

Review

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

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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.

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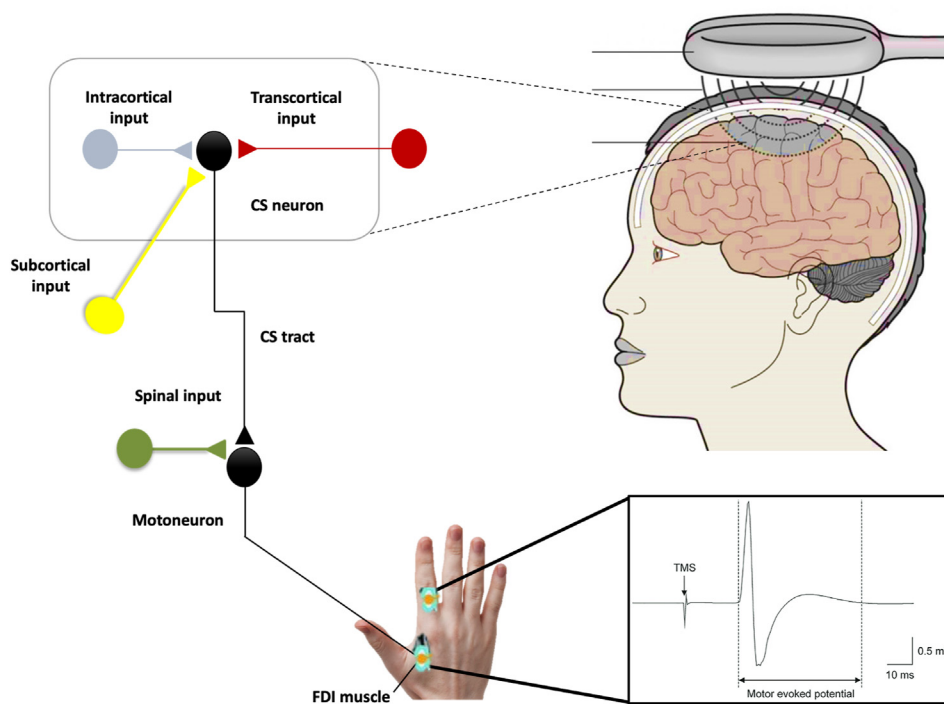


Fig. 1. Schematic representation of transcranial magnetic stimulation demonstrating the magnetic field generated with a magnetic coil placed over the hand area of the primary motor cortex. This, in turn, induces electrical current to activate cortical circuits (lightning bolts indicating the electromagnetic 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: SIC1, 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 GABA_A receptor activity or block Na⁺ and Ca²⁺ 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 μ s, 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].

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

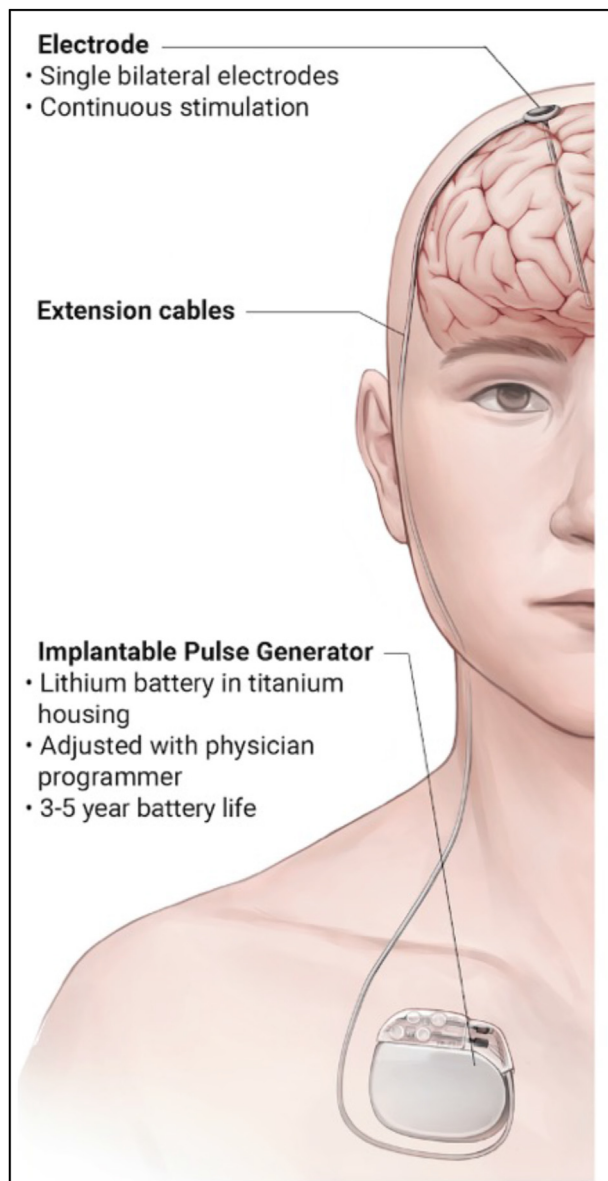


Fig. 2. Typical Deep Brain Stimulation (DBS) setup (Adapted with permission from Krauss et al., 2021 [140]).

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 paresthesias in the patient's painful dermatome—a sign that the SCS is potentially blocking painful sensory transmission. However, newer paresthesia-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 selectivity 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 coeruleus, 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].

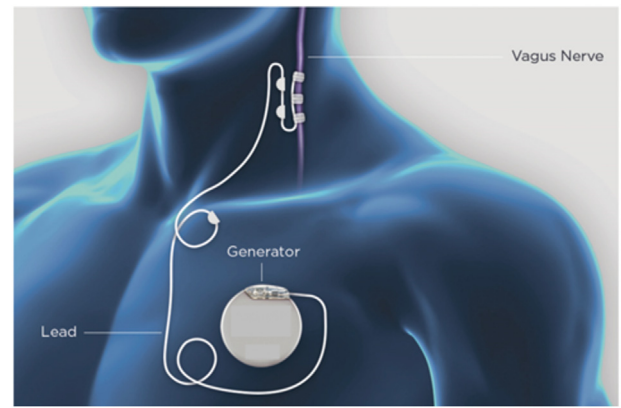


Fig. 4. Typical vagus nerve stimulation implantable system. (Adapted with permission from Wheless et al., 2018 [185]).

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 μ s, 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 coeruleus 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).

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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.

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