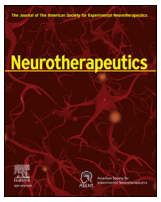
Neurotherapeutics 21 (2024) e00330

Contents lists available at ScienceDirect

Neurotherapeutics

journal homepage: www.sciencedirect.com/journal/neurotherapeutics



Review

Neuromodulation techniques – From non-invasive brain stimulation to deep brain stimulation

Benjamin Davidson [a,1], Amitabh Bhattacharya [b,1], Can Sarica [a,b,1], Ghazaleh Darmani [b], Nasem Raies [b], Robert Chen [b,c], Andres M. Lozano [a,b,*]

[a] Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, Canada
[b] Krembil Research Institute, University Health Network, Toronto, ON, Canada
[c] Edmond J. Safra Program in Parkinson's Disease Morton and Gloria Shulman Movement Disorders Clinic, Division of Neurology, University of Toronto, Toronto, ON, Canada

ARTICLE INFO

Keywords:
Transcranial magnetic stimulation
Transcranial direct current stimulation
Transcranial alternating current stimulation
Deep brain stimulation
Spinal cord stimulation
Vagus nerve stimulation

ABSTRACT

Over the past 30 years, the field of neuromodulation has witnessed remarkable advancements. These developments encompass a spectrum of techniques, both non-invasive and invasive, that possess the ability to both probe and influence the central nervous system. In many cases neuromodulation therapies have been adopted into standard care treatments. Transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial ultrasound stimulation (TUS) are the most common non-invasive methods in use today. Deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS), are leading surgical methods for neuromodulation. Ongoing active clinical trials using are uncovering novel applications and paradigms for these interventions.

Introduction

Dramatic leaps forward in both technology and neuroscience have allowed researchers and clinicians alike to study and treat neurological pathologies using neuromodulation. Neuromodulation can be delivered through a variety of means, including non-invasive modalities such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial ultrasound stimulation (TUS), as well as invasive modalities such as deep brain stimulation (DBS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS). Each tool has its advantages and disadvantages, and plays a critical role in both research endeavours and clinical therapeutics. The following article will provide an update on these modalities, outlining the delivery system and science behind these modalities, as well their current and forthcoming clinical uses.

Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) technique which uses a magnetic field to induce electric currents in the brain [1]. This can be used with diagnostic intent – to detect subtle deficits in brain inhibition or excitation - as well as therapeutically [2]. For diagnostic purposes, single-pulse TMS can assess cortical excitability using parameters such as the amplitude of motor evoked potentials (MEPs), resting or active motor threshold (RMT/AMT), the silent period (silence in the electromyography activity following a MEP), and recruitment curve (higher MEP amplitude with increasing stimulation intensity) (Fig. 1) [3]. Using paired-pulse TMS, several inhibitory and facilitatory intracortical circuits such as short interval cortical inhibition (SICI) and intra-cortical facilitation (ICF) can also be measured [4–6]. SICI arises from the interplay of inhibitory and excitatory circuits in the brain. A weak conditioning stimulus, followed by a test stimulus within a short interval (usually 1–6 ms), activates inhibitory interneurons. These interneurons release inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA), reducing the excitatory response in target neurons. This leads to decreased neural output, representing a short-latency inhibitory effect. On the other hand, ICF involves a similar protocol but with a longer inter-stimulus interval (ISI) of 8–30 ms. Here, excitatory neurotransmitters such as glutamate enhance synaptic transmission, amplifying neural response. ICF represents a brief facilitation of neural pathways.

* Corresponding author.
E-mail address: lozano@uhnresearch.ca (A.M. Lozano).
[1] Contributed equally to the manuscript.

https://doi.org/10.1016/j.neurot.2024.e00330
Received 11 October 2023; Received in revised form 14 January 2024; Accepted 28 January 2024

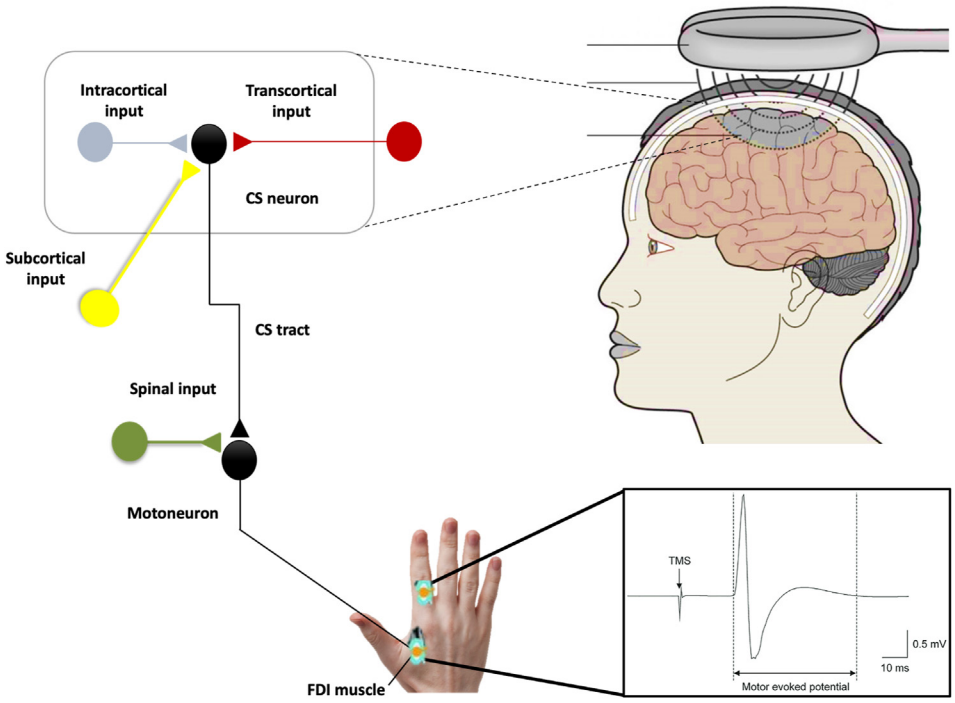


Fig. 1. Schematic representation of transcranial magnetic stimulation demonstrating the magnetic field generated with a magnetic coil placed over the hand area of the primary motor cortex. This, in turn, induces electrical current to activate cortical circuits (lightning bolts indicating the electromagnetic 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 (Adapted with permission from Bhattacharya et al., 2022 [5]).

As the effects of a single pulse of TMS are transient, repetitive TMS (rTMS) protocols are used to achieve a longer-lasting effect [7,8]. When applied to the motor cortex (M1), rTMS leads to changes in MEP amplitudes that outlast the stimulus duration [9]. High-frequency (>5 Hz) rTMS increases cortical excitability, whereas low frequency (1 Hz or lower) rTMS decreases cortical excitability [10,11]. Excitatory and inhibitory changes induced by rTMS may be the result of long-term potentiation (LTP) and long-term depression (LTD), respectively. LTP and LTD effects of rTMS can be blocked by administration of *N*-methyl-D-aspartate (NMDA) receptors antagonists [12,13].

In psychiatric disorders, the minimally-invasive nature of NIBS allows the flexibility to be added to ongoing behavioral/pharmacologic therapies [14]. The use of rTMS to treat refractory major depressive disorder (MDD) was first described in 1993 [15]. Currently, 10-Hz rTMS to the left dorsolateral prefrontal cortex (DLPFC) is an accepted treatment option for MDD [16]. rTMS is applied in daily sessions for up to 6 weeks, with previous studies indicating that at least 20 to 30 sessions are needed for optimal effects [17,18]. More recently, deep rTMS, using an H-coil to deliver high-frequency (20 Hz) stimulation to the bilateral anterior cingulate gyrus and dorsomedial prefrontal cortex, was approved in the treatment of obsessive compulsive disorder (OCD) [19]. rTMS has also shown promise in the field of addiction, with numerous studies, largely using high frequency stimulation of the DLPFC, reporting reduced cravings and usage for smoking and alcohol use disorder [20]. This effect is hypothesized to be due to modulation of neural circuits involved in reward processing and impulse control, which are often dysregulated in addiction. In addition to psychiatric disorders, rTMS shows evidence of therapeutic benefit in conditions such as neuropathic pain, Parkinson's disease (PD), multiple sclerosis (MS), and tinnitus [21–26]. rTMS was recommended by a consensus panel for treatment of neuropathic pain, posttraumatic brain injury-related headaches, postoperative pain, and migraine [27].

TMS can be combined with brain mapping and physiological recording techniques such as neuro-navigation and electroencephalography (EEG), which can lead to clinical and research applications [28]. A study utilizing TMS-EEG to stimulate four brain regions in PD patients and healthy controls revealed significant neurophysiological differences in the PD group. These included reduced waveform adherence, early phase deflection, and connectivity, highlighting TMS-EEG's utility in uncovering the pathophysiological mechanisms of PD and its potential for broader applications in neurological disorder research [29]. Moreover, TMS-EEG has been increasingly used to personalize neuromodulation therapies, as it allows for the identification of individual-specific cortical responses, thereby aiding in the personalization of treatment protocols.

Theta burst stimulation (TBS) is a rTMS protocol that involves magnetic pulses administered in bursts of three pulses at high frequency (50 Hz) with an inter-burst interval of 200 ms or 5 Hz (i.e., theta frequency) [30]. The mechanism of cTBS primarily induces inhibitory effects on the targeted brain region through LTD [30,31]. Intermittent TBS (iTBS) is applied in intermittent bursts, usually 2 s of stimulation followed by an 8-s pause, repeated over a period of ~190 s to produce excitatory effects, through long-term potentiation (LTP) [32]. iTBS to the left DLPFC has also been shown to be effective for treatment of refractory MDD, with similar success rates as the standard 10 Hz rTMS protocol [16,33]. TBS has the advantage of shorter administration times, which can allow rTMS clinics to deliver more daily treatments [16,34,35].

