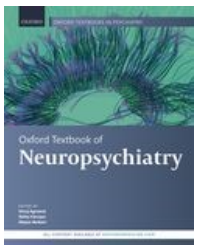

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CHAPTER

41 Neurostimulation technologies in neurology and neuropsychiatry

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Abstract

Novel neurostimulation technologies are gaining momentum in both basic and applied clinical research and have the potential to become an important tool in the management of a range of neurological and neuropsychiatric conditions. This chapter reviews some of these technologies and summarizes their current applications. The mechanisms of therapeutic effect remain speculative, but contributions from computational, imaging, and behavioural neurosciences, along with potential insights from immunology, are gradually increasing our understanding. This area of brain research and therapeutics is set to exponentially increase in relevance and importance, with possible advances in therapeutic applications in more neurological and neuropsychiatric disorders. Clinicians need to be aware and be informed about this changing clinical horizon.

Keywords: Neurostimulation, neuromodulation, non-invasive brain stimulation, occipital nerve stimulation, transcranial nerve stimulation, transcranial magnetic stimulation, vestibular stimulation, vagal nerve stimulation, deep brain stimulation

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Introduction

Neurostimulation technologies comprise distinctive methods for invasively or non-invasively *intervening* in brain function, although defining exactly what *the intervention* is and what the *intervention is doing* at either a neuronal or a cellular level is not obviously clear and awaits the outcome of further current and future research effort.

The broad term ‘neurostimulation technologies’ encompasses stem cell therapy, tissue engineering, and neural repair and regeneration, but in a brief review such as this, it simply is not possible to cover all these approaches. It is important to note that the terms ‘neurostimulation’ and ‘neuromodulation’, though used interchangeably in practice, do not actually mean the same thing. *Neuromodulation* is defined by the International Neuromodulation Society as ‘the alteration of nerve activity (*sic firing patterns*) through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites’ (International Neuromodulation Society, 2016). *Neurostimulation* means induction of these firing patterns (although, of course, it is likely that some neurostimulation techniques have the potential to be neuromodulatory as well). Neurostimulation has generally been the preserve of invasive techniques, but induction of the neural tissue of the central nervous system (CNS), which includes the brain, spinal cord, and peripheral nerves, can now also be done using non-invasive techniques, the most important ones of which will be described in this chapter.

Historical roots and future directions

The history of interest in neurostimulation methods is not new. Records dating to Roman times described the use of electric fish for the treatment of pain by the Roman physician Scribonius Largus (43–48 AD). In later centuries, notable contributions were made by Galvani (1791), Volta (1792), and Aldini (1804) (Utz et al., 2010). Readers are recommended the excellent review by Grabherr et al. (2015) for a detailed historical account.

Since 1995, the number of relevant published articles in major US and UK print media sources related to neurostimulation has seen an exponential increase (Racine et al., 2007). The commercial market in neurostimulation devices is set to reach an estimated $10.8 billion by 2022 (International Neuromodulation Society, 2016).

Although drugs and surgery have been the predominant approach to managing disease since the last century, their limitations are at least one reason driving the current interest in novel neurostimulation technologies. In the field of psychopharmacology, generations of antidepressants, antipsychotics, anxiolytics, and other classes of psychoactive drugs have still left some patients with neuropsychiatric and neurological disorders which are considered resistant to treatment or inadequately responsive. The adverse effects of drugs also limit tolerability for many patients. It is estimated that up to 20% of patients may not respond to treatment or become resistant to treatment over time, particularly in the context of progressive neurodegenerative disease (Danilov et al., 2014).

Further advances in drug treatment are also difficult to predict. New medicines are extremely expensive to research, develop, and deliver, with the time lag from basic research to approved clinical use often lengthy, up to 10–15 years. It is in this context that novel neurostimulation technologies are being seen as important for research and potentially offer a new dawn in neuropsychiatric therapeutics. The need for an understanding of cellular and systems-level processes has enabled researchers from across neuroscience to join the crusade. Hence the field is rapidly changing.

It is important to note that, in parallel with this interest, there has been an ongoing debate on the ethical implications of such new potential treatments (see, for example, Hariz et al., 2015; Heinrichs, 2012). While the ethics of using a new technology in conditions already refractory to treatment (e.g. severe dyskinesia in Parkinson’s disease), in which the main motivation is the therapeutic relief of an intolerable condition, seems relatively non-controversial, the possibility of using similar techniques for psychiatric disorders has raised ethical concerns beyond merely adverse effects and side effects. Should, for example, these methods, if effective, be used to treat anti-social behaviour, or for enhancing cognitive abilities (if that proves possible) in healthy individuals? Additionally, would it be ethical to use such techniques for military advantage in training future combat soldiers?

Perhaps understandably, as with any new thing, there seems to be an optimism about this research which is disproportionate to the currently available evidence. There is no doubt a need for in-depth consideration of the potential positive, and also the possible societal consequences, including fair access, and public involvement in shaping policy. Further reading is recommended at the end of the chapter to inform interested readers about this important debate.

