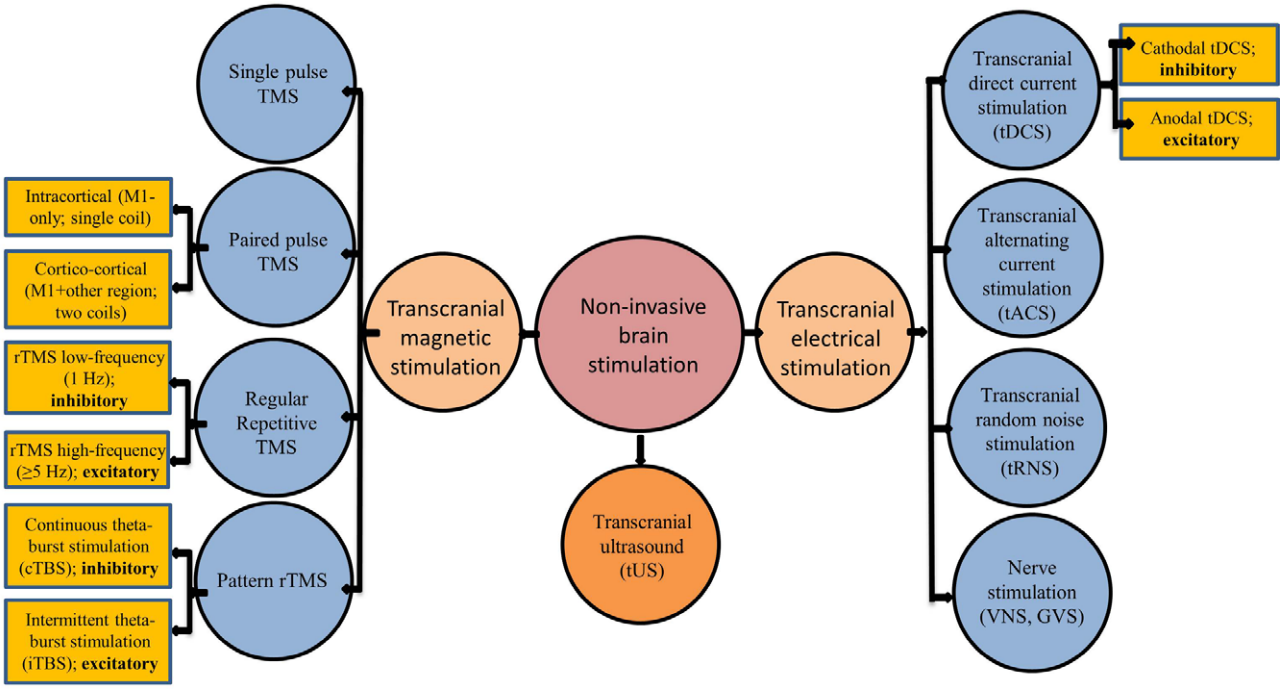

Figure 1: *Different modes of noninvasive brain stimulation: GVS: Galvanic vestibular stimulation; tACS: transcranial alternating current stimulation; TBS: theta-burst stimulation; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; tRNS: transcranial random noise stimulation, TUS: transcranial ultrasound stimulation; VNS: vagal nerve stimulation.*

Introduction

Brain stimulation has become an exciting development in neurosciences to understand the concepts of plasticity and to treat various brain disorders. Brain stimulation can be broadly classified as invasive (e.g., deep brain stimulation [DBS]) and noninvasive brain stimulation (NIBS) techniques. Although DBS plays a significant role in the treatment of several neurological and psychiatric disorders, it requires surgery and cannot be used in healthy subjects to understand brain physiology. Hence, in this narrative review, we discuss several NIBS techniques and their potential role in inducing as well as measuring brain plasticity. NIBS can broadly be classified as electrical, magnetic, or sonographic[1] modes of stimulation. A representation of various modes of stimulation under these three subtypes is as depicted in Figure 1 and summarized in Table 1.

Transcranial Magnetic Stimulation (TMS)

Basics of TMS

TMS is a noninvasive neurophysiological technique of stimulating the brain through the intact skull.[2] It has been widely used to access changes in cortical excitability associated with neurological and psychiatric disorders due to its ability to identify subtle deficits in brain inhibition and excitation.[3]

TMS and Cortical Excitability

Single-pulse TMS can assess cortical excitability using parameters such as the amplitude of motor evoked potentials (MEPs), resting or active motor thresholds (RMT/AMT: minimal intensity to generate small MEP of specific amplitude when the target muscle is at rest or active, respectively), the silent periods (silence in the electromyography activity following magnetic stimulation generated MEP during the active contraction of the muscle of interest), recruitment curves (input–output curve, greater cortical activation with increasing stimulation intensity), and mapping of muscle representation in motor homunculus in the motor cortex (Figure 2). Using paired-pulse TMS, several inhibitory and facilitatory intracortical circuits such as short-interval cortical inhibitions (SICIs) and intracortical facilitations (ICFs) can be measured.[4,5]

Mechanistic Basis of TMS

A TMS device consists of a series of capacitors connected to a wire coil which has inductance as well as resistance. When a rapidly changing electrical current passes through a wire coil placed on the scalp, a changing magnetic field is generated which penetrates the cranium. This generates eddy currents which lead to action potentials in the neurons in the brain.[6,7] The commonly used figure-of-eight coil is usually composed of two wires coiled side by side on the same plane passing currents in opposite directions. The figure-of-eight coil has better focality than other coils such as the circular coil because the point of maximum stimulation is at the junction of the two loops.[8] TMS administered over the motor cortex elicits a series of waves over corticospinal axons that can be recorded over the spinal cord, with the direct (D) wave followed by a series of indirect (I) waves. TMS at low intensities preferentially activates I waves which arises from the transsynaptic activation of corticospinal neurons and at higher intensities also evoke the D wave which represents direct stimulation of the corticospinal axon.[9]

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Table 1: Key features of different modes of NIBS