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a NIBS technique that uses scalp electrodes to deliver a weak electric current to modulate neural activity [36]. In general, anodal tDCS increases cortical excitability through depolarization of the resting membrane potentials, and cathodal tDCS reduces cortical excitability, due to hyperpolarization of the resting membrane potential [37,38]. These effects are dependent on stimulation intensity, duration, and the radial electric field [37]. Anodal stimulation enhances local neuronal excitability, leading to increased blood flow and metabolic changes in stimulated regions, as shown in functional near-infrared spectroscopy (fNIRS) studies [39]. Furthermore, tDCS affects neurotransmitter systems, modulating synaptic transmissions through AMPA and NMDA receptors, essential for excitatory synaptic transmission and neuroplasticity. The role of neurotransmitters such as dopamine, serotonin, and acetylcholine in mediating tDCS effects is also documented, indicating a complex interplay in synaptic modulation [40–42]. tDCS also impacts functional connectivity across brain

regions, altering dynamics in psychiatric disorders like schizophrenia and bipolar disorder [43].

tDCS can also induce plasticity, measured by altered MEP amplitudes, for some time beyond the administration of tDCS. As with TMS, a primary mechanism of inducing plasticity is through the action of glutamatergic synapses and NMDA receptors [44]. This is supported by pharmacological studies in humans showing that NMDA antagonists prevent plasticity and NMDA agonists enhance plasticity [45,46]. Other neurotransmitters and neuromodulators, such as acetylcholine, dopamine, serotonin are also involved and may play important roles in the effects of tDCS [47,48]. For instance, dopamine blockers have been shown to block plasticity induction by tDCS [49,50]. There is also evidence that tDCS can induce changes in gene activation and regulation, changes in intrinsic firing properties, and de novo protein expression [44].

tDCS has been trialed in the treatment of several psychiatric conditions. In MDD, tDCS to the DLPFC has shown promising results [51,52], and in a large randomized controlled trial (RCT), it was non-inferior compared to a standard antidepressant medication [53]. In patients with schizophrenia, tDCS with inhibitory (cathodal) stimulation over the left temporal-parietal cortex and excitatory (anodal) stimulation over the left DLPFC led to robust reductions in hallucinations [54], and improvements in negative symptoms [55].

Previous studies have also delved into administration of tDCS to patients with neurological disorders such as PD for its potential to modulate motor and cognitive symptoms. However, with varying protocols, its efficacy remains subject to individual and disease-specific factors. Typical tDCS protocols involve administering 1–2 mA current for 10–30 min, targeting either the motor cortex for motor symptoms or the DLPFC for cognitive symptoms. A study implemented anodal tDCS over the motor cortex, observing improvements in motor function [56], while another study demonstrated cognitive enhancement through prefrontal cortex stimulation [57]. Despite these positive outcomes, there are contradictory studies which report minimal improvements, suggesting that factors such as stimulation intensity, duration, electrode placement, and individual patient characteristics critically influence tDCS efficacy [58]. A study which integrated tDCS with rehabilitation seemed to amplify the benefits via concurrent stimulation and training sessions, underscoring the necessity for refined and patient-tailored tDCS protocols, which balance stimulation parameters with individualized therapeutic needs [59].

Cerebellar tDCS has been evaluated in patients with movement disorders or motor weakness. In patients with neurodegenerative ataxia, a single session of anodal tDCS administered over the bilateral cerebellar cortex led to significant improvements in ataxia and gait [60], an observation which has since been supported in an RCT [61]. In stroke, a meta-analysis of 11 studies suggested that tDCS is effective in supporting recovery from stroke when applied over the contra-lesional or bilateral motor cortices [62]. Another appealing aspect of tDCS is that it can be administered remotely, with preserved safety and efficacy [63,64].

Transcranial Alternating Current Stimulation (tACS)

Transcranial alternating current stimulation (tACS) is a variant of tDCS [65]. Like tDCS, tACS is also a therapeutic tool to restore dysfunctional cortical oscillation patterns in neurological disorders [66–70]. tACS applies a sinusoidal current between two electrodes where current and polarity alternate according to a sine wave pattern [71]. tACS can be applied in a range of frequencies: from DC to 5 kHz for induction of sustained changes in cortical excitability and 200 kHz for tumor therapy [72,73]. Non-human primates research demonstrated that tACS affects the timing of neuron spiking activity in the target cortical region [74]. A study assessed the effects of tACS on motor cortex excitability in young and older adults using individual alpha peak frequency recorded using EEG [75]. In both groups, tACS increased motor cortical excitability as measured by increased MEP amplitude. The inhibitory circuits showed different results between groups: SICI, a measure of the $GABA_A$ receptor-mediated inhibitory circuit, decreased in young subjects but increased in older subjects. Another study used tACS at the alpha-frequency (8–12 Hz) and compared intermittent or sham tACS to investigate the mechanism of the aftereffects of tACS [76]. The results provided further support for plasticity as the underlying mechanism of the aftereffects of tACS and ruled out entrainment echoes (entrained activities that remain stable after the end of stimulation) as an explanation. The study also suggested using α-tACS as a therapeutic tool for inducing short term neural plasticity rather than entrained activity [76]. Studies have demonstrated that individualized alpha frequency tACS could enhance cognitive functions by modulating brain oscillatory activity [77]. Another study highlighted the effectiveness of gamma frequency tACS in improving working memory, suggesting its potential in cognitive rehabilitation [78]. These findings align with earlier research which reported enhanced working memory performance through alpha frequency tACS [79].

Other studies using alpha frequency tACS also showed enhancement of EEG amplitude for 10–30 min after stimulation, indicating that tACS may modulate spontaneous cortical oscillatory activity [79,80]. These findings suggested that the cellular mechanism of tACS involves altering calcium entry in the presynaptic terminals, leading to short-term synaptic plasticity [81]. Despite these promising outcomes, there are discrepancies in tACS efficacy, partly due to variation in stimulation parameters and individual differences. The debate also extends to the depth and specificity of tACS effects, prompting further investigation. Future research focusing on personalized tACS protocols based on neurophysiological profiles to optimize therapeutic outcomes, as well as exploring long-term effects of tACS in neuropsychiatric conditions are needed.

Several studies have used tACS to modulate the primary motor cortex (M1). This includes the application of tACS within the beta (13–30 Hz) or high-gamma (60–90 Hz) frequency ranges during a visuomotor task and concurrent functional magnetic resonance imaging (fMRI). tACS modulated neural activities underneath the stimulation electrode and led to compensatory modulation within connected and functionally related brain networks [82,83]. A previous study aimed to determine whether the effects of tACS on iTBS-induced plasticity are explained by changes in GABA-A receptor-mediated interneuronal activity. The authors co-stimulated the M1 in healthy participants with tACS during intermittent TBS (iTBS), a protocol known to induce LTP-like plasticity [84]. Gamma frequency tACS (γ-tACS), but not beta frequency tACS, led to an increased and prolonged iTBS-induced LTP-like plasticity in the human M1, indicating a link between gamma oscillations, interneuronal GABA-A receptor activity, and LTP-like plasticity in the human M1 [84]. Another study investigated the after-effects of 10 and 20 Hz tACS of the parietal cortex on bimanual coordination. The study did not find an effect of tACS on bimanual coordination, but there was a rise in the right parietal alpha activity following the 20 Hz tACS, suggesting that tACS affects cortical physiology [85]. The behavioral effects of tACS have been reported in many studies. tACS applied at 0.75 Hz frequency to subjects during early nocturnal non-rapid-eye-movement sleep enhanced EEG delta activity, leading to improved recall of memory the next morning [86]. Applying tACS to the left parietal cortex at theta frequency improved performance on working memory, led to decrement in P300 latency in the left hemisphere [87]. A recent paper proposed using tACS to enhance inter-brain synchronization (IBS) to optimize collaboration and improve teamwork in military pilots [88]. Also, γ-tACS has shown promise in enhancing cognitive functions in neurodegenerative disorders. A study demonstrated improved memory performance in patients with Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD), likely through modulating cholinergic neurotransmission [89]. This aligns with the theory that gamma oscillations play a crucial role in cognitive processes and neuroplasticity [90]. Such findings suggest γ-tACS is a viable non-invasive intervention for cognitive enhancement in neurodegenerative conditions.

tACS applied to the motor cortex led to reduced tremor amplitude in patients with PD [70,91]. Patients with PD show reduced γ oscillatory

activity in the basal ganglia-thalamo-cortical network [92,93] and iTBS-induced plasticity is reduced in these patients [94,95]. A study showed that using γ frequency tACS in patients with PD restored iTBS induced plasticity [96]. Furthermore, applying tACS to the orbitofrontal cortex in patients with OCD over the course of 3 months improved OCD symptoms [97]. tACS of the cerebellum was also found to improve essential tremor. Tremor suppression is thought to be the result of disrupting the temporal coherence of the aberrant oscillations in the olivocerebellar loop using transcranial electrical stimulation of the cerebellum phase-locked to the tremor [98]. The use of tACS in tumor management is also a promising area of research. A study found that applying 200 kHz tACS to patients with recurrent glioblastoma can safely inhibit the growth of this treatment-resistant tumor [73].

It is noteworthy that there is also an approach using alternating currents to generate alternating magnetic fields to modulate structures in the brain. Tumor treating fields (TTFields), are an approach whereby superficial wearable electrodes placed against a shaved scalp deliver high frequency electric fields (100–500 kHz). TTFields has been approved in the treatment of first-time presentation and recurrent glioblastoma, potentially extending survival in some cases by more than 5 months [99]. Increased usage time through the day and increased electric field dose delivery to the tumour are both associated with improved survival [100]. The mechanism by which TTFields inhibits tumor growth is not well understood, but there is evidence supporting disruption of the mitotic spindle and activation of a localized immune response as potential mechanisms [101,102].

Transcranial Ultrasound Stimulation

Transcranial ultrasound stimulation (TUS) is an innovative NIBS technique that delivers low-intensity ultrasonic waves through the skull to target both cortical and deep brain regions with millimeter-level spatial resolution [103]. While medical ultrasound has a history dating back over a century, the recent surge in interest has been catalyzed by compelling demonstrations of its ability to stimulate neuronal activity in both *in vitro* and *in vivo* mouse models [104,105]. Soon after these initial preclinical studies, human studies in healthy subjects began, showcasing the neuromodulatory effects of TUS, primarily targeting the primary somatosensory cortex (S1) and primary motor cortex (M1) [106]. The effects of TUS on these two targets exhibited either excitatory or inhibitory characteristics, depending on the specific sonication parameters used and varied in magnitude based on those parameters [107–110]. In addition to these two common targets, a few studies have delved into neuromodulatory TUS effects on the primary visual cortex (V1), prefrontal cortex, middle temporal complex, thalamus, amygdala, entorhinal cortex and basal ganglia [106,111,112].