As stated, this review cannot cover the whole field of novel neurotechnology, and as the field is rapidly evolving, the principal aim of the chapter will be to enable readers an acquaintance with this subject and an appreciation of its relevance for potential clinical benefits, likely future commercial impact, and possible current and future uses in an expanding range of neurological and psychiatric disorders.

The putative mechanisms of effect of neurostimulation are intriguing (e.g. McIntyre et al., 2004b) but remain speculative, and are a focus of intense research activity. This chapter will consider, albeit briefly, the most recent theories which touch on mechanisms of neural entrainment and immunomodulation.

What is neuronal stimulation?

Neuronal cell membranes consist of a phospholipid bilayer across which selective ion pumps, e.g. sodium (Na^+) and potassium (K^+), work to create a separation of charge, ultimately resulting in a resting cell membrane polarization where the intracellular potential is between 60 and 80 mV below the extracellular fluid and where the bilayer acts as the dielectric of a capacitor. Neuronal stimulation causes depolarization of part of the cell membrane. If this is enough to reduce the transmembrane potential to a threshold level, voltage-gated Na^+ ion channels open, creating a positive feedback loop that amplifies the small depolarization to a full reverse polarization of the membrane, creating an action potential. This, in turn, depolarizes the surrounding membrane and ultimately causes the action potential to propagate along the axon (Luan et al., 2014).

There are several dozen forms of neuronal stimulation currently undergoing research, development, and evaluation as potential interventions in neurological and psychiatric disorders (Danilov et al., 2014). These include electrical or magnetic stimulation, ultrasound, radio waves, and also optical stimulation, all of which can be used to alter the excitability of neural tissue.

This chapter considers neurostimulation technologies either being used or being developed for use in neurological, and psychiatric disorders. Invasive methods (i.e. those involving surgery) include deep brain stimulation (DBS), vagus nerve stimulation (VNS), and spinal cord stimulation. To a lesser extent, peripheral nerve stimulation (PNS) and occipital nerve stimulation (ONS) also involve surgical placement of electrical wires and electrodes subcutaneously.

There are a wide range of non-invasive neurostimulation methods. (*Non-invasive* in this context means non-surgical or non-penetrative through the skin). Examples of non-invasive neurostimulation methods include transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), transcutaneous electrical nerve stimulation (TENS), motor cortex stimulation (MCS), magnetic seizure therapy (MST), and caloric/galvanic vestibular stimulation (CVS/GVS), but this list is not exhaustive. The two most commonly used non-invasive techniques for neurostimulation are either via a direct current to the surface of the scalp using applied electrodes or via an electrical pulse through a magnetic coil placed over the scalp. The oldest, but not most novel, form of established non-invasive brain stimulation (NIBS)—electroconvulsive therapy (ECT)—merits a brief mention at this point.

In general adult psychiatric practice, the use of ECT is considered effective, even though the public perception of ECT is generally negative. However, in reality, ECT is a safe and efficacious treatment, particularly when

treatments for depression (and for other psychiatric disorders, e.g. psychosis) have failed and there is imminent and significant threat to physical and mental health.

Historically, ECT was first investigated by Bini and Cerletti in the 1930s. It remains the 'gold standard' for treatment-resistant depression (TRD). Electrode placement in ECT includes the traditional bilateral and right unilateral placements, and bifrontal and left anterior right temporal (LART) placements. Bitemporal lead placement induces a high level of seizure generalization and hence has high efficacy, but also more side effects, in particular headache and memory loss post-ECT (Akhtar et al., 2016). ECT delivery requires administration of anaesthesia and muscle relaxant to prevent movement. Hence the application of ECT can be a lengthy process, consuming a significant degree of medical and nursing time. Results are slow to appear, and ECT is by no means always successful, hence the need for other options (see Magnetic seizure therapy, p. 488).

Methods employing invasive brain stimulation

Deep brain stimulation

DBS is at present the most widely used form of invasive neurostimulation in neurosurgical practice for nearly all disorders—neurological and psychiatric (Holtzheimer et al., 2011; Kennedy et al., 2011). The procedure, which had its origins in France, around 1987, evolved as a technique for elective ablative and lesional procedures with heat probes applied to small areas of the brain. DBS has now become established as a technique for the implantation of electrode arrays into deep subcortical matter using image-guided stereotactic neurosurgical techniques (Nuffield, 2013). As well as a stereotactic head frame, software may be utilized for determining target coordinates and entry points for safe electrode trajectory to help minimize the risk of brain injury from haemorrhage.