Type of NIBS	Major features	Type of stimulation	Possible utility or clinical indications
TMS	Noninvasive magnetic stimulation	Magnetic	TMS has the largest number of studies for clinical applications. It is the only NIBS with approved clinical indication (treatment-resistant depression) and recommendation for clinical use
tDCS	Noninvasive and direct current	Electrical	tDCS is potentially a valuable tool to treat neuropsychiatric disorders such as depression and anxiety
tACS	Noninvasive and alternating current	Electrical	Can modulate altered oscillatory patterns such as in Parkinson's disease (PD) leading to reduced tremor amplitude
tRNS	Noise based on stochastic resonance	Electrical	This stimulation can temporarily increase cortical excitability and can lead to increased perception or improved cognition. Low frequency-tRNS may reduce tinnitus loudness and tRNS may improve neuropathic pain.
taVNS	Noninvasive and auricular	Electrical	As alternative to the invasive VNS procedure. taVNS applied to patients with drug-resistant epilepsy may decrease seizure frequency
TUS	Transcranial ultrasound	Ultrasound	Modulate the human cortical and subcortical functions with high degree of spatial specificity
GVS	Galvanic vestibular stimulation	Electrical	GVS has been found to improve stability during balance tasks in healthy individuals and may have application in PD and related disorders

GVS: galvanic vestibular stimulation; NIBS: noninvasive brain stimulation; TMS: transcranial magnetic stimulation; tACS: transcranial alternating current stimulation; tRNS: transcranial random noise stimulation; tDCS: transcranial direct current stimulation; taVNS: transcutaneous auricular vagal nerve stimulation.

Clinical Applications of Single and Paired TMS

TMS has been very helpful in diagnosing spinal cord compressions in patients with myelopathy. Central motor conduction time of the upper and lower limb correlated with the severity of cord compression with TMS having 100% sensitivity and 84.8% specificity.[10] Patients with cerebellar impairment have increased RMT of the contralateral motor cortex.[11] In patients with Parkinson's disease (PD), RMT was found to be decreased in very rigid patients and AMT was increased in chronic bradykinetic patients.[12,13] MT is reduced in patients with tics and obsessive compulsive disorder.[14] One study showed that SICI was reduced in PD patients and levodopa partly normalized this impaired inhibition.[15,16] Interestingly, a study showed that short-interval ICF, which is caused by summation of activation of different facilitatory interneurons in the M1, is increased in PD patients.[17] Studies have demonstrated that patients with upper limb dystonia,[18] cervical dystonia,[19] and blepharospasm have reduced SICI.[20] Also, TMS can be combined with a wide range of brain mapping modalities such as magnetic resonance imaging (MRI) or magnetic resonance spectroscopy and has great scientific and clinical potential.[21–24]

Limitations of TMS

The extent of the induced current in the brain can be variable. It is not known which type of neurons are stimulated by TMS and whether the effects of TMS on the neurons are excitatory, inhibitory, or state dependent.[25] Another limitation is that the TMS most affects the cortical structures. It is difficult to specifically target subcortical regions, and TMS pulse cannot stimulate subcortical areas without affecting cortical ones.[26,27]

Summary of Single and Paired TMS

An important feature of magnetic stimulation that differentiates it from electrical stimulation is that the current induced flows parallel to the surface of coil in the brain. Different TMS techniques and parameters have demonstrated potential diagnostic utility with promising results. However, further studies with large sample sizes are needed to establish the sensitivity and specificity of the techniques in each condition.

Repetitive TMS (rTMS)

Basics of rTMS

The use of rTMS as a treatment was first described in 1993 as a treatment for drug-resistant major depression.[28] Since TMS indirectly activates pyramidal neurons of layer V of the motor cortex (M1) through interneurons in layers II and III, it is believed that rTMS triggers the same set of synaptic connections multiple times.

rTMS and Cortical Excitability

rTMS over the motor cortex leads to lasting changes in MEP amplitudes that persist post stimulation. Previous studies showed that high-frequency (>5 Hz) rTMS increases cortical excitability, whereas low frequency (1 Hz or lower) rTMS decreases cortical excitability.[29,30] These changes are likely caused by synaptic long-term potentiation and depression (LTP/LTD) since effects of rTMS are blocked by administration of drugs that interfere with N-methyl-D-aspartate (NMDA) receptors, which are known to be involved in LTP/LTD processes.[31,32] The physiological effects of a single session of rTMS lasts around 30–60 min based on the protocol administered.[32] Repeated rTMS administration leads to cumulative effects, depending on the number of sessions.[33,34]

Clinical Applications

For the treatment of psychiatric disorders such as depression, the remission rates were higher with longer duration of rTMS treatment (daily up to 6 weeks), and previous studies indicate that at least 20 to 30 sessions are needed to have