Early neurophysiological and neuroimaging studies laid the foundation for the development of novel stimulation protocols, including the theta-burst TUS (tbTUS) protocol, designed to induce motor cortex plasticity [109,110]. Analysis of magnetoencephalography data following tbTUS-induced motor cortex plasticity demonstrated spectral power shifts within supplementary motor areas, along with increased local and inter-regional coherence in motor areas, correlating with alterations in motor evoked potentials [113]. Subsequently, it was demonstrated that this induced motor cortex plasticity can be inhibited by pharmaceutical agents that enhance GABAa receptor activity or block Na^{+} and Ca^{2+} channels [114]. A recent study suggested that tbTUS changes overall excitability by reducing GABAergic inhibition and increases functional connectivity of the stimulated regions [115].

In parallel with advancements in human studies, recent preclinical research has elucidated the mechanism underlying ultrasound's impact on neurons. It has been revealed that ultrasound exerts a mechanical influence on cells, leading to the activation of specific calcium-permeable mechanosensitive ion channels, namely TRPP1/2, TRPC1, and Piezo1, in contrast to earlier notions that emphasized mechanisms like bubble formation, cavitation, or temperature elevation [116]. Preclinical research also suggests that long-term TUS has the potential to alter gene expression [117].

TUS is a clinically safe technique, as it has not been associated with any severe adverse events related to sonication. Only a small percentage of subjects (app. 3 %) reported mild and mostly transient symptoms such as headaches, mood deterioration, scalp heating, or cognitive problems [106]. It has undergone testing across a range of distinct patient cohorts, encompassing AD, PD, epilepsy, MDD, chronic pain, disorders of consciousness, and schizophrenia [106,118]. Patients with AD and PD dementia experienced short- and long-term cognitive improvement by the utilization of transcranial pulse stimulation (TPS). This innovative technique employs single ultrashort ultrasound pulses lasting 3 μs, with pulse frequencies ranging from 1 to 5 Hz. This approach diverges from focused TUS, which utilizes high-frequency periodic waves, such as sinusoids, and long sonication trains lasting several hundred milliseconds. The TPS method is believed to offer improved safety by minimizing brain heating and mitigating secondary stimulation maxima. Furthermore, its enhanced skull penetrance is attributed to the lower frequency of pulses compared to focused TUS [119]. Subsequently, another patient cohort experiencing post-stroke cognitive impairment demonstrated cognitive improvement through focused TUS in a RCT [120]. Apart from the cognitive improvement, TPS also improved depression scores and normalized connectivity in AD patients [121]. This effect was later tested in patients with MDD through a RCT, revealing a significant reduction in depressive symptoms lasting up to three months [122]. A separate RCT confirmed comparable improvements with focused TUS in MDD patients [123]. Schizophrenia was another psychiatric disorder under examination, revealing significant improvements in negative symptoms among participants who received repetitive TUS in the active stimulation group, whereas those in the sham group did not experience similar benefits [118]. The safety of TUS has been established in patients with epilepsy, chronic pain, and disorders of consciousness through pilot trials. Three patients with disorders of consciousness underwent two thalamic focused TUS sessions spaced one week apart. The Coma Recovery Scale-Revised scores initially showed improvement at 6 months for the first patient, followed by a decline [124]. In contrast, the scores improved for the second patient and declined for the third [124]. Focused TUS to seizure-onset zone decreased or increased the seizure frequency and interictal epileptiform discharges in different epilepsy patients [125]. Diagnostic ultrasound to frontal cortex significantly improved subjective mood scores compared to placebo; however, pain scores did not change [126]. Nonetheless, larger patient cohorts are required to provide more definitive and conclusive results for these indications [124–126]. A recent advancement in the field demonstrated the safety of an accelerated theta burst protocol (a-tbTUS) in PD patients, involving three consecutive TUS sessions separated by 30-min intervals. While our pilot study confirmed the safety of a-tbTUS and observed changes in motor cortical excitability, clinical improvements, as assessed by the UPDRS score, did not reach statistical significance [127,128].

Temporal Interference

Temporal interference (TI) brain stimulation is an exciting new non-invasive approach for stimulating deep structures in the brain [129]. By applying two high frequency alternating fields of slightly different frequencies in the area where the fields overlap, neurons can be activated at the difference in frequency between the fields (i.e. two separate fields of 2 kHz and 2.01 kHz will drive neurons to fire at 10 Hz) [129,130]. While early work has primarily focused on pre-clinical studies, TI offers both the temporal and spatial precision of DBS without the invasiveness, and has remarkable potential in all areas being studied for DBS [129,130].

Deep Brain Stimulation

Deep brain stimulation (DBS) is a surgical procedure in which electrodes are implanted semi-permanently in the brain through burr holes

drilled in the skull, and connected via subcutaneous extension wires to an implantable pulse generator battery placed below the clavicle (Fig. 2) [131]. Electricity is transmitted along the extension cables, down the intracranial electrodes, and into an intracranial target. Through wireless programming, clinicians can control the amplitude, frequency, and pulse-width of stimulation, as well as select the contacts to be activated. The stimulator battery requires replacement, typically every 3–5 years, and in some cases, rechargeable batteries are implanted, which extends replacement surgeries to every 15 years or longer [132,133].

Contemporary DBS was borne out of the observation that subcortical electrical stimulation can mimic the effects of lesioning in the treatment of movement disorders [134]. In some sense, DBS can be thought of as a titratable lesion, although it has become apparent that the mechanism of action underlying DBS is more complex, involving elements of both inhibition, excitation, and other more subtle modulations [135,136]. DBS is often thought of as an 'informational lesion', blocking pathologic oscillatory activity traveling through a circuit [137,138]. In other instances, such as DBS of the fornix in the treatment of AD, stimulation appears to drive downstream activity in memory circuits [139]. Since the early 1990's, over 200,000 DBS implantation surgeries have been performed worldwide [140]. DBS is primarily used in the treatment of movement disorders, such as PD, essential tremor, and dystonia, for which it has widely earned regulatory approval [141–143]. DBS is also approved for the treatment of focal-onset epilepsy, and under humanitarian grounds, in the treatment of obsessive-compulsive disorder [131]. Emerging indications for DBS include other neuropsychiatric disorders (most commonly MDD and Tourette syndrome), AD, addiction, chronic pain, and post-stroke hemiparesis (Fig. 3 [144]) [145–149].

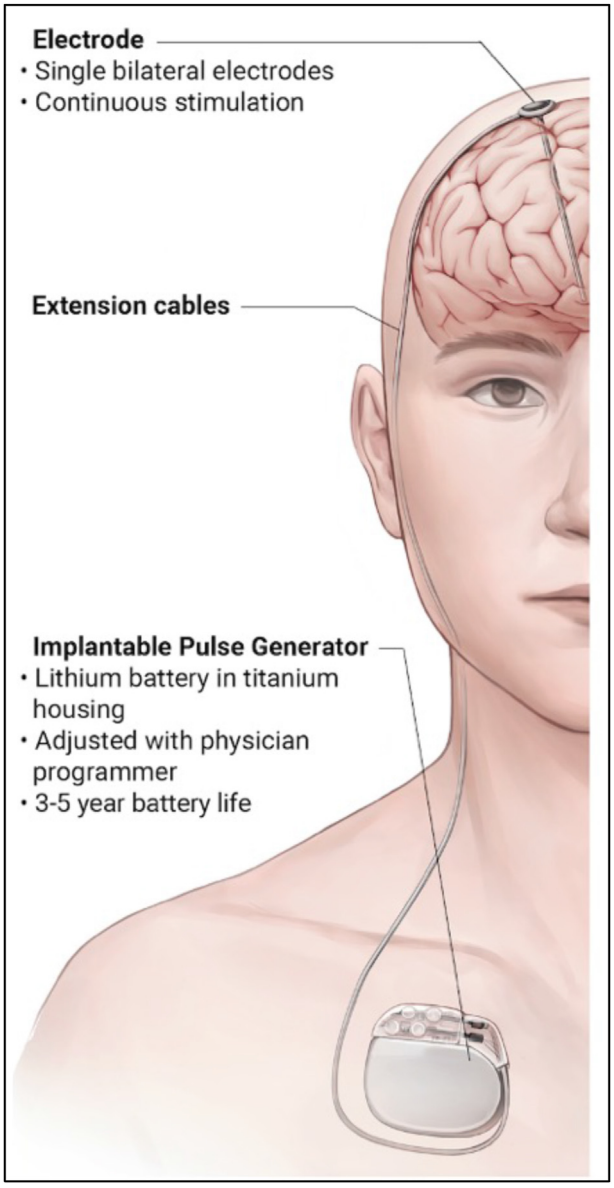


Fig. 2. Typical Deep Brain Stimulation (DBS) setup (Adapted with permission from Krauss et al., 2021 [140]).

Most commonly, stimulation is delivered continuously, 24 h/day in an 'open-loop' fashion. In order to improve battery life, reduce side effects, and mitigate tolerance, 'closed-loop' stimulation is an attractive approach to optimizing DBS. Most closed loop models involve chronic sensing in order to detect a neurophysiologic biomarker that triggers a burst of active stimulation. This has gained mainstream use in epilepsy, where epileptiform discharges are used as a trigger-point to initiate a burst of stimulation to dissipate a potential clinical seizure [150].

Closed-loop DBS is on the cusp of standard use in PD, dystonia, and essential tremor, where the oscillatory power of specific frequency ranges found in local field potentials have been established as reliable biomarkers [151–153]. In PD, increased power in the beta range (13–35 Hz) tracks closely with fluctuations in rigidity and bradykinesia, and experimental models using stimulation activated only when STN beta power exceeds a certain threshold, demonstrate both reduced energy usage and improved clinical outcomes [154]. Other frequency bands also correlate with clinical findings in PD, including gamma-power with dyskinesia and alpha-power with impulsivity [155,156]. In dystonia, oscillatory power in the theta range (4–7 Hz) scales with dystonic symptoms; in a patient with cervical dystonia, an experimental closed-loop stimulation paradigm utilized theta rhythms recorded from the motor cortex to trigger bursts of stimulation to the globus pallidus, which resulted in more efficient and effective results than continuous stimulation [157]. In essential tremor, a pilot trial demonstrated that using the full spectral range from thalamic recordings to train an adaptive DBS system, led to significantly less battery usage, albeit similar clinical results [151]. In psychiatric indications, where biomarkers are less established and clinical response is more difficult to classify [158], early work is looking at personalized versions of closed loop stimulation [159]. The movement to develop neurophysiologic biomarkers to facilitate closed-loop stimulation has recently benefited from the development of DBS systems capable of concurrent stimulation and recording [160].