Target placement of electrodes in DBS (unilateral and bilateral) depends on the condition being treated. DBS electrodes are connected to battery-driven stimulus generators placed subcutaneously under the chest wall (see Fig. 41.1). Stimulus parameters are determined by the condition being treated. Stimulation frequency (Hz), pulse width (μs), and voltage (V) are variable parameters. High-frequency DBS of the thalamus, globus pallidus interna (GPi), and subthalamic nucleus (STN) has been widely used as a treatment for motor symptoms of Parkinson's disease, in particular, treatment-resistant dyskinesias, and tremor. STN stimulation can result in immediate improvement of motor symptoms. It has been suggested that STN DBS appears to exhibit greater anti-parkinsonian effect than GPi DBS (Goto et al., 2004).

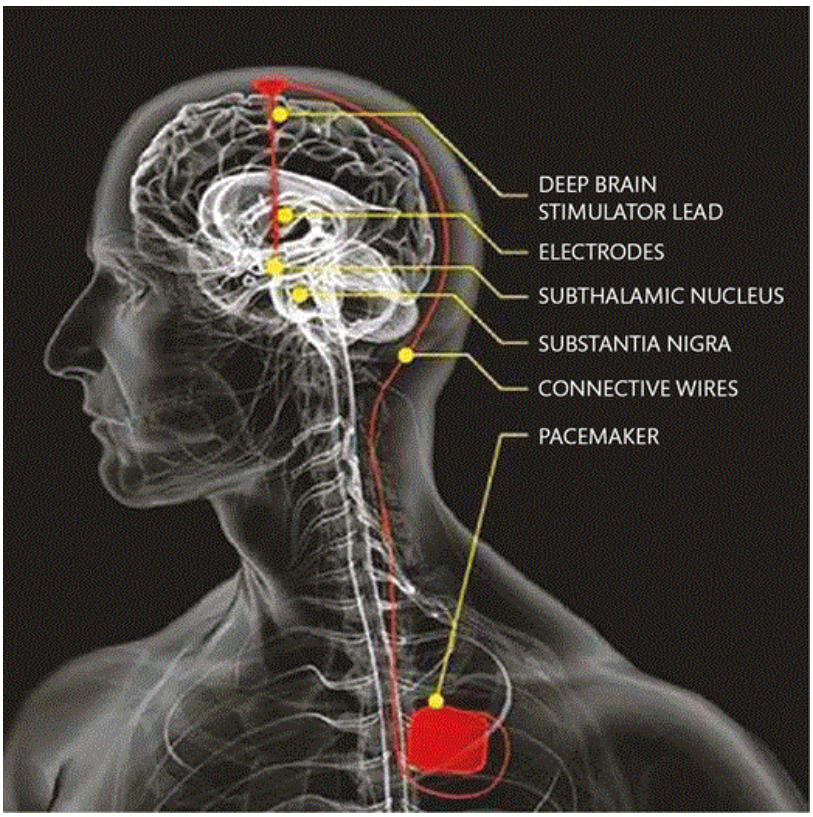

Fig. 41.1 Possible targets for DBS.

Courtesy of The Brain Stimulator, Inc. www.thebrainstimulator.com.

DBS surgery is expensive and invasive, with a risk of serious adverse events which may be anaesthesia- and/or surgery-related. Surgical risk includes intracranial haemorrhage, infection, and seizure. The DBS system may also 'malfunction', e.g. breakage or migration of the implant's wires or electrodes, leading to a possible need for additional surgery. Concerns have been raised about a possible increase in suicide rates after DBS in patients with movement disorders. It is important for preoperative assessment to include an assessment of risk to patients with a pre-existing history of depression (Marangell et al., 2007).

Other reported adverse effects of DBS include mania, cognitive dysfunction, anxiety, and change in personality (Nuffield, 2013, paragraph 2.53). The beneficial and adverse effects most likely depend on where the electrodes are placed but may also include other factors such as intensity and frequency of stimulus pulses.

NICE (UK) recommends that DBS for patients with drug-resistant Parkinson's disease should be assessed by a multidisciplinary team, including a neurologist, a neurosurgeon, and a psychologist, on a case-by-case basis (National Institute for Health and Care Excellence, 2003). DBS has been approved for use in Europe (but not in the UK) to treat chronic severe treatment-resistant obsessive–compulsive disorder (OCD). FDA approval for use in trials on OCD has also been granted (Nuffield, 2013, paragraph 2.44). DBS has also been tried for analgesic treatment-resistant neuropathic pain and is approved for this purpose by NICE, if treatment is assessed and carried out by specialists in chronic pain management. Novel applications of DBS continue to emerge, with case studies suggesting use in obesity, addiction, epilepsy, dementia, headache, and minimally conscious states, among others.

The mechanism of potential benefit of DBS remains speculative, but the most plausible theory relates to excitation (or inhibition) of neuronal cell bodies and axons in the near vicinity of the stimulating electrode, with possible onward effects on brain networks (Nuffield, 2013, paragraph 2.49). High-frequency DBS appears

to be the functional equivalent of a brain lesion. DBS is reversible (by switching the current off) and adjustable, but further research studies are clearly needed.