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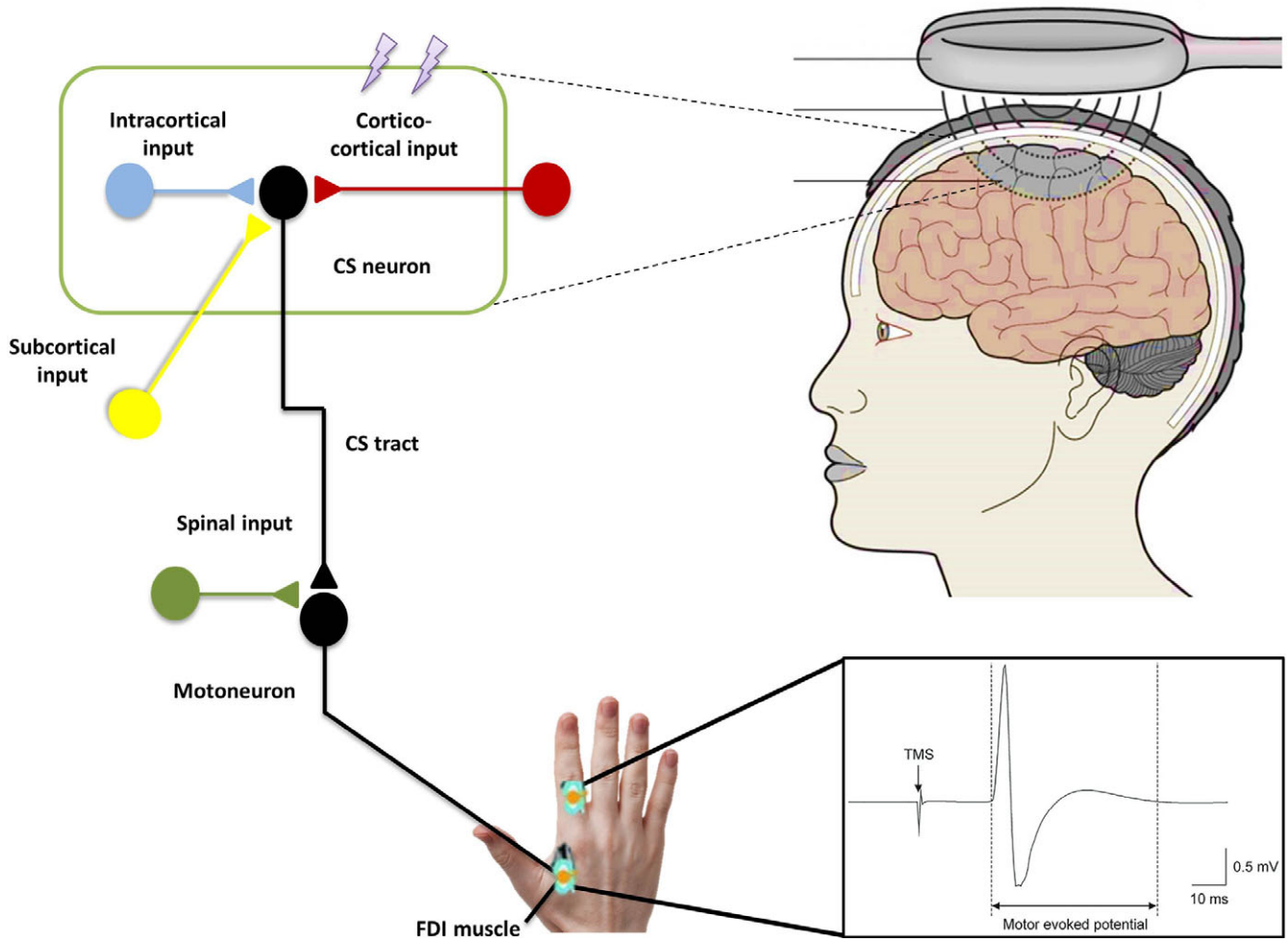

Figure 2: *Schematic representation of the transcranial magnetic stimulation demonstrating the magnetic field generated with the magnetic coil placed over the hand area of the primary motor cortex. This, in turn, induces electrical current to activate cortical circuits (lightning bolts indicating the electromagnetic pulses) leading to activation of corticospinal neurons and subsequently and alpha motor neurons in the spinal cord that innervate the muscle of interest (first dorsal interosseous muscle). This leads to motor evoked potential recorded with surface electromyography.*

optimal effects.[35,36] rTMS also induced changes in the functional and structural connectivity of the associated networks.[37] In addition to the frequency of rTMS, the number of pulses is also important. In a study in patients with tinnitus, patients who received 6000 pulses did not improve but patients who received 12,000 pulses reported a beneficial effect on tinnitus.[38] Theta-burst stimulation (TBS) protocol involves magnetic pulses dispensed in bursts of three pulse at high frequency (50 Hz) with an interburst interval of 200 ms or 5 Hz (i.e., at the theta frequency).[39] A meta-analysis suggested TBS may be an effective treatment for depression.[40] A non-inferiority study showed similar efficacy of intermittent TBS (iTBS) and 10 Hz rTMS in the treatment of depression, but TBS has the advantage that it can be administered in a much shorter time.[41] Both high-frequency rTMS and the theta-burst TMS of the left dorsolateral prefrontal cortex (DLPFC) have been approved by the United States Federal Drug Administration and Health Canada for treatment of medication-resistant depression.[41,42] The therapeutic use of rTMS is usually as add-on treatment, especially for refractory symptoms. A consensus panel reported that TMS can be recommended for treatment of major depressive disorder, neuropathic pain (NP), post-traumatic brain injury-related headaches, postoperative pain, and migraine.[42,43] However, many conditions such as NP, motor symptoms of PD, stroke, and its complications: dysphagia, aphasia, hemispatial neglect, multiple sclerosis, tinnitus, schizophrenia, obsessive-compulsive disorder showed promising therapeutic evidence as shown by Class II and III studies or level B recommendation.[41]

Adverse Effects of rTMS

Although very rare, TMS can induce seizures under ordinary clinical use in 1 out of 30,000 treatments.[44] According to the safety guidelines of Rossi et al. (2021), stimulation parameters within the safety guidelines usually have minimal side effects.[24] An interesting observation that even the highest intensity (within the technical limitations of the machine) of TBS could not induce seizures in a series of eight patients in an epilepsy monitoring unit.[45] Syncope is another potential side-effects of rTMS especially in patients with high degree of anxiety, dehydration, or hypoglycemia.[46]

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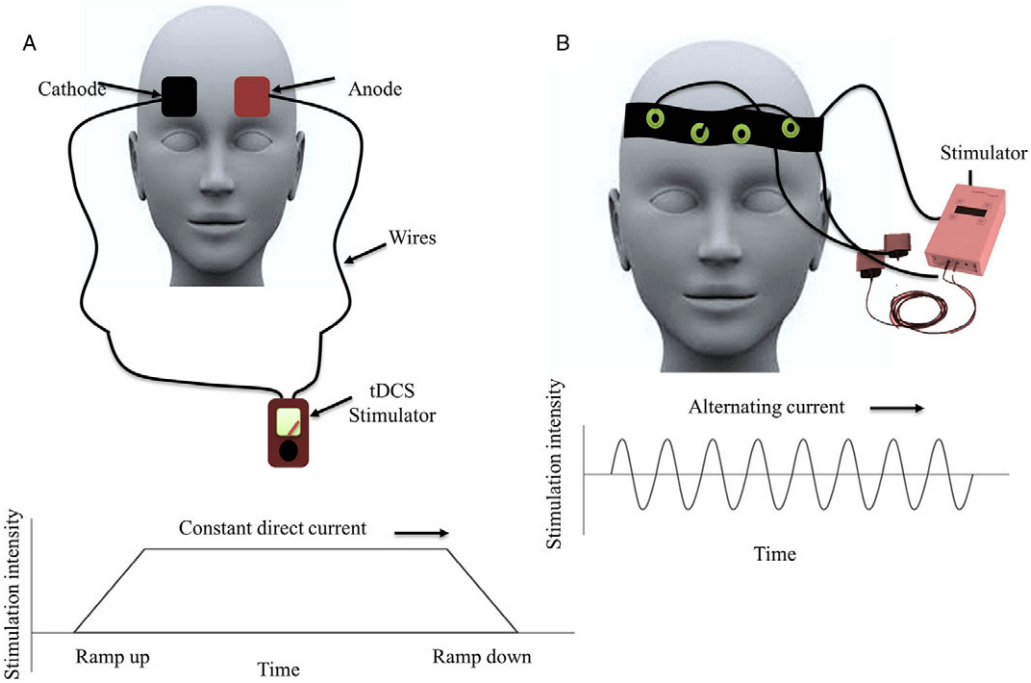