Spinal Cord Stimulation

Spinal cord stimulation (SCS) is an established therapy for many forms of chronic neuropathic pain, particularly failed back surgery syndrome and complex regional pain syndrome [161]. Annually, over 30,000 individuals receive SCS implantation for chronic pain, with sales exceeding 1.8 billion dollars [162]. Being a massive, multi-billion dollar industry has helped fuel numerous clinical trials and technical advancements in the field. SCS is also under investigation for other indications, including recovery after spinal cord injury and gait impairment in PD [163].

Spinal cord stimulation is performed by placing electrodes in the epidural space over the dorsal aspect of the spinal cord, at a level that corresponds to the affected dermatomes to be modulated [164]. In most cases, the electrodes are externalized, and the patient undergoes a trial period of stimulation to ensure adequate pain relief prior to internalization and connection to an implanted pulse generator. Traditional SCS is performed with tonic stimulation delivered at 40–60 hertz, set at an amplitude sufficient to elicit mild but non-bothersome paresthesias [165,166].

Mechanistically, SCS was originally thought to work as an application of the gate control theory of pain, whereby stimulation of interneurons in the substantia gelatinosa inhibits ascending pain pathways, essentially blocking painful neuropathic pain signals [167]. In favor of this, programming a spinal cord stimulator involves selecting stimulation settings

Trials by clinical disorder.

Clinical disorder	Number of studies	Percent of total studies (%)
Parkinson's disease	151	39.3
Tremor	16	4.2
Dystonia	28	7.3
Huntington's disease	3	0.8
Other movement disorder (dyskinesia, multiple sclerosis, multiple system atrophy, cerebellar ataxia)	8	2.1
Mixed movement disorder	26	6.8
Major depressive disorder	26	6.8
Bipolar disorder	2	0.5
Obsessive-compulsive disorder	27	7.0
Post-traumatic stress disorder	3	0.8
Anorexia nervosa	5	1.3
Schizophrenia	3	0.8
Alcohol/Drug addiction	11	2.9
Mixed psychiatric disorder	6	1.6
Obesity	6	1.6
Pain (including neuropathic pain and headache)	5	1.3
Epilepsy	13	3.4
Alzheimer's disease	9	2.3
Non-Alzheimer's dementia	2	0.5
Tourette's syndrome	7	1.8
Coma/Decreased level of consciousness	3	0.8
Traumatic brain injury/Spinal injury/Stroke	6	1.6
Mixed movement disorder/psychiatric/memory	6	1.6
Other (tinnitus, lower urinary tract symptoms)	4	1.0
Not specified	8	2.1
Total	384	100

Fig. 3. Table of investigational indications/studies in Deep Brain Stimulation (DBS) (Adapted with permission from Harmsen et al., 2021 [144]).

that induce parasthesias in the patient's painful dermatome-a sign that the SCS is potentially blocking painful sensory transmission. However, newer parasthesia-free stimulation paradigms have been introduced, including high-frequency stimulation (>400 Hz, sometimes as high as 10,000 Hz) and burst-stimulation, challenging the gate control theory of pain as a mechanistic explanation. These paradigms seem to result in similar efficacy rates, and raise the question of whether other theories, such as supraspinal pathways or segmental modulation of neuroglia, could explain the effect of SCS [128,162,168]. High-frequency and burst stimulation paradigms are sometimes capable of rescuing recurrent pain in patients who had previously benefiting from traditional SCS [169].

In another similarity to DBS, there is an enormous 'parameter space' when it comes to selecting active contacts, and stimulation settings (amplitude, frequency, pulse width) [128]. This can place a potential time-consuming and ill-defined task of selecting optimal patient-specific stimulation settings on the clinician (for a helpful guide towards programming, see Ref. [166]).

As with DBS, the SCS field is also adopting closed-loop approaches. Most recently, SCS devices have become capable of dual sensing and recording, allowing them to record evoked compound action potentials (ECAPs). ECAPs can be used to estimate the effect of stimulation being delivered to the dorsal columns, and in real time, SCS stimulation can be modulated to maintain a constant effective level of stimulation. The main reason such modulation is needed, is due to the fluctuating distance between the dura and the spinal cord, which can vary with heartbeats, respiration, and position [170,171]. Randomized controlled trial evidence suggests that ECAP-modulated SCS results in improved pain relief and a reduced occurrence of troublesome paresthesias [172]. While current closed-loop systems modulate amplitude, it is likely that future iterations will also include pulse-width and frequency modulation.

SCS has been utilized in the treatment of pain since the 1970's, and among the early reports, are several descriptions of unexpected motor improvements in patients with pre-existing weakness from MS or traumatic spinal cord injury [173]. Through excitation of large-diameter afferents at the level of the dorsal root entry zone, SCS is thought to have an excitatory effect on local spinal motor circuitry, and an inhibitory effect on descending cortical inhibitory pathways (disinhibition) [174]. In 2018, three independent trials reported remarkable yet consistent findings, of enabling patients with traumatic spinal cord injury causing complete motor paralysis to regain movement, and in some cases, the ability to walk with an assistive device [175–177]. The key feature across all three trials was the presence of a testing period to individualize stimulation for each patient to maximize activation of segmental motor neurons to the legs, as well as intensive physical therapy paired with active stimulation.

Exciting advancements are occurring in the field of transcutaneous spinal cord stimulation. With skin-surface electrodes, it is still possible to activate low-threshold proprioceptive fibers, albeit with less rostral-caudal selectively than SCS [178]. Several studies in humans with spinal cord injury have demonstrated promising improvements in balance, hand function, and even gait, after transcutaneous SCS [173].

Recently, a translational study implemented a closed-loop lumbosacral SCS system to treat gait impairments in PD [179]. After decoding 6 'hotspots' within the dorsal lumbosacral cord critical for the production of gait, this group used electromyography feedback from the legs to trigger SCS, in the 30–80 Hz range, improving gait impairment and freezing of gait [179]. It appears that some degree of intact spinal circuitry through the lesioned area is necessary for improvement, and future studies will hope to identify ideal patients for further SCS neuromodulation trials for motor rehabilitation.

Vagal Nerve Stimulation

Vagus nerve stimulation (VNS) is a widely-approved standard of care treatment option for treatment resistant epilepsy and MDD, and is under intense investigation as a treatment for autoimmune and other inflammatory disorders [180]. In epilepsy, VNS is offered as a means of reducing seizure frequency and duration in cases where respective surgery is not a viable option. In refractory MDD, VNS can improve 12-month response rates from 20 % with treatments as usual to over 40 % [181].

VNS is performed by wrapping an electrode around the left cervical vagus nerve. Left-sided implantation is typically chosen, as the right sided vagus nerve innervates the heart's sinoatrial node, and its stimulation can result in arrhythmias (although cases of right-sided VNS performed safely have been reported) [182]. The most common side effects of VNS-dysphonia, cough, and hoarseness-are well controlled by adjusting stimulation parameters [183,184]. As with DBS, VNS electrodes are connected to a subclavicular implantable pulse generator, and programmed with a wireless handheld device (Fig. 4) [185].

The vagus nerve is composed of 80 % sensory afferents and 20 % motor efferents for the viscera (gastrointestinal tract, lungs/diaphragm, liver, heart, aorta) [186], making the vagus nerve an intermediary between the brainstem and the rest of the body. While the efferent motor fibers to the viscera are myelinated, the afferent sensory fibers are unmyelinated, and therefore the relatively low levels of stimulation delivered by a VNS system preferentially stimulate axons traveling towards the brain. In the brainstem, the nucleus of the tractus solitarius receives most vagus sensory inputs, from which signals are projected to the locus coeuleus, the dorsal raphe nuclei, and other structures that collectively have been termed the vagus afferent network [187]. VNS is thought of as a titratable means of modulating the brain through ascending vagus nerve afferents to the brainstem, and the rest of the brain.

The mechanism by which VNS suppresses seizures is not well understood. There is evidence to suggest VNS reduces the kindling effect in hyperexcitable regions including the thalamocortical circuits, limbic system, and thalamus itself [188]. It may do this by reducing synchronicity, as functional connectivity studies demonstrate that VNS-ON periods are associated with less EEG synchronicity and hyperconnectivity than VNS-OFF periods [189]. VNS also results in modulation of norepinephrine and serotonin release from locus coeruleus and raphe nuclei, which can have anti-epileptic effects [187,190]. The mechanism of action of VNS in the treatment of MDD is even less clear, but it likely involves modulation through diffusely projecting norepinephrine and serotonin pathways.

Initial evidence supporting VNS in the treatment of epilepsy came from two randomized clinical trials in the 1990's demonstrating superior seizure-reduction with standard stimulation compared with minimal stimulation in patients with refractory partial seizures [191,192]. This was followed by a 1999 report demonstrating that 40 % of patients treated obtained at least a 50 % reduction in seizure frequency after 2–3 years, including both partial and generalized epilepsy [193]; A 40–60 % seizure reduction in 50 % of patients at 2–3 years has been reproduced in numerous series over the past two decades, regardless of age or seizure semiology [183,185]. VNS stimulation was performed using 30 s of 30 Hz stimulation every 5 min, with patients able to use a hand-held magnet to activate their device to abort an aura or seizure [191].

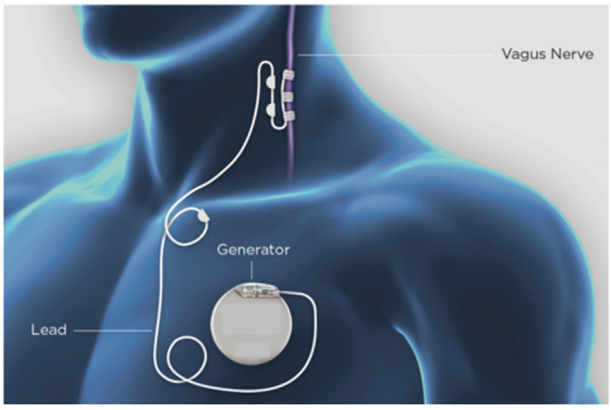


Fig. 4. Typical vagus nerve stimulation implantable system. (Adapted with permission from Wheless et al., 2018 [185]).

Subsequent reports have demonstrated that the anti-epileptic effect of VNS is independent of age, seizure semiology, or epilepsy syndrome; this makes VNS a particularly attractive therapy option in pediatric epilepsy, where effective therapies are often lacking [183,185]. Similarly, in the treatment of refractory MDD, VNS is associated with a >50 % response rate at long-term follow-up [194,195].

The optimal stimulation parameters for VNS are still unknown [185]. Typical parameters for both epilepsy and MDD use 20–30 Hz and a pulse width of 250–500 μs, cycling between 30 s of ON time followed by 5 min of OFF time. Current is generally started at a low level (i.e. 0.25 mA) and gradually increased over weeks to months depending on tolerability and clinical effect (though clinical effects may gradually accrue beyond 1 year) [196].