Vagal nerve stimulation

The vagus nerve, or tenth cranial nerve, subserves a number of autonomic regulatory functions, with an anatomical course from the brain to the thorax and abdomen. Constituted within the vagus are a mixture of myelinated and unmyelinated fibres of different sizes. Electrical stimulation of the vagus nerve (VNS) has been used for both neurological (epilepsy) and psychiatric disorders (depression).

VNS involves intermittent repeated stimulation of the left vagus nerve via electrical pulses generated by an implanted neurostimulator to a bipolar lead encircling the nerve in the neck (see Fig. 41.2) (Schlaepfer et al., 2010). Stimulation of the nerve non-invasively, though possible via the skin, had until recently insufficient evidence to support its use in this way for clinical purposes (Huston et al., 2007), but data is now emerging that lends potential promise. VNS is used for treatment-resistant epilepsy adjunctively with antiepileptic medications in tertiary epilepsy treatment centres. VNS for partial seizures has been evaluated as effective and well tolerated when used with one or more antiepileptic drugs in those with treatment-resistant epilepsy (Panebianco et al., 2015).

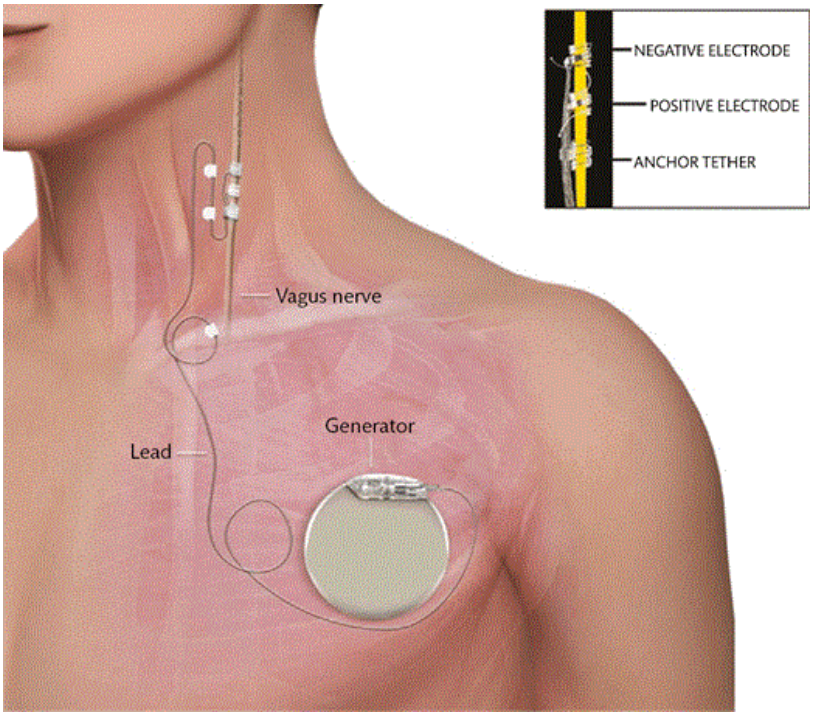

Fig. 41.2 Placement of VNS device.

Reproduced with permission from Verrier, R.L. Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial. *Epilepsy & Behavior*, 62: 85–89. © 2016 The Authors. Published by Elsevier Inc. https://doi.org/10.1016/j.yebeh.2016.06.016.

Complications of VNS surgery appear minimal, and excluding surgical complications (wound infection, rarely left vocal cord paresis, and temporary asystole), the main side effects reported in the acute period are voice alteration, cough, pain, and dyspnoea (in which stimulation intensity is considered a relevant factor after the acute period) (Schlaepfer et al., 2010).

With regard to the use of VNS for TRD, in 2005, the US FDA approved treatment for patients with chronic or recurrent depression (unipolar or bipolar) if there is failed response to at least four antidepressant trials. Hypomania and frank mania have been reported as adverse events, particularly in patients with a prior history of bipolar disorder. Despite having a licensed indication, VNS for depression is rarely used in clinical practice in the UK. NICE only recommends VNS for TRD in rare cases (National Institute for Health and Care Excellence, 2009). Further research is recommended, as evidence on safety and efficacy was considered *inadequate in quality and quantity* by NICE when assessed in 2009.

In TRD outpatients, VNS treatment appears to have improved both depression and sleep (Armitage et al., 2003), as evidenced in sleep EEGs by decreased awake time, decreased stage 1 sleep, and increased stage 2 sleep (although these results did not achieve statistical significance).

Occipital nerve stimulation

A large number of headache syndromes are resistant to treatment with medication alone. For such individuals, there may exist the possibility of relief with invasive stimulation therapy, e.g. ONS.