Figure 3: *Schematic representation of the transcranial direct (tDCS) and alternating (tACS) current stimulation: (A) tDCS: transcranial direct current stimulation showing anodal and cathodal electrodes placed over bifrontal regions and the graph below plots stimulation intensity overtime demonstrating that the intensity ramps up and down, and the intensity provided over the stipulated time. (B) tACS: transcranial alternating current stimulation showing headband containing electrodes and the graph below shows that the stimulation intensities vary in a sinusoidal manner overtime with the alternating polarity of current applied.*

Summary of rTMS

rTMS is a safe, noninvasive NIBS therapy which is being increasingly incorporated into clinical practice. Additional research to test the therapeutic application of rTMS in neurological and psychiatric disorders is warranted.

Transcranial Direct Current Stimulation (tDCS)

Basics of tDCS

tDCS is a commonly used NIBS technique that stimulates the brain using electric current (typically 1–2 mA) through the electrodes placed on the scalp (as anode and cathode; Figure 3A).

Changes in Brain Excitability with tDCS

Studies have demonstrated that anodal tDCS (positive stimulation) increases cortical excitability likely due to depolarization of the resting membrane potential that increases neuronal excitability, leading to increased spontaneous neuronal firing. On the other hand, cathodal tDCS (negative stimulation) reduces cortical excitability, likely related to hyperpolarization of the resting membrane potential.[47,48] The efficacy of these changes depends on the duration of stimulation.[49] Animal studies in the 1960s had demonstrated that a few minutes of direct current (DC) stimulation of the sensorimotor cortex caused a prolonged change in neuronal activities for 1–5 h.[50] Glutamatergic synapses are involved in DC induced plasticity, especially with the involvement of NMDA receptors. Pharmacological studies in humans have revealed that blockade of NMDA receptors with dextromethorphan prevents anodal and cathodal tDCS induced plasticity.[51] Moreover, NMDA receptor agonist D-Cycloserine led to an increase in anodal tDCS induced excitability.[52]

Mechanistic Basis of tDCS

The influx of calcium ions (Ca^{2+}) into the cell due to the activation of NMDA receptors is needed for the generation of LTP and LTD as demonstrated in animal slice preparation studies using patch-clamping techniques. Several neurotransmitters are involved in the induction of LTP and LTD. With a rapid rise in postsynaptic Ca^{2+} concentration, Ca^{2+} binds to the C-terminal of calmodulin which activates the kinase pathways, resulting in an increase of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor density on the postsynaptic membrane leading to LTP. On the other hand, with a slower increase in postsynaptic Ca^{2+} concentration, Ca^{2+} binds to the N-terminal of calmodulin activating the phosphatase pathways, resulting in a decrease of AMPA receptor density on the postsynaptic membrane, leading to LTD (Figure 4).[24,53]

Duration and strength of stimulation were too long (≥25 min) or too strong (≥2 mA) can change the direction of the tDCS effects.[53–56] These changes are presumed to occur because of calcium ion changes in the postsynaptic cells due to changes in membrane polarity. However, other neurotransmitters and neuromodulators are also involved such as acetylcholine, dopamine, and serotonin, and they may play important roles.[57,58]

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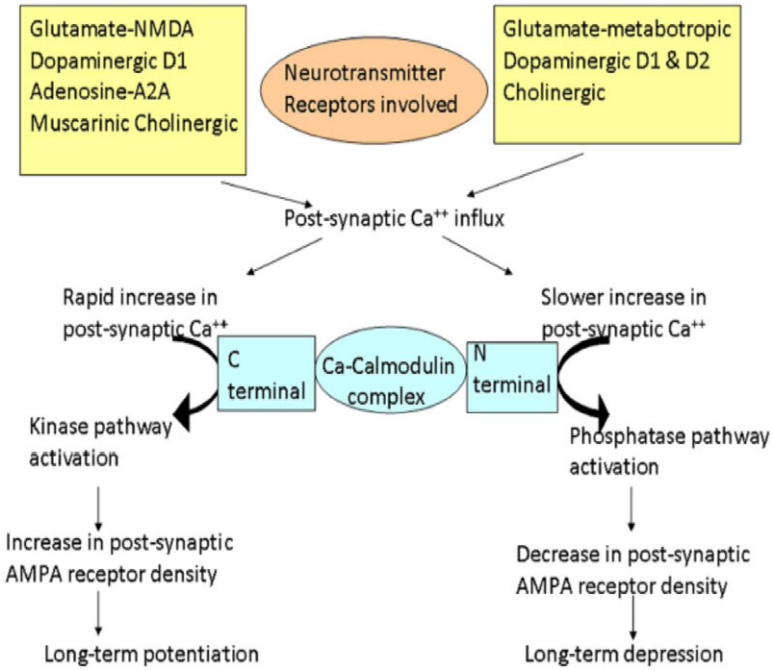

Figure 4: Schematic representation of the cascades of events involved in long-term potentiation (LTP) and depression (LTD). Different neurotransmitters are involved in these cascades. Different neurotransmitter and their receptors are shown in yellow rectangular boxes. Glutamate acting through N-methyl D-Aspartate, dopamine through D1, adenosine through A2A, and acetylcholine through muscarinic receptors leads to LTP. On the other hand, glutamate acting through metabotropic receptors, dopamine through both D1 and D2 receptors, and cholinergic activation lead to LTD. Different changes occur depending on the rate of increase of postsynaptic calcium (Ca^{2+}). The rapid influx of Ca^{2+} preferentially promotes binding of Ca^{2+} to the C-terminal of calmodulin, activating the kinase pathways. These reactions lead to an increase in AMPA receptor density on the postsynaptic membrane resulting in LTP. On the other hand, slower release of Ca^{2+} leads to Ca^{2+} binding to the N-terminal of calmodulin, activating the phosphatase pathways. This leads to a decrease in AMPA receptor density on the postsynaptic membrane, resulting in LTD. (Adapted from Udupa K and Chen R, Motor Cortical Plasticity in Parkinson's Disease, Front. Neurol. 4 [2013].)