Closed loop applications of VNS for epilepsy have already been implemented. The most common approach uses ictal-tachycardia as a trigger for stimulation. Ictal tachycardia is seen with >80 % of seizures (both generalized and partial), and stimulation triggered by a heart-rate over 100 beats/minute with at least a 55 % or 35 beats/minute increase above baseline has been shown to be an effective means of closed loop stimulation [196,197]. Open-label data suggests ictal-tachycardia triggered VNS may result in improved seizure control over traditional open-label stimulation [198].

Serendipitously, epileptic patients receiving VNS were found to have improved mood regardless of improvement in seizure frequency, which was eventually followed by positive RCT's and regulatory approval in many countries [192,199–202]. The mechanism may be related to increased serotonin and norepinephrine release from the locus ceruleus and raphe nuclei, respectively, but it also appears to elicit widespread network-level changes [202]. Given its positive mood effects during epilepsy treatment, similar stimulation frequency and duty-cycle parameters have been used, with a dose-finding study suggesting higher pulse width and amplitudes (within a tolerable range) are optimal [195]. Without clear depression biomarkers, there has been less progress in developing a closed-loop system.

VNS is also thought to reduce systemic levels of inflammation through activation of the cholinergic anti-inflammatory pathway [180,203]. With the rationale of reducing systemic levels of inflammation, VNS is under active investigation in the treatment of sepsis, diabetes, cardiovascular disease, fibromyalgia, migraine, stroke, and traumatic brain injury. Inadvertent weight loss seen in patients treated for epilepsy has also sparked interest in using VNS to treat obesity [204]. Over the past decade, transcutaneous vagus nerve stimulation has been introduced, and researchers are now trying to reproduce previous clinical success and neuroimaging findings with this NIBS option [205,206].

As with SCS, the field of VNS has also benefited from developments in non-invasive alternatives. With skin-electrodes placed behind the ear, the auricular branch of the vagus nerve may be stimulated, and remarkably,

can elicit similar neurophysiologic effects to what is seen with invasive VNS [205]. VNS (invasive or transcutaneous) acts through stimulation of A-Beta fibers, and the auricular branch of the vagus contains a lower proportion of these fibers, with more variation between individuals [207]; therefore, the exact placement of electrodes may be crucial, and not all patients may be able to benefit from transcutaneous approaches to VNS. Transcutaneous VNS is promising but still relatively understudied, and will require rigorous head-to-head trials with VNS to assess its efficacy.

This review outlines the primary neuromodulation techniques in clinical use across a spectrum of invasiveness. Each modality has varying degrees of supporting evidence for specific clinical indications. In the absence of comparative trials of the various neuromodulatory treatments described here, it is necessary for the clinician to understand the evidence, advantages, and disadvantages of each and make a pragmatic decision for the individual patient. In general, moving from less to more invasive is a logical progression. These neuromodulation techniques will continue to improve, which will bring better clinical results and more insightful mechanistic understanding.

Authors' Contributions

Benjamin Davidson made significant contributions to conceptualization, data curation, methodology, validation, visualization, writing (original draft) and writing (review/editing).

Amitabh Bhattacharya made significant contributions to conceptualization, data curation, methodology, validation, visualization, writing (original draft) and writing (review/editing).

Can Sarica made significant contributions to conceptualization, data curation, methodology, validation, visualization, writing (original draft) and writing (review/editing).

Ghazaleh Darmani made significant contributions to conceptualization, data curation, methodology, validation, visualization, writing (original draft) and writing (review/editing).

Nasem Raies made significant contributions to conceptualization, data curation, methodology, validation, visualization, writing (original draft) and writing (review/editing).

Robert Chen made significant contributions to conceptualization, methodology, project administration, resources, supervision, writing (original draft) and writing (review/editing).

Andres Lozano made significant contributions to conceptualization, methodology, project administration, resources, supervision, writing (original draft) and writing (review/editing).

Declaration of conflicts of interest

Andres Lozano is the co-founder of Functional Neuromodulation (a DBS-related company) and is a consultant for Boston Scientific, Medtronic and Abbott (companies that produce DBS hardware).

None of the other authors have conflicts of interest to declare.

References

[1] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;1(8437):1106–7.

[2] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126(6):1071–107.

[3] Ngomo S, Leonard G, Moffet H, Mercier C. Comparison of transcranial magnetic stimulation measures obtained at rest and under active conditions and their reliability. J Neurosci Methods 2012;205(1):65–71.

[4] Chen R, Fitzgerald PB, Blumberger DM. A practical guide to transcranial magnetic stimulation neurophysiology and treatment studies. Oxford University Press; 2022.

[5] Bhattacharya A, Mrudula K, Sreepada SS, Sathyaprabha TN, Pal PK, Chen R, et al. An overview of noninvasive brain stimulation: basic principles and clinical applications. Can J Neurol Sci 2022;49(4):479–92.

[6] Vucic S, Stanley Chen KH, Kiernan MC, Hallett M, Benninger DH, Di Lazzaro V, et al. Clinical diagnostic utility of transcranial magnetic stimulation in neurological disorders. Updated report of an IFCN committee. Clin Neurophysiol 2023;150:131–75.

[7] Baumer T, Demiralay C, Hidding U, Bikmullina R, Helmich RC, Wunderlich S, et al. Abnormal plasticity of the sensorimotor cortex to slow repetitive transcranial magnetic stimulation in patients with writer's cramp. Mov Disord 2007;22(1):81–90.

[8] Schulze L, Feffer K, Lozano C, Giacobbe P, Daskalakis ZJ, Blumberger DM, et al. Number of pulses or number of sessions? An open-label study of trajectories of improvement for once-vs. twice-daily dorsomedial prefrontal rTMS in major depression. Brain Stimul 2018;11(2):327–36.

[9] Klomjai W, Katz R, Lackmy-Vallee A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med 2015;58(4):208–13.

[10] Pascual-Leone A, Gomez-Tortosa E, Grafman J, Alway D, Nichelli P, Hallett M. Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. Neurology 1994;44(3 Pt 1):494–8.

[11] Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48(5):1398–403.

[12] Ziemann U, Paulus W, Nitsche MA, Pascual-Leone A, Byblow WD, Berardelli A, et al. Consensus: motor cortex plasticity protocols. Brain Stimul 2008;1(3):164–82.

[13] Hoogendam JM, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimul 2010;3(2):95–118.

[14] De Risio L, Borgi M, Pettorruso M, Miuli A, Ottomana AM, Sociali A, et al. Recovering from depression with repetitive transcranial magnetic stimulation (rTMS): a systematic review and meta-analysis of preclinical studies. Transl Psychiatry 2020;10(1):393.

[15] Höflich G, Kasper S, Hufnagel A, Ruhrmann S, Möller H-J. Application of transcranial magnetic stimulation in treatment of drug-resistant major depression—a report of two cases. Hum Psychopharmacol Clin Exp 1993;8(5):361–5.

[16] Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 2018;391(10131):1683–92.

[17] O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatr 2007;62(11):1208–16.

[18] Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatr 2016;61(9):561–75.

[19] Carmi L, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, et al. Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. Am J Psychiatr 2019;176(11):931–8.

[20] Harmelech T, Hanlon CA, Tendler A. Transcranial magnetic stimulation as a tool to promote smoking cessation and decrease drug and alcohol use. Brain Sci 2023;13(7).

[21] Attal N, Poindessous-Jazat F, De Chauvigny E, Quesada C, Mhalla A, Ayache SS, et al. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. Brain 2021;144(11):3328–39.

[22] Zhang W, Deng B, Xie F, Zhou H, Guo JF, Jiang H, et al. Efficacy of repetitive transcranial magnetic stimulation in Parkinson's disease: a systematic review and meta-analysis of randomised controlled trials. EClinicalMedicine 2022;52:101589.

[23] Chen X, Yin L, An Y, Yan H, Zhang T, Lu X, et al. Effects of repetitive transcranial magnetic stimulation in multiple sclerosis: a systematic review and meta-analysis. Mult Scler Relat Disord 2022;59:103564.

[24] Liang Z, Yang H, Cheng G, Huang L, Zhang T, Jia H. Repetitive transcranial magnetic stimulation on chronic tinnitus: a systematic review and meta-analysis. BMC Psychiatr 2020;20(1):547.

[25] Wagner E, Honer WG, Sommer IE, Koops S, Blumberger DM, Daskalakis ZJ, et al. Repetitive transcranial magnetic stimulation (rTMS) for schizophrenia patients treated with clozapine. World J Biol Psychiatr 2021;22(1):14–26.

[26] Fitzsimmons S, van der Werf YD, van Campen AD, Arns M, Sack AT, Hoogendoorn AW, et al. Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder: a systematic review and pairwise/network meta-analysis. J Affect Disord 2022;302:302–12.

[27] Leung A, Shirvalkar P, Chen R, Kuluva J, Vaninetti M, Bermudes R, et al. Transcranial magnetic stimulation for pain, headache, and comorbid depression: INS-nans expert consensus panel review and recommendation. Neuromodulation 2020;23(3):267–90.

[28] Lioumis P, Rosanova M. The role of neuronavigation in TMS-EEG studies: current applications and future perspectives. J Neurosci Methods 2022;380:109677.

[29] Maidan I, Zifman N, Hausdorff JM, Giladi N, Levy-Lamdan O, Mirelman A. A multimodal approach using TMS and EEG reveals neurophysiological changes in Parkinson's disease. Parkinsonism Relat Disord 2021;89:28–33.

[30] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45(2):201–6.

[31] Batra D, Kamble N, Bhattacharya A, Sahoo L, Yadav R, Pal PK. Modulatory effect of continuous theta burst stimulation in patients with essential tremor. Parkinsonism Relat Disord 2022;94:62–6.