ONS involves subcutaneous insertion of a stimulating lead in the occipital region of the cranium. Rather than direct contact with the occipital nerve, the lead provides several metallic contact points which generate a 'field' of stimulation. Although the mechanism of effect is not fully understood, research with, for example, PET imaging has suggested brainstem activation in patients treated with ONS (Trentman et al., 2016). Modest benefits have been reported in chronic migraine (Reed et al., 2010) and cluster headache (Walter and Kaube, 2012). However, due to the lack of sufficiently well-designed and powered studies employing a sham condition and randomization, use of ONS is currently limited to the most refractory cases, usually as part of research studies. NICE has stated that ONS for intractable chronic migraine may have short-term efficacy, but evidence for longer-term benefit is lacking. Its clinical use in the UK hence remains limited (National Institute for Health and Care Excellence, 2013). It should be noted, however, that for some sufferers, ONS has been 'life-changing', although predicting beforehand who is likely to benefit the most is unclear.

Methods employing non-invasive neuronal stimulation

Transcranial direct current stimulation

Transcranial electrical stimulation (TES) has evolved into a number of different forms, as newer technologies have become incorporated. The various forms currently include transcranial pulsed current stimulation (tPCS), cranial electrical stimulation (CES), transcerebral electrotherapy (TCET), and neuro-electric therapy (NET), but also many others (Kumar and Sarkar, 2016). Irrespective of the method, the key feature remains, which is electrical stimulation of the brain transcranially using placed electrodes.

In tDCS, a low-intensity, constant current is applied to the cranium via scalp electrodes. The current used typically ranges from 0.5 to 2 mA, and the duration of stimulation between 5 and 40 minutes. The size of the electrodes (which varies from 3 to 100 cm^2) determines the current density (in A/m^2) and the total charge applied in coulombs (Tortella et al., 2015). The actual current delivered to the cortex also depends on other factors such as cephalic impedance.

The electric current applied can be subthreshold (i.e. sufficient to modulate neuronal excitability without triggering action potentials) but while still allowing for facilitation or inhibition of spontaneous neural activity, depending on the polarity of the electrodes. Anodal (+) stimulation induces an increase in cortical excitability, whereas cathodal (–) stimulation decreases cortical excitability. This is an oversimplification, as inward current

flow at the cortex (or anodal tDCS) generates hyperpolarization of apical dendritic regions of pyramidal cortical neurones and depolarization of somatic regions; and outward current flow (cathodal tDCS) results in somatic hyperpolarization and apical dendrite depolarization of pyramidal cortical neurones (Zaghi et al., 2010, as cited by Tortella et al., 2015). Stimulation effects may last beyond the stimulation period, possibly 30–120 minutes.

EEG studies have demonstrated that stimulation of a specific brain area (e.g. frontal) induces changes to oscillatory activity that synchronizes throughout the brain. Neural changes take place rapidly and persist for several minutes after stimulation has ended. This, however, still does not explain how these effects are transmitted and whether the observed clinical effects are mediated primarily through the area of the cortex being stimulated or secondarily via activation/inhibition of other cortical/subcortical areas. At the molecular level, it is also not known if the mechanism of action of tDCS is via the migration and collection of transmembrane proteins in a prolonged constant electric field or via steric/conformational changes in these proteins inducing functional effects (Zaghi et al., 2010). In addition to modulation of synaptic connectivity, the indications are that tDCS induces neuroplastic changes regulated by several neurotransmitter systems, including dopamine, acetylcholine, serotonin, and brain-derived neurotrophic factor (BDNF). Almost all tissues and cells are sensitive to electric fields, and therefore, tDCS might, in addition to neuronal tissue, elicit changes in non-neuronal brain tissue such as endothelial cells, lymphocytes, or glial cells (Lefaucheur et al., 2017).

Transcranial alternating current stimulation

Transcranial alternating current stimulation (tACS) uses a sine-wave electric field to induce oscillatory activity in stimulated regions. The main difference with tDCS is that the sine-wave field can lead to entrainment of a pattern of oscillatory activity at the frequency of stimulation. Studies using EEG and tACS suggest that stimulating in the alpha frequency band (8–12 Hz) can lead to enhancement at that frequency. The use of tACS has potential for tailoring stimulation, based on an individual's oscillatory activity, as ascertained by EEG. Synchronous neural activity is thought to be a way in which disparate neural regions communicate and are identified as part of the same functional network (Moseley et al., 2016). tACS is an experimental technology. The long-term effects of administering tACS are unknown. The effect of tACS might also be highly dependent on the state of the brain before stimulation. The use of tACS as a treatment for psychiatric disorders is currently extremely limited, but trials of tACS have been suggested for conditions associated with atypical oscillatory activity, e.g. in patients with auditory verbal hallucinations. Entraining or enhancing oscillatory activity in such patients, with scalp electrodes placed over the inferior frontal and superior temporal areas, may enhance gamma synchrony between these areas, which could improve functioning of forward-model systems, which ultimately contributes to experiencing inner speech as self-generated (Moseley et al., 2016).