For example, dopamine blockers prevent plasticity induction by tDCS.[59,60] Therefore, these neurotransmitters affect plasticity induction.[58] In summary, tDCS induces calcium-dependent plasticity at glutamatergic synapses, which is gated by the reduction of gamma-aminobutyric acid (GABA) activity.[57,58]

Clinical Applications

Studies have reported that anodal tDCS over the DLPFC improves cognitive functions as well as emotional processes in patients with major depression.[61] In patients with bipolar or unipolar depression, five tDCS sessions of 20 min each with anodal stimulation over the left DLPFC led to a reduction in depressive symptoms after the fifth session.[62] In patients with schizophrenia refractory to antipsychotic drugs, auditory verbal hallucinations were reduced by tDCS relative to sham stimulation as indicated by the Positive and Negative Syndrome Scale.[63]

Apart from improving psychiatric symptoms, tDCS administered bilaterally over the cerebellar cortex to treat neurodegenerative ataxic symptoms has shown significant improvement based on the Scale for the Assessment and Rating of Ataxia, the International Cooperative Ataxia Rating Scale, the 9-Hole Peg Test, and the 8-Meter Walking Time. These results suggested that a single session of anodal tDCS over the cerebellar cortex may enhance motor performance, and improve motor and upper limb coordination in patients with neurodegenerative ataxia.[64] Another study reported that 10 sessions of anodal tDCS over the cerebellar area improved symptoms for 3 months and modulated cerebello-motor connectivity measured by cerebellar inhibition in patients with cerebellar ataxia.[65]

Previous studies demonstrated that the benefits of tDCS may require multiple sessions. In a study in patients with fibromyalgia,[66] a home-based tDCS device that permits daily use for 20 min with a minimal interval of 12 h between session was used and suggested that a portable device for home use is feasible with proper monitoring of adherence and contact impedance.[66] Studies have also investigated the accessibility of tDCS on patients with PD using a remotely supervised tDCS protocol paired with cognitive training to reduce clinician, patient, and caregiver burden. It was found that remotely supervised tDCS was safe, tolerable with minimal side effects such as mild sensations of transient itching, and patients with PD reported improvement of fatigue as well as increased cognitive performance.[67]

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Side Effects and Limitations of tDCS

A study summarized the adverse effects of tDCS sessions over motor and non-motor cortical areas in healthy subjects, neurological, and psychiatric patients. The results demonstrated that during an around 18,000 sessions of tDCS administration, no serious adverse events have been reported. Moderate adverse events were rare; however, skin burns due to suboptimal electrode-skin contact have been reported. Rarely cases such as mania or, hypomania were induced in patients with depression. Fatigue and headache were also reported followed by light itching and burning sensation under the stimulation electrodes.[68] Skin redness has also been reported.[69,70] The low spatial resolution and difficulty in precisely localizing the electric field current in the brain are some of the limitations of tDCS. It is to be noted that the inability to target deeper structures except superficial cortex is a limitation for most NIBS techniques except for transcranial ultrasound stimulation (TUS).

Summary of tDCS

tDCS is an NIBS technique which has been applied in psychiatric and neurological disorders with some promising results. While there are a large number of tDCS studies, the mechanisms and neural correlates underlying tDCS are not fully understood. The behavioral and neural effects of different montages of tDCS should be systematically tested.

Transcranial Alternating Current Stimulation (tACS)

Basics of tACS

tACS is an NIBS technique which delivers oscillating electrical currents to the brain.[71–73] tACS is a variant of tDCS, was designed to modulate the brain oscillations and the cognitive functions, and to serve as a therapeutic tool in restoring dysfunctional cortical oscillations in neurological disorders.[74–78] tACS involves the application of sinusoidal current between two electrodes where current and polarity alternates according to the sine wave pattern.[71,79] tACS can be applied in any frequency. Previous studies have used a range from DC to 5 kHz for induction of sustained changes in cortical excitability[80] and 200 kHz for tumour therapy[81] (Figure 3B).

Entrainment

The main effect of tACS is to modulate and entrain ongoing rhythmic brain activities.[82] Studies in nonhuman primates have demonstrated that tACS affect the timing of neuron spiking activity in the region targeted.[83] A study performed in young and older adults stimulated at the individual alpha frequency for 10 min (1.5 mA) over the left motor cortex to understand the relationship between effects of tACS and electroencephalography (EEG) alpha power, which decreases with ageing. Although tACS increased motor cortical excitability (increased MEP amplitude) in both groups, short-interval intracortical inhibition (SICI, a measure of GABA-A receptor-mediated inhibitory circuit) decreased in young subjects but increased with older subjects. Since the increase in cortical excitability was similar in both groups, there is no indication that tACS was more effective in the elderly population i.e., the group with lower alpha power.[84] Another study applied tACS at the alpha frequency (8–12 Hz) for 11–15 min in four sessions with intermittent or sham tACS to investigate as to what extent plasticity can account for tACS aftereffects when controlling for entrainment "echoes" (an entrained activity that remains stable after the end of rhythmic stimulation). The study used successive tACS events which were either phase continuous or phase discontinuous for short (3 s) or long (8 s) duration. The study suggested that α-tACS can be used as a therapeutic tool with induction of short term neural plasticity rather than entrained activity.[85] Previous studies have demonstrated that tACS applied at an alpha frequency range resulted in enhancement of EEG amplitude for 10–30 min after stimulation. These studies indicate that tACS modulates spontaneous cortical oscillatory activity.[86,87] Furthermore, synaptic modifications from exposure to the alternating electrical field might alter neurochemical mechanisms such as calcium entry in the presynaptic terminals that can lead to short-term synaptic plasticity.[88]