[32] Di Lazzaro V, Pilato F, Saturno E, Oliviero A, Dileone M, Mazzone P, et al. Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. J Physiol 2005;565(Pt 3):945–50.
[33] Berlim MT, McGirr A, Rodrigues Dos Santos N, Tremblay S, Martins R. Efficacy of theta burst stimulation (TBS) for major depression: an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res 2017;90:102–9.
[34] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). Clin Neurophysiol 2020;131(2):474–528.
[35] Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford neuromodulation therapy (snt): a double-blind randomized controlled trial. Am J Psychiatr 2022;179(2):132–41.
[36] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol 2016;127(2):1031–48.
[37] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527 Pt 3(Pt 3):633–9.
[38] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1(3):206–23.
[39] Merzagora AC, Foffani G, Panyavin I, Mordillo-Mateos L, Aguilar J, Onaral B, et al. Prefrontal hemodynamic changes produced by anodal direct current stimulation. Neuroimage 2010;49(3):2304–10.
[40] Nitsche MA, Kuo MF, Karrasch R, Wachter B, Liebetanz D, Paulus W. Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol Psychiatr 2009;66(5):503–8.
[41] Thirugnanasambandam N, Grundey J, Adam K, Drees A, Skwirba AC, Lang N, et al. Nicotinergic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans. Neuropsychopharmacology 2011;36(4):879–86.
[42] Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 2013;6(3):424–32.
[43] Kunze T, Hunold A, Haueisen J, Jirsa V, Spiegler A. Transcranial direct current stimulation changes resting state functional connectivity: a large-scale brain network modeling study. Neuroimage 2016;140:174–87.
[44] Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, et al. Neurobiological after-effects of non-invasive brain stimulation. Brain Stimul 2017;10(1):1–18.
[45] Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 2003;553(Pt 1):293–301.
[46] Nitsche MA, Jaussi W, Liebetanz D, Lang N, Tergau F, Paulus W. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology 2004;29(8):1573–8.
[47] Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 2010;66(2):198–204.
[48] Nitsche MA, Muller-Dahlhaus F, Paulus W, Ziemann U. The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. J Physiol 2012;590(19):4641–62.
[49] Nitsche MA, Lampe C, Antal A, Liebetanz D, Lang N, Tergau F, et al. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. Eur J Neurosci 2006;23(6):1651–7.
[50] Marquez-Ruiz J, Leal-Campanario R, Sanchez-Campusano R, Molaee-Ardekani B, Wendling F, Miranda PC, et al. Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. Proc Natl Acad Sci U S A 2012;109(17):6710–5.
[51] Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 2006;8(2):203–4.
[52] Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry 2011;35(1):96–101.
[53] Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med 2017;376(26):2523–33.
[54] Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, et al. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatr 2012;169(7):719–24.
[55] Valiengo L, Goerigk S, Gordon PC, Padberg F, Serpa MH, Koebe S, et al. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in schizophrenia: a randomized clinical trial. JAMA Psychiatr 2020;77(2):121–9.
[56] Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, et al. Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Mov Disord 2006;21(10):1693–702.
[57] Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 2006;249(1):31–8.
[58] Broeder S, Nackaerts E, Heremans E, Vervoort G, Meesen R, Verheyden G, et al. Transcranial direct current stimulation in Parkinson's disease: neurophysiological mechanisms and behavioral effects. Neurosci Biobehav Rev 2015;57:105–17.
[59] Manenti R, Brambilla M, Benussi A, Rosini S, Cobelli C, Ferrari C, et al. Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy. Mov Disord 2016;31(5):715–24.
[60] Benussi A, Koch G, Cotelli M, Padovani A, Borroni B. Cerebellar transcranial direct current stimulation in patients with ataxia: a double-blind, randomized, sham-controlled study. Mov Disord 2015;30(12):1701–5.
[61] Benussi A, Dell'Era V, Cantoni V, Bonetta E, Grasso R, Manenti R, et al. Cerebello-spinal tDCS in ataxia: a randomized, double-blind, sham-controlled, crossover trial. Neurology 2018;91(12):e1090–101.
[62] Veldema J, Gharabaghi A. Non-invasive brain stimulation for improving gait, balance, and lower limbs motor function in stroke. J NeuroEng Rehabil 2022;19(1):84.
[63] Dobbs B, Pawlak N, Biagioni M, Agarwal S, Shaw M, Pilloni G, et al. Generalizing remotely supervised transcranial direct current stimulation (tDCS): feasibility and benefit in Parkinson's disease. J NeuroEng Rehabil 2018;15(1):114.
[64] Pilloni G, Vogel-Eyny A, Lustberg M, Best P, Malik M, Walton-Masters L, et al. Tolerability and feasibility of at-home remotely supervised transcranial direct current stimulation (RS-tDCS): single-center evidence from 6,779 sessions. Brain Stimul 2022;15(3):707–16.
[65] Chase HW, Boudewyn MA, Carter CS, Phillips ML. Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. Mol Psychiatr 2020;25(2):397–407.
[66] Krause V, Wach C, Sudmeyer M, Ferrea S, Schnitzler A, Pollok B. Cortico-muscular coupling and motor performance are modulated by 20 Hz transcranial alternating current stimulation (tACS) in Parkinson's disease. Front Hum Neurosci 2013;7:928.
[67] Sreeraj VS, Shanbhag V, Nawani H, Shivakumar V, Damodharan D, Bose A, et al. Feasibility of online neuromodulation using transcranial alternating current stimulation in schizophrenia. Indian J Psychol Med 2017;39(1):92–5.
[68] Mellin JM, Alagapan S, Lustenberger C, Lugo CE, Alexander ML, Gilmore JH, et al. Randomized trial of transcranial alternating current stimulation for treatment of auditory hallucinations in schizophrenia. Eur Psychiatr 2018;51:25–33.
[69] Del Felice A, Castiglia L, Formaggio E, Cattelan M, Scarpa B, Manganotti P, et al. Personalized transcranial alternating current stimulation (tACS) and physical therapy to treat motor and cognitive symptoms in Parkinson's disease: a randomized cross-over trial. Neuroimage Clin 2019;22:101768.
[70] Ahn S, Mellin JM, Alagapan S, Alexander ML, Gilmore JH, Jarskog LF, et al. Targeting reduced neural oscillations in patients with schizophrenia by transcranial alternating current stimulation. Neuroimage 2019;186:126–36.
[71] Antal A, Herrmann CS. Transcranial alternating current and random noise stimulation: possible mechanisms. Neural Plast 2016;2016:3616807.
[72] Chaieb L, Antal A, Paulus W. Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. Restor Neurol Neurosci 2011;29(3):167–75.
[73] Kirson ED, Dbaly V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A 2007;104(24):10152–7.
[74] Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. Proc Natl Acad Sci U S A 2019;116(12):5747–55.
[75] Fresnoza S, Christova M, Feil T, Gallasch E, Korner C, Zimmer U, et al. The effects of transcranial alternating current stimulation (tACS) at individual alpha peak frequency (iAPF) on motor cortex excitability in young and elderly adults. Exp Brain Res 2018;236(10):2573–88.
[76] Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (alpha-tACS) reflects plastic changes rather than entrainment. Brain Stimul 2015;8(3):499–508.
[77] Kasten FH, Duecker K, Maack MC, Meiser A, Herrmann CS. Integrating electric field modeling and neuroimaging to explain inter-individual variability of tACS effects. Nat Commun 2019;10(1):5427.
[78] Alekseichuk I, Turi Z, Amador de Lara G, Antal A, Paulus W. Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. Curr Biol 2016;26(12):1513–21.
[79] Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One 2010;5(11):e13766.
[80] Neuling T, Rach S, Herrmann CS. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front Hum Neurosci 2013;7:161.
[81] Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology 2008;33(1):18–41.
[82] Pogosyan A, Gaynor LD, Eusebio A, Brown P. Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol 2009;19(19):1637–41.
[83] Moisa M, Polania R, Grueschow M, Ruff CC. Brain network mechanisms underlying motor enhancement by transcranial entrainment of gamma oscillations. J Neurosci 2016;36(47):12053–65.
[84] Guerra A, Suppa A, Bologna M, D'Onofrio V, Bianchini E, Brown P, et al. Boosting the LTP-like plasticity effect of intermittent theta-burst stimulation using gamma transcranial alternating current stimulation. Brain Stimul 2018;11(4):734–42.
[85] Berger A, Pixa NH, Steinberg F, Doppelmayr M. Brain oscillatory and hemodynamic activity in a bimanual coordination task following transcranial alternating current stimulation (tACS): a combined EEG-fNIRS study. Front Behav Neurosci 2018;12:67.
[86] Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444(7119):610–3.
[87] Jausovec N, Jausovec K. Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). Biol Psychol 2014;96:42–7.