Transcranial random noise stimulation (tRNS) is a variant of tACS, in which stimulation occurs at a randomly changing frequency (usually between 0.1 and 640 Hz). The therapeutic benefits of tRNS are a focus of further research activity, but studies are limited to single case reports, e.g. trials involving a patient with tinnitus and a patient with schizophrenia with negative symptoms. Moderate effect sizes have been shown, but further studies are clearly needed.

Transcranial magnetic stimulation

The technique of TMS is based on Faraday's principle of electromagnetic induction (1831). Simply stated, a varying magnetic field induces electrical current in a conductor placed within that field. In any nerve (or axon), neuronal activity occurs by movement of action potentials along the axon. Axons hence are electrical conductors.

This principle was exploited by Barker et al. (1985) who connected a wire coil to a source of electric current and placed the coil on the scalp over the motor cortex. They were able to demonstrate a motor action potential

following application of a single brief pulse of current through the coil. It was hypothesized (correctly) that neuronal activation was due to current induced in the brain tissue by the rapid, time-varying magnetic field. Subsequent investigation has confirmed that the electrical potential associated with this brain current is sufficient to depolarize neurones in the motor cortex and generate a motor evoked potential (MEP) (Leuchter et al., 2013).

Current methods of TMS employ coil electrodes placed on the scalp regions overlying the areas to be stimulated (see Fig. 41.3). Subjects are conscious; no anaesthetic is required, and serious side effects (e.g. seizure) are uncommon. TMS is delivered in high-frequency bursts for up to 190 s or in low-frequency trains (1 Hz) for up to 30 minutes, with the aim of modulating the activity in underlying brain networks. In general, low-frequency stimulation decreases excitability, and high-frequency stimulation increases neuronal excitability. Magnetic field intensity is in the order of 1–2 tesla.

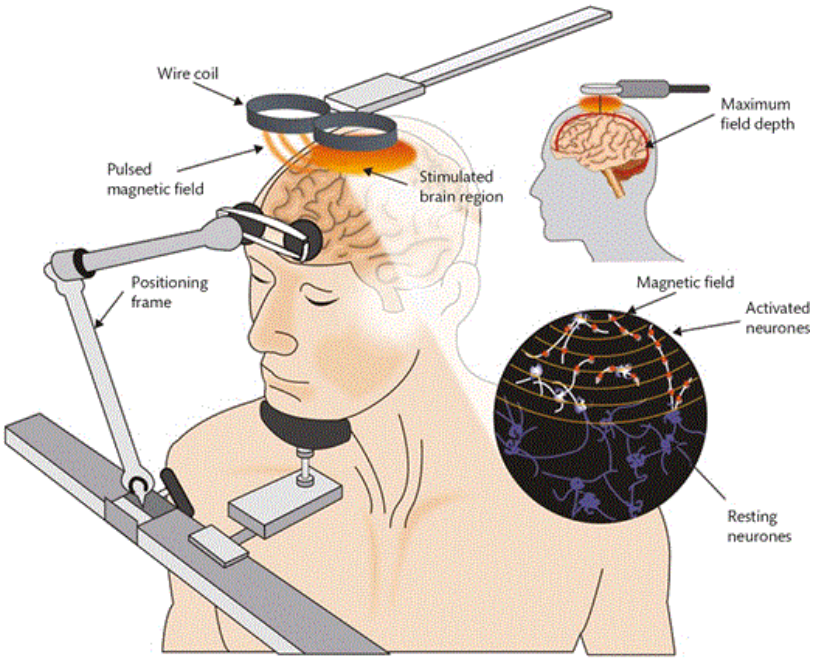

Fig. 41.3 Schematic showing the set-up for generic TMS.

Courtesy of The Brain Stimulator, Inc. www.thebrainstimulator.com.

TMS can be used with a single pulse (single-pulse TMS), as a pair of applied pulses with a variable interval (paired-pulse TMS), or with repeating pulses (repetitive; rTMS). The frequency of stimulation in rTMS can be varied, as with TMS. rTMS is considered to initiate changes to synaptic long-term depression (LTD) and long-potentiating (LTP) mechanisms, activation of feedback loops, and changes in neuronal excitability (Rokyta et al., 2015).

Low-frequency rTMS can induce nausea and painful axial spasms when applied to the premotor cortex in generalized secondary dystonia. Other side effects include induction of epileptic seizures (<1%), which is more likely with high-frequency rTMS (Rokyta et al., 2015).

Magnetic seizure therapy

The need for an electrical stimulus to induce seizures is both the main effect of ECT and its most fundamental limitation. Control over the spatial distribution and magnitude of intracerebral current density is limited by high skull impedance which shunts most of the electrical stimulus through the scalp and cerebrospinal fluid and away from the brain, resulting in widespread stimulation of cortical and subcortical brain regions. Individual differences in skull anatomy result in uncontrolled variation in intracerebral current density. Computer models support the view that current dissipation in ECT is considerable and that the electrode placement associated with the most severe cognitive side effects (bitemporal) is also the placement with higher shunting (Cretaz et al., 2015) and deeper brain stimulation.