tACS and Behavioural Changes

tACS over the M1 may improve cortical functions as identified by the improved cognition compared with sham or no stimulation.[89] tACS has been used to modulate the M1 when applied within the beta (13–30 Hz) or the high-gamma (60–90 Hz) frequency ranges during a visuomotor task and concurrent functional MRI. The results showed that tACS not only changed neural activities underneath the stimulation electrode but also led to compensatory modulation within connected and functionally related brain networks.[90,91] Furthermore, tACS improves motor performance which correlated with increased synchronization of the gamma frequency band in M1.[91,92] A study co-stimulated the M1 in healthy subjects with tACS during iTBS which is known to induce LTP-like plasticity to determine whether gamma tACS on iTBS-induced plasticity are related to changes in GABA-A receptor-mediated interneuronal activity.[73] Gamma frequency tACS but not beta frequency tACS increased as well as prolonged iTBS-induced LTP-like plasticity in the human M1, indicating a link between gamma oscillations, interneuronal GABA-A-ergic activity, and LTP-like plasticity in the human M1.[73] A study examined the aftereffects of tACS (10 and 20 Hz) of the parietal cortex on bimanual coordination. The participants received 10 and 20 Hz tACS, or sham stimulation of 1 mA at the parietal brain areas (P3/P4 positions) for 20 min. No specific effect of tACS on the bimanual coordination task was observed. However, there was a rise in the parietal alpha activity following the 20 Hz tACS in the right parietal area which was accompanied by decreased oxygenated haemoglobin (Hb) concentration in the right motor cortex as measured by functional near-infrared spectroscopy. Thus, tACS affects cortical physiology.[93] The behavioral effects of tACS have been reported in many studies. tACS has been found to modulate auditory perception as thresholds of detection were dependent on the phase of the oscillation that was entrained by α-tDCS, establishing a correlation between stimulation phase and modulation of perception.[94] tACS applied at 0.75 Hz frequency to subjects during early nocturnal non-rapid-eye-movement sleep enhanced EEG delta activity resulting in the improved recall of memory the next morning.[95] Another study found that left parietal tACS at theta frequency improved performance on working memory of an attention task along with decrement in

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P300 latency in the left hemisphere.[96] Multiple studies on tACS suggested that cross-frequency phase-amplitude coupling of theta and gamma oscillations play a role in neuronal computation, communication, and learning.[97,98]

Clinical Applications

tACS can modulate impaired oscillatory patterns such as in PD leading to reduced tremor amplitude[99] and attenuation or resetting pathological oscillations in schizophrenia.[78] Patients with PD have been found to have reduced γ oscillatory activity in the basal ganglia-thalamo-cortical network,[100,101] and plasticity induced by iTBS is reduced in these patients.[102] A recent study showed that iTBS induced plasticity in PD patients was normalized when iTBS was applied during tACS at γ frequency.[103] Furthermore, tACS administered over 3 months to the orbitofrontal cortex personalized to the intrinsic beta gamma frequency in patients with obsessive compulsive disorder modulated reward learning and improved obsessive compulsive behavior.[104] A study used 200-kHz tACS in patients with recurrent glioblastoma suggested that this type of stimulation may inhibit the growth of this treatment-resistant tumor, with little or no side effects.[81] Another study applied tACS of the cerebellum phase locked to the tremor in patients with essential tremor and showed that tremor suppression was due to disruption of temporal coherence of the aberrant oscillations in the olivocerebellar loop.[105]

Side Effects of tACS

The most common side effects in tACS studies are nausea, discomfort, and twitching. tACS administered over the motor cortex can lead to perception of phosphenes or flashes in the subjects' visual field.[71] Phosphene perception peaks at stimulation frequencies between 10–20 Hz.[106] Posterior montages with frequency of 4 Hz have caused dizziness due to stimulation of the vestibular nerve.[107]

Summary of tACS

tACS acts by modulating ongoing brain rhythms and altering neuronal properties and networks. While tACS is the only method of modulating the individual alpha frequency, larger studies to validate results are required due to variability in the response to tACS protocols. Despite advances in the field of neuromodulation, further studies are need to unravel the effects of tACS at multiple levels from molecular to animal neurophysiology and to clinical applications. It is also important to explore the utility of this technique in understanding the aberrations in neuronal networks in neurological and psychiatric disorders and to use this technique effectively to bring about optimal clinical benefits.

Transcranial Random Noise Stimulation (tRNS)

Basics of tRNS

tRNS is a unique kind of tACS where low-intensity alternating current is administered with randomized intensity and frequency.[79] tRNS has so far been explored within the frequency spectrum of 0.1–640 Hz (full spectrum) or 101–640 Hz (high-frequency stimulation) with a "white noise" characteristic.[108,109] The probability function of the RNS is a Gaussian curve with zero mean and a variance. In most studies, the current intensity used to stimulate is around 1 mA.[79] The physiological mechanisms of tRNS remain unclear. Higher frequencies of tRNS are supposed to modulate brain activity. However, due to the neuronal membrane acting as a low pass filter, a very small amount of current reaches the neuron with high frequencies tRNS. For example, AC electric fields at 1 V/m (max) in the brain at 100 Hz can polarize neurons by only 50 μV.[110] However, this small change in many connected neurons can provide amplification of stimulation leading to physiological effects.[111,112] The effect of tRNS could be contingent on other mechanisms such as stochastic resonance.[113] Stochastic resonance is a ubiquitous and conspicuous phenomenon—where a weak signal is amplified by adding noise to exceed its threshold of stimulation.[114] tRNS might increase neural firing by amplifying subthreshold oscillatory activity, also leading to decrement in the endogenous noise. This improved signal to noise ratio in the brain could lead to increased perception or cognition.[114–116]

tRNS and Cortical Excitability Changes

tRNS administered over the primary motor cortex (M1) for 10 min with 1 mA application of full-spectrum or high-frequency transcranial random noise (hf-tRNS) elevated cortical excitability for 1–1.5 h.[108] Five to six minutes of stimulation also showed significant facilitation but with shorter duration of plasticity post stimulation.[117] In another study, it was observed that unilateral M1-tRNS enhanced motor learning.[118] tRNS at low intensity of 0.4 mA had greater inhibitory aftereffects compared with cathodal tDCS at 1 mA or 140-Hz tACS at 0.4 mA, which suggests that inhibitory neurons might have lower thresholds for tRNS.[119] In healthy subjects, it was noted that tRNS had an immediate effect of increased MEP amplitude with a duration of 40 min post stimulation, whereas anodal tDCS induced a gradual increase until 60 min following stimulation.[120] tRNS applied over the lateral occipital cortex was found to facilitate facial identity perception.[121] hf-tRNS over the auditory cortex either unilaterally or bilaterally during a verbal dichotic listening task led to a significant increase in right ear advantage during bilateral hf-tRNS compared with sham stimulation.[122]