[88] Lu H, Zhang Y, Huang P, Zhang Y, Cheng S, Zhu X. Transcranial electrical stimulation offers the possibility of improving teamwork among military pilots: a review. Front Neurosci 2022;16:931265.
[89] Benussi A, Cantoni V, Cotelli MS, Cotelli M, Brattini C, Datta A, et al. Exposure to gamma tACS in Alzheimer's disease: a randomized, double-blind, sham-controlled, crossover, pilot study. Brain Stimul 2021;14(3):531–40.
[90] Herrmann CS, Struber D, Helfrich RF, Engel AK. EEG oscillations: from correlation to causality. Int J Psychophysiol 2016;103:12–21.
[91] Brittain JS, Probert-Smith P, Aziz TZ, Brown P. Tremor suppression by rhythmic transcranial current stimulation. Curr Biol 2013;23(5):436–40.
[92] Anzak A, Tan H, Pogosyan A, Foltynie T, Limousin P, Zrinzo L, et al. Subthalamic nucleus activity optimizes maximal effort motor responses in Parkinson's disease. Brain 2012;135(Pt 9):2766–78.
[93] Florin E, Erasmi R, Reck C, Maarouf M, Schnitzler A, Fink GR, et al. Does increased gamma activity in patients suffering from Parkinson's disease counteract the movement inhibiting beta activity? Neuroscience 2013;237:42–50.
[94] Suppa A, Marsili L, Belvisi D, Conte A, Iezzi E, Modugno N, et al. Lack of LTP-like plasticity in primary motor cortex in Parkinson's disease. Exp Neurol 2011;227(2):296–301.
[95] Udupa K, Chen R. Theta burst stimulation to explore the sensory-motor integration of cortical circuits. Clin Neurophysiol 2014;125(11):2146.
[96] Guerra A, Asci F, D'Onofrio V, Sveva V, Bologna M, Fabbrini G, et al. Enhancing gamma oscillations restores primary motor cortex plasticity in Parkinson's disease. J Neurosci 2020;40(24):4788–96.
[97] Grover S, Nguyen JA, Viswanathan V, Reinhart RMG. High-frequency neuromodulation improves obsessive-compulsive behavior. Nat Med 2021;27(2):232–8.
[98] Schreglmann SR, Wang D, Peach RL, Li J, Zhang X, Latorre A, et al. Non-invasive suppression of essential tremor via phase-locked disruption of its temporal coherence. Nat Commun 2021;12(1):363.
[99] Ballo MT, Conlon P, Lavy-Shahaf G, Kinzel A, Vymazal J, Rulseh AM. Association of Tumor Treating Fields (TTFields) therapy with survival in newly diagnosed glioblastoma: a systematic review and meta-analysis. J Neuro Oncol 2023;164(1):1–9.
[100] Glas M, Ballo MT, Bomzon Z, Urman N, Levi S, Lavy-Shahaf G, et al. The impact of tumor treating fields on glioblastoma progression patterns. Int J Radiat Oncol Biol Phys 2022;112(5):1269–78.
[101] Giladi M, Schneiderman RS, Voloshin T, Porat Y, Munster M, Blat R, et al. Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. Sci Rep 2015;5:18046.
[102] Chen D, Le SB, Hutchinson TE, Calinescu AA, Sebastian M, Jin D, et al. Tumor Treating Fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma. J Clin Invest 2022;132(8).
[103] Darmani G, Bergmann TO, Butts Pauly K, Caskey CF, de Lecea L, Fomenko A, et al. Non-invasive transcranial ultrasound stimulation for neuromodulation. Clin Neurophysiol 2022;135:51–73.
[104] Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. PLoS One 2008;3(10):e3511.
[105] Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, et al. Transcranial pulsed ultrasound stimulates intact brain circuits. Neuron 2010;66(5):681–94.
[106] Sarica C, Nankoo JF, Fomenko A, Grippe TC, Yamamoto K, Samuel N, et al. Human Studies of Transcranial Ultrasound neuromodulation: a systematic review of effectiveness and safety. Brain Stimul 2022;15(3):737–46.
[107] Fomenko A, Chen KS, Nankoo JF, Saravanamuttu J, Wang Y, El-Baba M, et al. Systematic examination of low-intensity ultrasound parameters on human motor cortex excitability and behavior. Elife 2020;9.
[108] Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, et al. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. Nat Neurosci 2014;17(2):322–9.
[109] Zeng K, Darmani G, Fomenko A, Xia X, Tran S, Nankoo JF, et al. Induction of human motor cortex plasticity by theta burst transcranial ultrasound stimulation. Ann Neurol 2022;91(2):238–52.
[110] Zhang Y, Ren L, Liu K, Tong S, Yuan TF, Sun J. Transcranial ultrasound stimulation of the human motor cortex. iScience 2021;24(12):103429.
[111] Butler CR, Rhodes E, Blackmore J, Cheng X, Peach RL, Veldsman M, et al. Transcranial ultrasound stimulation to human middle temporal complex improves visual motion detection and modulates electrophysiological responses. Brain Stimul 2022;15(5):1236–45.
[112] Kuhn T, Spivak NM, Dang BH, Becerra S, Halavi SE, Rotstein N, et al. Transcranial focused ultrasound selectively increases perfusion and modulates functional connectivity of deep brain regions in humans. Front Neural Circuits 2023;17:1120410.
[113] Samuel N, Zeng K, Harmsen IE, Ding MYR, Darmani G, Sarica C, et al. Multi-modal investigation of transcranial ultrasound-induced neuroplasticity of the human motor cortex. Brain Stimul 2022;15(6):1337–47.
[114] Shamli Oghli Y, Grippe T, Arora T, Hoque T, Darmani G, Chen R. Mechanisms of theta burst transcranial ultrasound induced plasticity in the human motor cortex. Brain Stimul 2023;16(4):1135–43.
[115] Yaakub SN, White TA, Roberts J, Martin E, Verhagen L, Stagg CJ, et al. Transcranial focused ultrasound-mediated neurochemical and functional connectivity changes in deep cortical regions in humans. Nat Commun 2023;14(1):5318.
[116] Yoo S, Mittelstein DR, Hurt RC, Lacroix J, Shapiro MG. Focused ultrasound excites cortical neurons via mechanosensitive calcium accumulation and ion channel amplification. Nat Commun 2022;13(1):493.
[117] Deveci E, Akbas F, Ergun AS, Kurtulmus A, Kocak AB, Boyraz RK, et al. The effects of transcranial focused ultrasound stimulation of nucleus accumbens on neuronal gene expression and brain tissue in high alcohol-preferring rats. Mol Neurobiol 2023;60(2):1099–116.
[118] Zhai Z, Ren L, Song Z, Xiang Q, Zhuo K, Zhang S, et al. The efficacy of low-intensity transcranial ultrasound stimulation on negative symptoms in schizophrenia: a double-blind, randomized sham-controlled study. Brain Stimul 2023;16(3):790–2.
[119] Beisteiner R, Matt E, Fan C, Baldysiak H, Schonfeld M, Philippi Novak T, et al. Transcranial pulse stimulation with ultrasound in alzheimer's disease-A new navigated focal brain therapy. Adv Sci 2020;7(3):1902583.
[120] Wang Y, Li F, He MJ, Chen SJ. The effects and mechanisms of transcranial ultrasound stimulation combined with cognitive rehabilitation on post-stroke cognitive impairment. Neurol Sci 2022;43(7):4315–21.
[121] Matt E, Dorl G, Beisteiner R. Transcranial pulse stimulation (TPS) improves depression in AD patients on state-of-the-art treatment. Alzheimers Dement (N Y). 2022;8(1):e12245.
[122] Cheung T, Li TMH, Ho YS, Kranz G, Fong KNK, Leung SF, et al. Effects of transcranial pulse stimulation (TPS) on adults with symptoms of depression-A pilot randomized controlled trial. Int J Environ Res Publ Health 2023;20(3).
[123] Oh J, Ryu JS, Kim J, Soojeong K, Soojeong HS, Kim KR, et al. Effect of low-intensity transcranial focused ultrasound stimulation in patients with major depressive disorder: a randomized, double-blind, sham-controlled clinical trial SSRN, 20232023 Available from: https://www.ssrn.com/abstract=4505487.
[124] Cain JA, Spivak NM, Coetzee JP, Crone JS, Johnson MA, Lutkenhoff ES, et al. Ultrasonic thalamic stimulation in chronic disorders of consciousness. Brain Stimul 2021;14(2):301–3.
[125] Lee CC, Chou CC, Hsiao FJ, Chen YH, Lin CF, Chen CJ, et al. Pilot study of focused ultrasound for drug-resistant epilepsy. Epilepsia 2022;63(1):162–75.
[126] Hameroff S, Trakas M, Duffield C, Annabi E, Gerace MB, Boyle P, et al. Transcranial ultrasound (TUS) effects on mental states: a pilot study. Brain Stimul 2013;6(3):409–15.
[127] Samuel N, Ding MYR, Sarica C, Darmani G, Harmsen IE, Grippe T, et al. Accelerated transcranial ultrasound neuromodulation in Parkinson's disease: a pilot study. Mov Disord 2023;38(12):2209–16.
[128] Darmani G, Arora T, Drummond NM, Cortez Grippe T, Saha U, Munhoz RP, et al. Thalamocortical spectral and coherence characteristics for clinically effective and ineffective spinal cord stimulation in chronic pain: a case study. Clin Neurophysiol 2023;146:18–20.
[129] Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk HJ, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell 2017;169(6):1029–1041 e16.
[130] Grossman N, Okun MS, Boyden ES. Translating temporal interference brain stimulation to treat neurological and psychiatric conditions. JAMA Neurol 2018;75(11):1307–8.
[131] Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol 2019;15(3):148–60.
[132] Furlanetti L, Raslan A, Khaleeq T, Hasegawa H, Tambirajoo R, Samuel M, et al. Fixed-life or rechargeable battery for deep brain stimulation: a prospective long-term study of patient's preferences. Stereotact Funct Neurosurg 2020;98(1):43–7.
[133] Sarica C, Iorio-Morin C, Aguirre-Padilla DH, Najjar A, Paff M, Fomenko A, et al. Implantable pulse generators for deep brain stimulation: challenges, complications, and strategies for practicality and longevity. Front Hum Neurosci 2021;15:708481.
[134] Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987;50(1-6):344–6.
[135] Jakobs M, Fomenko A, Lozano AM, Kiening KL. Cellular, molecular, and clinical mechanisms of action of deep brain stimulation-a systematic review on established indications and outlook on future developments. EMBO Mol Med 2019;11(4).
[136] Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. Prog Neurobiol 2015;133:27–49.
[137] Neumann WJ, Steiner LA, Milosevic L. Neurophysiological mechanisms of deep brain stimulation across spatiotemporal resolutions. Brain 2023;146(11):4456–68.
[138] Grill WM, Snyder AN, Miocinovic S. Deep brain stimulation creates an informational lesion of the stimulated nucleus. Neuroreport 2004;15(7):1137–40.
[139] Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 2010;68(4):521–34.
[140] Krauss JK, Lipsman N, Aziz T, Boutet A, Brown P, Chang JW, et al. Technology of deep brain stimulation: current status and future directions. Nat Rev Neurol 2021;17(2):75–87.
[141] Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nat Rev Neurol 2019;15(4):234–42.
[142] Lu G, Luo L, Liu M, Zheng Z, Zhang B, Chen X, et al. Outcomes and adverse effects of deep brain stimulation on the ventral intermediate nucleus in patients with essential tremor. Neural Plast 2020;2020:2486065.
[143] Moro E, LeReun C, Krauss JK, Albanese A, Lin JP, Walleser Autiero S, et al. Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis. Eur J Neurol 2017;24(4):552–60.