Whereas, with ECT, generalized seizures are electrically induced by electrodes focally placed on the scalp, in MST, focal seizure activity is induced by applying TMS. The fact that TMS could induce seizures was initially considered a complication, but eventually the possibility of increasing the magnetic stimulus into the convulsive range as a deliberate action, under controlled conditions, in a patient under anaesthesia, as a treatment came to be explored. Since 2001, there have been several reports of MST in human subjects (Cretaz et al., 2015). The seizure induced by MST is quite different to that produced by ECT. Magnetic pulses, as employed by rTMS and MST, are capable of focusing stimulation to a specific area, since these pass unhindered into the brain without resistance and are not shunted through the scalp and skull, as with ECT. Whereas magnetic pulses penetrate only a few centimetres deep, electrical current can penetrate much deeper structures. Therefore, MST can focus stimulation on superficial regions of the cortex, while with ECT, electrical activity passes deep through the brain. In this way, MST may produce therapeutic benefits in the treatment of depression, as with ECT, but does not induce memory-related side effects, as there is no direct stimulation of medial temporal lobe structures.

Vestibular stimulation

The vestibular system is a target for therapeutic neuromodulation/stimulation. The system detects bodily movement and spatial orientation, and provides an early sensory reference frame for developing systems in the brainstem, cerebellum, and cortex. As a result, signals from the vestibular system have become deeply integrated with processes linked to balance, body schema, mood, well-being, and cognition, most notably memory. The vestibular system is unique among the senses due to the entirely multi-sensory nature of its cortical projections and its overlap with limbic, interoceptive, and cognitive networks.

The inner ear contains receptors for both the auditory and the vestibular systems. The bony labyrinth contains a series of communicating cavities which enclose the cochlea, the vestibule, and the semicircular canals. The three semicircular canals are perpendicular to each other and correspond to the axes of three-dimensional space. They are the lateral or horizontal canal, the superior or anterior canal, and the posterior or vertical canal (see Fig. 41.4). Together the semicircular canals detect head rotation. By contrast, the utricle and saccule detect linear movement of the head, including that associated with gravity.

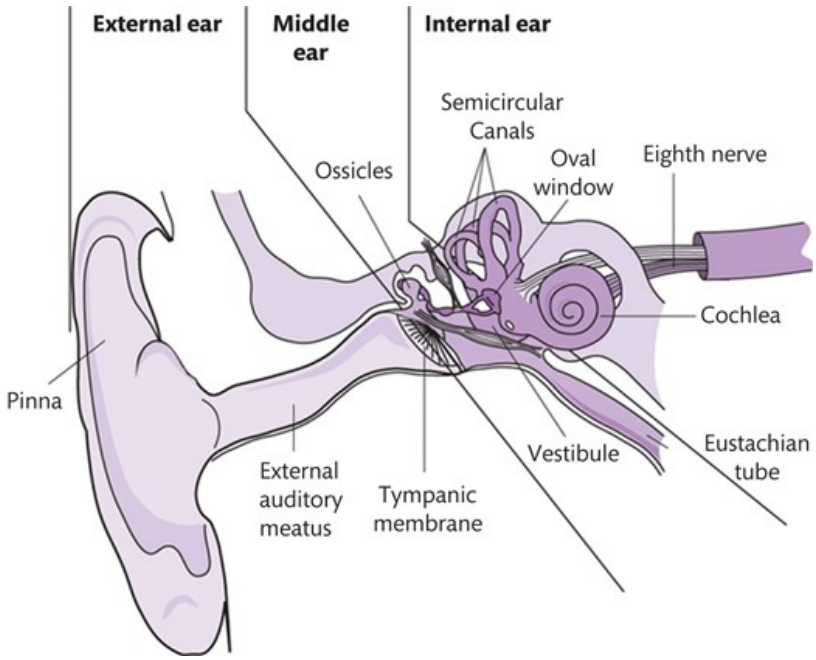

Fig. 41.4 Anatomy of the peripheral audio-vestibular system.

The vestibular nerve, a division of the vestibulocochlear nerve (cranial nerve VIII), conveys the primary sensory axons of the vestibular system. The central axonal processes enter the brainstem at the cerebellopontine angle, conveying information to the brainstem vestibular nuclei. Pathways from these nuclei project to the thalamus (vestibulothalamocortical pathway) and the cerebral cortex. The dominant vestibular area in man is in the posterior insula, corresponding to the monkey parieto-insular vestibular cortex (PIVC).

Methods of vestibular stimulation

Stimulation of the vestibular organs can be achieved using several different techniques (which include whole-body rotation and optokinetic stimulation). However, CVS and GVS have been the most investigated approaches. Commercial devices are available for GVS, and investigational devices are available for CVS. These devices have been used in patients with a range of disorders, including aphasia after stroke (Wilkinson et al., 2016), conversion disorder (Noll-Hussong et al., 2014), mania (Dodson et al., 2004), balance function (Goel et al., 2015), and many others (mostly as case reports).