Clinical Applications

A study reported that tRNS over the temporoparietal cortex in patients with nonpulsatile tinnitus reduces tinnitus loudness when low frequency-tRNS (0.1–100 Hz) or hf-tRNS (100–640 Hz) were applied.[123] A study investigated the efficacy of tRNS over the left DLPFC on attention and NP in patients with multiple sclerosis and reported that tRNS decreased the N2–P2 amplitudes of pain-related evoked potentials and improved pain ratings.[124] However, there were no improvements in attention and mood scales.

Side Effects of tRNS

Although tRNS is a safe technique, burns on the skin where the electrode was applied have been reported. tRNS can cause headache in subjects.[68]

Summary of tRNS

tRNS is a painless, noninvasive, as well as reversible neuromodulation that can temporarily enhance the excitability of the

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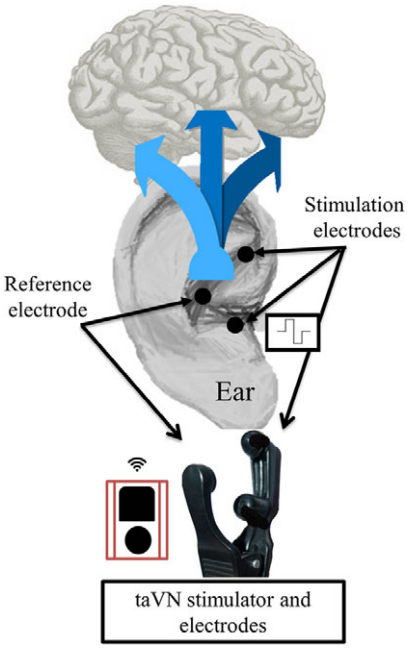

Figure 5: *Illustration of transcutaneous auricular vagal nerve stimulation showing the locations of the stimulating electrodes over the auricle which send impulses to the brainstem, frontal, parietal, and other subcortical regions through the auricular branch of the vagus and its neuronal connections. The stimulation current figure indicates the stimulation parameters, and the bottom figure shows a portable stimulator which generates the impulses with specific stimulation parameters with a wireless design.*

cortex. The high-frequency tRNS can increase cortical excitability.[125] However, the side effects are generally mild and temporary.[126] Also, multiple sessions are required to produce clinical benefit. Larger sample size studies with standardized protocols are required to validate the results of earlier studies.

Transcutaneous Auricular Vagus Nerve Stimulation (taVNS)

Basics of taVNS

The vagus nerve (10th cranial nerve) is a mixed parasympathetic nerve which is an important component of the autonomic nervous system. It plays a key role in several body functions including swallowing, heart rate control, speech, respiratory control, gastric secretion, as well as intestinal motility.[127] The vagus nerve can be stimulated in two different ways: by a direct invasive stimulation (most frequent application) or by an indirect transcutaneous noninvasive stimulation (Figure 5). Vagus nerve stimulation (VNS) is a common invasive neuromodulation approach with a pulse generator implanted below the clavicle, and the lead is wrapped around the vagus nerve in the carotid sheath.[128] VNS therapy reduces seizure frequency and improves the quality of life in patients with epilepsy.[129] Previous studies have applied VNS therapy in patients with partial seizures. A study found that high-frequency VNS led to least 50% reduction in seizure frequency and low-frequency VNS also led to a 50% reduction in seizure frequency after 14 weeks.[130] Another study found that high-frequency VNS resulted in an average reduction of 28% in total seizure frequency compared with a 15% reduction in the low-frequency stimulation group.[131] Invasive VNS is a safe and efficacious therapeutic technique and newer VNS systems have the advantage of minimizing VNS related adverse events such as infection and vocal cord paresis.[130,132]

The outer ear of a human is supplied by three sensory nerves: the auriculo-temporal nerve, the great auricular nerve, and the auricular branch of the vagus nerve (ABVN) (Figure 2).[133] taVNS is a relatively new method of noninvasive neural stimulation which targets the cutaneous receptive field of the ABVN at the outer ear.[134] It has been introduced as an alternative to the invasive VNS procedure.[135] taVNS is given at 10–25 Hz with a pulse width of 250–500 μs. The amplitude of stimulation varies from 0.25 to 10 mA depending on the experimental protocol, and some groups investigated different intensities as a function of individual perceptual threshold.[136–138] taVNS has been reported to increase heart rate variability (HRV), suggestive of a shift in cardiac autonomic function toward parasympathetic predominance. Thus, taVNS can influence human autonomic balance and provides an alternative to invasive VNS.[139]

taVNS and Behavioural Changes

taVNS was used to test the causal relationship between VNS and the flow (pleasant psychological state of mind that individuals tend to experience when completely absorbed into specific action) measured using the Flow Short Scale. It was found that active compared with sham taVNS decreased the flow (as indexed by absorption scale scores), suggesting that the vagus nerve and the noradrenergic system are causally involved in-flow.[137] To complete a complex task, different responses need to be prioritized and organized into different actions. 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 and helped in cascading different actions, and vagal stimulation might have improved performance in action cascading by modulating the noradrenergic and GABA systems.[140] taVNS has also been found to increase the efficiency of action cascading measured by a stop-change paradigm.[140] An interesting study investigated whether taVNS can reduce negative thought intrusions in high worriers. Participants exposed to taVNS reported less negative thought intrusions.[141] To examine whether taVNS affects autonomic modulation and spontaneous cardiac baroreflex sensitivity (cBRS), a study showed decreased resting HRV and increased cBRS, indicating modulation of autonomic functions by taVNS.[142] A recent study found that participants who received taVNS tend to have lower declarative fear during fear extinction.[143]