[144] Harmsen IE, Elias GJB, Beyn ME, Boutet A, Pancholi A, Germann J, et al. Clinical trials for deep brain stimulation: current state of affairs. Brain Stimul 2020;13(2):378–85.
[145] Davidson B, Gouveia FV, Rabin JS, Giacobbe P, Lipsman N, Hamani C. Deep brain stimulation for treatment-resistant depression: current status and future perspectives. Expet Rev Med Dev 2020;17(5):371–3.
[146] Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos JM, Munro C, Oh E, et al. A phase II study of fornix deep brain stimulation in mild alzheimer's disease. J Alzheimers Dis 2016;54(2):777–87.
[147] Davidson B, Giacobbe P, George TP, Nestor SM, Rabin JS, Goubran M, et al. Deep brain stimulation of the nucleus accumbens in the treatment of severe alcohol use disorder: a phase I pilot trial. Mol Psychiatr 2022;27(10):3992–4000.
[148] Machado A, Rezai AR, Kopell BH, Gross RE, Sharan AD, Benabid AL. Deep brain stimulation for Parkinson's disease: surgical technique and perioperative management. Mov Disord 2006;21(Suppl 14):S247–58.
[149] Machado AG, Baker KB, Plow E, Malone DA. Cerebral stimulation for the affective component of neuropathic pain. Neuromodulation 2013;16(6):514–8.
[150] Nair DR, Laxer KD, Weber PB, Murro AM, Park YD, Barkley GL, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology 2020;95(9):e1244–56.
[151] He S, Baig F, Mostofi A, Pogosyan A, Debarros J, Green AL, et al. Closed-Loop deep brain stimulation for essential tremor based on thalamic local field potentials. Mov Disord 2021;36(4):863–73.
[152] Gilron R, Little S, Perrone R, Wilt R, de Hemptinne C, Yaroshinsky MS, et al. Long-term wireless streaming of neural recordings for circuit discovery and adaptive stimulation in individuals with Parkinson's disease. Nat Biotechnol 2021;39(9):1078–85.
[153] Nakajima A, Shimo Y, Fuse A, Tokugawa J, Hishii M, Iwamuro H, et al. Case report: chronic adaptive deep brain stimulation personalizing therapy based on parkinsonian state. Front Hum Neurosci 2021;15:702961.
[154] Little S, Tripoliti E, Beudel M, Pogosyan A, Cagnan H, Herz D, et al. Adaptive deep brain stimulation for Parkinson's disease demonstrates reduced speech side effects compared to conventional stimulation in the acute setting. J Neurol Neurosurg Psychiatry 2016;87(12):1388–9.
[155] Swann NC, de Hemptinne C, Miocinovic S, Qasim S, Wang SS, Ziman N, et al. Gamma oscillations in the hyperkinetic state detected with chronic human brain recordings in Parkinson's disease. J Neurosci 2016;36(24):6445–58.
[156] Ricciardi L, Fischer P, Mostofi A, Tinkhauser G, Torrecillos F, Baig F, et al. Neurophysiological correlates of trait impulsivity in Parkinson's disease. Mov Disord 2021;36(9):2126–35.
[157] Johnson V, Wilt R, Gilron R, Anso J, Perrone R, Beudel M, et al. Embedded adaptive deep brain stimulation for cervical dystonia controlled by motor cortex theta oscillations. Exp Neurol 2021;345:113825.
[158] Davidson B, Scherer M, Giacobbe P, Nestor S, Abrahao A, Rabin JS, et al. Mood biomarkers of response to deep brain stimulation in depression measured with a sensing system. Brain Stimul 2023;16(5):1371–3.
[159] Scangos KW, Khambhati AN, Daly PM, Makhoul GS, Sugrue LP, Zamanian H, et al. Closed-loop neuromodulation in an individual with treatment-resistant depression. Nat Med 2021;27(10):1696–700.
[160] Jimenez-Shahed J. Device profile of the percept PC deep brain stimulation system for the treatment of Parkinson's disease and related disorders. Expet Rev Med Dev 2021;18(4):319–32.
[161] Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 2008;63(4):762–70. discussion 70.
[162] Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. Brain Res 2014;1569:19–31.
[163] Sarica C, Zemmar A, Yousefi O, Yang AC, Uzuner A, Sheng Z, et al. Spinal cord stimulation for Parkinson's disease: a systematic review and meta-analysis of pain and motor outcomes. Stereotact Funct Neurosurg 2023;101(4):244–53.
[164] Mekhail NA, Mathews M, Nageeb F, Guirguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. Pain Pract 2011;11(2):148–53.
[165] Guzzi G, Della Torre A, La Torre D, Volpentesta G, Stroscio CA, Lavano A, et al. Spinal cord stimulation in chronic low back pain syndrome: mechanisms of modulation, technical features and clinical application. Healthcare (Basel) 2022;10(10).
[166] Sheldon B, Staudt MD, Williams L, Harland TA, Pilitsis JG. Spinal cord stimulation programming: a crash course. Neurosurg Rev 2021;44(2):709–20.
[167] Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150(3699):971–9.
[168] Stephens KE, Chen Z, Sivanesan E, Raja SN, Linderoth B, Taverna SD, et al. RNA-seq of spinal cord from nerve-injured rats after spinal cord stimulation. Mol Pain 2018;14. 1744806918817429.
[169] De Ridder D, Lenders MW, De Vos CC, Dijkstra-Scholten C, Wolters R, Vancamp T, et al. A 2-center comparative study on tonic versus burst spinal cord stimulation: amount of responders and amount of pain suppression. Clin J Pain 2015;31(5):433–7.
[170] Mekhail N, Levy RM, Deer TR, Kapural L, Li S, Amirdelfan K, et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. Lancet Neurol 2020;19(2):123–34.
[171] Holsheimer J, den Boer JA, Struijk JJ, Rozeboom AR. MR assessment of the normal position of the spinal cord in the spinal canal. AJNR Am J Neuroradiol 1994;15(5):951–9.
[172] Mekhail N, Levy RM, Deer TR, Kapural L, Li S, Amirdelfan K, et al. Durability of clinical and quality-of-life outcomes of closed-loop spinal cord stimulation for chronic back and leg pain: a secondary analysis of the evoke randomized clinical trial. JAMA Neurol 2022;79(3):251–60.
[173] Seanez I, Capogrosso M. Motor improvements enabled by spinal cord stimulation combined with physical training after spinal cord injury: review of experimental evidence in animals and humans. Bioelectron Med 2021;7(1):16.
[174] Benavides FD, Jo HJ, Lundell H, Edgerton VR, Gerasimenko Y, Perez MA. Cortical and subcortical effects of transcutaneous spinal cord stimulation in humans with tetraplegia. J Neurosci 2020;40(13):2633–43.
[175] Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, et al. Recovery of over-ground walking after chronic motor complete spinal cord injury. N Engl J Med 2018;379(13):1244–50.
[176] Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. Nature 2018;563(7729):65–71.
[177] Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nat Med 2018;24(11):1677–82.
[178] de Freitas RM, Sasaki A, Sayenko DG, Masugi Y, Nomura T, Nakazawa K, et al. Selectivity and excitability of upper-limb muscle activation during cervical transcutaneous spinal cord stimulation in humans. J Appl Physiol 2021;131(2):746–59 (1985).
[179] Milekovic T, Moraud EM, Macellari N, Moerman C, Raschella F, Sun S, et al. A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease. Nat Med 2023;29(11):2854–65.
[180] Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res 2018;11:203–13.
[181] Bottomley JM, LeReun C, Diamantopoulos A, Mitchell S, Gaynes BN. Vagus nerve stimulation (VNS) therapy in patients with treatment resistant depression: a systematic review and meta-analysis. Compr Psychiatr 2019;98:152156.
[182] Navas M, Navarrete EG, Pascual JM, Carrasco R, Nunez JA, Shakur SF, et al. Treatment of refractory epilepsy in adult patients with right-sided vagus nerve stimulation. Epilepsy Res 2010;90(1-2):1–7.
[183] Elliott RE, Rodgers SD, Bassani L, Morsi A, Geller EB, Carlson C, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. J Neurosurg Pediatr 2011;7(5):491–500.
[184] Smyth MD, Tubbs RS, Bebin EM, Grabb PA, Blount JP. Complications of chronic vagus nerve stimulation for epilepsy in children. J Neurosurg 2003;99(3):500–3.
[185] Wheless JW, Gienapp AJ, Ryvlin P. Vagus nerve stimulation (VNS) therapy update. Epilepsy Behav 2018.
[186] Foley JO, DuBois FS. Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory to motor fibers. J Comp Neurol 1937;67(1):49–67.
[187] Hachem LD, Wong SM, Ibrahim GM. The vagus afferent network: emerging role in translational connectomics. Neurosurg Focus 2018;45(3):E2.
[188] Bonaz B, Picq C, Sinniger V, Mayol JF, Clarencon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. Neuro Gastroenterol Motil 2013;25(3):208–21.
[189] Bodin C, Aubert S, Daquin G, Carron R, Scavarda D, McGonigal A, et al. Responders to vagus nerve stimulation (VNS) in refractory epilepsy have reduced interictal cortical synchronicity on scalp EEG. Epilepsy Res 2015;113:98–103.
[190] Krahl SE, Clark KB. Vagus nerve stimulation for epilepsy: a review of central mechanisms. Surg Neurol Int 2012;3(Suppl 4):S255–9.
[191] Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia 1994;35(3):616–26.
[192] Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51(1):48–55.
[193] Morris 3rd GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology 1999;53(8):1731–5.
[194] Bajbouj M, Merkl A, Schlaepfer TE, Frick C, Zobel A, Maier W, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. J Clin Psychopharmacol 2010;30(3):273–81.
[195] Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, et al. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. Am J Psychiatr 2017;174(7):640–8.
[196] Perez-Carbonell L, Faulkner H, Higgins S, Koutroumanidis M, Leschziner G. Vagus nerve stimulation for drug-resistant epilepsy. Practical Neurol 2020;20(3):189–98.
[197] Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure 2014;23(7):496–505.
[198] Tzadok M, Harush A, Nissenkorn A, Zauberman Y, Feldman Z, Ben-Zeev B. Clinical outcomes of closed-loop vagal nerve stimulation in patients with refractory epilepsy. Seizure 2019;71:140–4.
[199] Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatr 2005;58(5):347–54.
[200] Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology 2008;33(2):368–77.
[201] Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL, et al. Vagus nerve stimulation therapy randomized to different amounts of

electrical charge for treatment-resistant depression: acute and chronic effects. Brain Stimul 2013;6(4):631–40.
[202] Kamel LY, Xiong W, Gott BM, Kumar A, Conway CR. Vagus nerve stimulation: an update on a novel treatment for treatment-resistant depression. J Neurol Sci 2022; 434:120171.
[203] Tracey KJ. The inflammatory reflex. Nature 2002;420(6917):853–9.
[204] Burneo JG, Faught E, Knowlton R, Morawetz R, Kuzniecky R. Weight loss associated with vagus nerve stimulation. Neurology 2002;59(3):463–4.
[205] Badran BW, Yu AB, Adair D, Mappin G, DeVries WH, Jenkins DD, et al. Laboratory administration of transcutaneous auricular vagus nerve stimulation (taVNS): technique, targeting, and considerations. J Vis Exp 2019;143.
[206] Austelle CW, O'Leary GH, Thompson S, Gruber E, Kahn A, Manett AJ, et al. A comprehensive review of vagus nerve stimulation for depression. Neuromodulation 2022;25(3):309–15.
[207] Butt MF, Albusoda A, Farmer AD, Aziz Q. The anatomical basis for transcutaneous auricular vagus nerve stimulation. J Anat 2020;236(4):588–611.