Clinical Applications

A study in patients with unilateral, nonpulsatile chronic tinnitus applied taVNS over 2 weeks (pulse width, 200 μs; frequency, 30 Hz; stimulation sites [in sequence], the cavum, cymba, and the outer surface of the tragus; stimulation duration 4 min for each site) found that taVNS can be used to improve tinnitus. A ball-type electrode was placed on the stimulation site with the intensity increased by 1 mA every 5 s as long as the patients could tolerate without pain. The study found that tinnitus distress level decreased and a positive correlation between the

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level of tinnitus distress and the initial stimulus intensity of taVNS was observed.[144] In a randomized, sham-controlled pilot study in patients with major depression, taVNS was administered for 15 min once or twice a day, five days per week, for two weeks. The Beck Depression Inventory scores improved with taVNS compared with sham stimulation.[145] A study in patients with chronic stroke administered taVNS combined with robotic rehabilitation to enhance upper limb functions and reported a slight improvement in the patients post-intervention.[146] taVNS has been applied to patients with drug-resistant epilepsy in a randomized, double-blinded, controlled trial. There was a significant decrease in seizure frequency after 20 weeks in the active treatment (25 Hz stimulation) group compared with the control (1 Hz) group.[147] taVNS has also been tested on a randomized, double-blinded pilot study in PD patients with gastrointestinal complaints. The authors reported that scores of the Gastrointestinal Symptom Rating Scale improved post taVNS in the real stimulation but not in the sham stimulation group.[148]

Side Effects and Limitations of taVNS

The side effects of taVNS are generally minimal and skin irritation or redness are the most common side effect.[138] A limitation of taVNS is the vast parameter space. It is still uncertain whether pulse width or frequency are more important.[149]

Summary of taVNS

taVNS is a noninvasive tool with few side effects and maybe a promising noninvasive therapy in patients with depression, migraine, and other neurological conditions compared with the invasive and more costly VNS. taVNS can increase or decrease activities in different brain areas. The mechanisms of action is not fully understood and optimal stimulation parameters have not been established. It is important to develop systematic studies which can elucidate the utility of taVNS and understand its mechanism of action.

Other Noninvasive Neuromodulation Techniques

In addition to transcranial magnetic or electric noninvasive neuromodulation techniques, transcranial ultrasound and vestibular stimulation are two NIBS techniques with potential utility in neurophysiology and clinical practice.

Low-intensity TUS is gaining traction as a method of neuromodulation. One study investigated the efficacy of TUS on sensory-evoked brain activity and sensory discrimination abilities.[150] TUS targeted to the human primary somatosensory cortex (S1) enhanced performance on sensory discrimination tasks without affecting task attention or response bias.[150] In a recent study, 16 subjects were administered low-intensity 500-kHz TUS coupled to a TMS coil and found that TUS suppressed motor cortical excitability with longer TUS duration leading to greater effects.[1] Another study used transcranial pulse stimulation (TPS) which involved ultrashort ultrasound pulses instead of periodic waves and long sonication trains to provide better skull penetration due to the dominance of lower frequencies.[151] Patients with probable Alzheimer's disease were treated in an open-labeled study with TPS for 2–4 weeks. There were significant improvements found in the language domain along with memory performance in the patients following TPS therapy.

Stochastic vestibular stimulation, or galvanic vestibular stimulation (GVS), is a simple and safe method to induce neuronal activity in both the semicircular canals as well as the otolith organs of the peripheral vestibular system.[152] GVS has been found to improve stability during balance tasks in healthy individuals by facilitating enhanced information transfer using stochastic resonance principles. A study found that GVS administered to 13 healthy subjects for 60 s while they were walking on a treadmill and simultaneously viewing perceptually matched linear optic flow resulted in improved walking stability. The results suggested that GVS can be used to improve dynamic stability during walking.[153] A study using GVS in patients with PD delivered at 70% of cutaneous thresholds (mean current intensity = 0.22 ± 0.02 mA) demonstrated that the sway frequency was mildly reduced following GVS.[154]

Comparison between Different NIBS Techniques

Inukai et al. (2016) compared different NIBS techniques (tDCS, tRNS, and tACS) with similar stimulation patterns (1.0 mA and 10 min) in healthy individuals. Cortical excitability was investigated via single-pulse TMS elicited MEPs. The study demonstrated that all three NIBS techniques increased MEP amplitudes compared with baseline but the effects of tRNS were most pronounced. The results suggest that tRNS may be the most effective transcranial electric stimulation (tES) method.[155]

In randomized controlled studies, sham stimulation is needed as a control condition. Sham stimulation is relatively easy with tDCS, tACS, and other electrical stimulation techniques. A typical sham stimulation setting is that the stimulation is applied and then slowly ramped down, and this usually cannot be perceived by the subject. Sham stimulation is more difficult with rTMS due to clicking sound, muscle twitches, and scalp sensations. New designs of sham coils produced some scalp sensation, and some studies used electrical scalp stimulation to mimic scalp sensation to produce a realistic sham condition for rTMS.

There are few studies that directly compared different NIBS modalities. Although, TMS is most established and the only approved modality for treatment of brain disorders, electrical stimulation techniques have the advantage of lower cost, more portable, potentially be applied at home, and can be combined with rehabilitation or training during the application. More research studies comparing different modalities of NIBS and a combination of these modes of stimulation in neurological and psychiatric disorders are needed.

Concluding Remarks

The different neuromodulation techniques of NIBS such as TMS, tDCS, tACS, RNS, VNS, TUS, and GVS not only helped in understanding the brain physiology but can be a useful treatment in some of the neurological and psychiatric disorders. Further research is needed to expand the clinical utility of NIBS and combine various modes of NIBS to optimize the neuromodulation induced clinical benefits.

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Conflicts of Interest

All authors declare no conflicts of interest related to this study.

Statement of Authorship

AB: prepared the initial draft and assisted in revision. KM and SS: assisted in preparation of the initial draft and subsequent drafts. STN, PKP, and RC: reviewed and suggested modification at various stages of preparation of the final draft and revision of the manuscript. KU: conceptualized the review and provided the guidance and overall supervision.

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