Vestibular stimulation alters the release of excitatory and inhibitory neurotransmitters such as glutamate, noradrenaline, serotonin, and acetylcholine (Wilkinson et al., 2013). Neuroimaging studies indicate that vestibular stimulation strongly activates temporal and perisylvian areas, in particular the parieto-insular vestibular cortex (or PIVC, as known in the monkey brain), while deactivating visual areas (Noll-Hussong et al., 2014). The ability of vestibular stimulation to activate so many diffuse, ascending pathways sets it apart from all other pharmacological and neuromodulatory procedures which are non-endogenous and chemically/anatomically localized. A further advantage over other techniques is that the site of stimulation remains unchanged across disease types and individuals. This simplifies administration and makes it especially amenable to home-based and portable use.

Caloric vestibular stimulation

CVS introduces warm or cool temperatures into the external ear canal. Traditionally, ice-cold water has been used to assess brainstem function in unconscious and unresponsive patients, although warmer currents are effective too. Local temperature changes create convection currents in the vestibular endolymph, which deflect the cupula within the ipsilateral horizontal semicircular canal, which, in turn, alters the firing rate of the vestibulocochlear nerve. This, in turn, elicits a widespread haemodynamic response across cortical and subcortical areas of the brain. Unlike tDCS and other forms of TES, patients with electronic implants and certain types of metal plates are not contraindicated.

In the case of expressive and receptive aphasia after a left cerebral stroke, CVS daily for 20 minutes over 4 weeks (20 days) resulted in variable degrees of improved response in three of the four patients investigated by Wilkinson et al., as suggested by outcome measures such as picture naming, sentence repetition, and auditory word discrimination. The speculated mechanism of improvement was suggested as CVS increasing blood flow to left hemispheric language networks, perhaps resulting in increased metabolic activity, with reactivation and reintegration of injured cortical areas (Wilkinson et al., 2013).

In a single case report, by Noll-Hussong , et al. (2014), a patient with a psychogenic movement disorder of 2 years standing, resistant to improvement with conventional treatments, showed immediate and sustained relief from his functional disability following left caloric water irrigation at 30°C for 20 s. The effect lasted several hours, but only at the first trial, and not subsequently. The possibility of ‘suggestion’ abetting apparent recovery cannot be ruled out, although the authors also speculated on more elaborate vestibular effects such as activation of thalamocortical mechanisms which may reintegrate impaired cortical regions.

The case described by Dodson (2004) has similar intriguing elements. A female patient with long-standing bipolar affective disorder was admitted to a psychiatric ward in a state of manic relapse. Her condition had some history of treatment resistance. Treatment with left caloric water irrigation at 4°C, over 2–3 minutes, resulted in the patient experiencing an immediate improvement in her symptoms of mania which lasted approximately 24 hours, before symptoms returned. Repetition of the procedure resulted in further partial recovery, but still with a gradual return to baseline manic symptoms. Once again, suggestion may have had a role to play in this case, but potential activation of vestibular-activated mood circuits involving the basal ganglia, insula, cingulate gyrus, and prefrontal and parieto-temporal regions has also been speculated.

A study in healthy volunteers assessed the effect of CVS on processing of affective information using a Go/NoGo task, in which participants were given cold left or right ear CVS (20°C) or sham stimulation (37°C). Positive or negative pictures were presented as targets requiring responses to targets (Go) and withholding of responses to distractors (NoGo). Positive mood ratings decreased during left ear CVS, when compared to sham stimulation, with no effect seen after right ear CVS. Affective control improved during right ear CVS when viewing positive stimuli but decreased during left ear CVS when compared to sham stimulation (Preuss, 2014). The authors concluded that activating left hemispheric vestibular areas by means of right ear CVS may interact with prefrontal emotional networks specifically for emotionally positive stimuli. Asymmetries in the effects of CVS have also been noted in experiments targeting vision, cognition, and attention.

In various other small-scale studies, repeated daily sessions of CVS have been associated with clinically relevant improvements in awareness and voluntary behaviour in patients in minimally conscious states (Vanzan et al., 2017), and in motor and non-motor features of Parkinson’s disease (Wilkinson et al., 2016).

Galvanic vestibular stimulation

GVS is transmitted via two electrodes placed over the mastoid processes (see Fig. 41.5). GVS stimulates and/or inhibits all peripheral afferents of both the semicircular canals and the otoliths. The type of stimulation depends on current flow. Modern devices deliver currents in the range of 0–3 mA. The usual maximum current is 5 mA to avoid skin irritation and the risk of burns. The advantage of GVS over CVS is that it allows stimulation to be delivered in brief, more tightly controlled waveforms (Grabherr et al., 2015), and GVS also has been shown to be clinically efficacious at subthreshold levels (typically <0.5 mA) which are well tolerated and possible to experimentally blind.

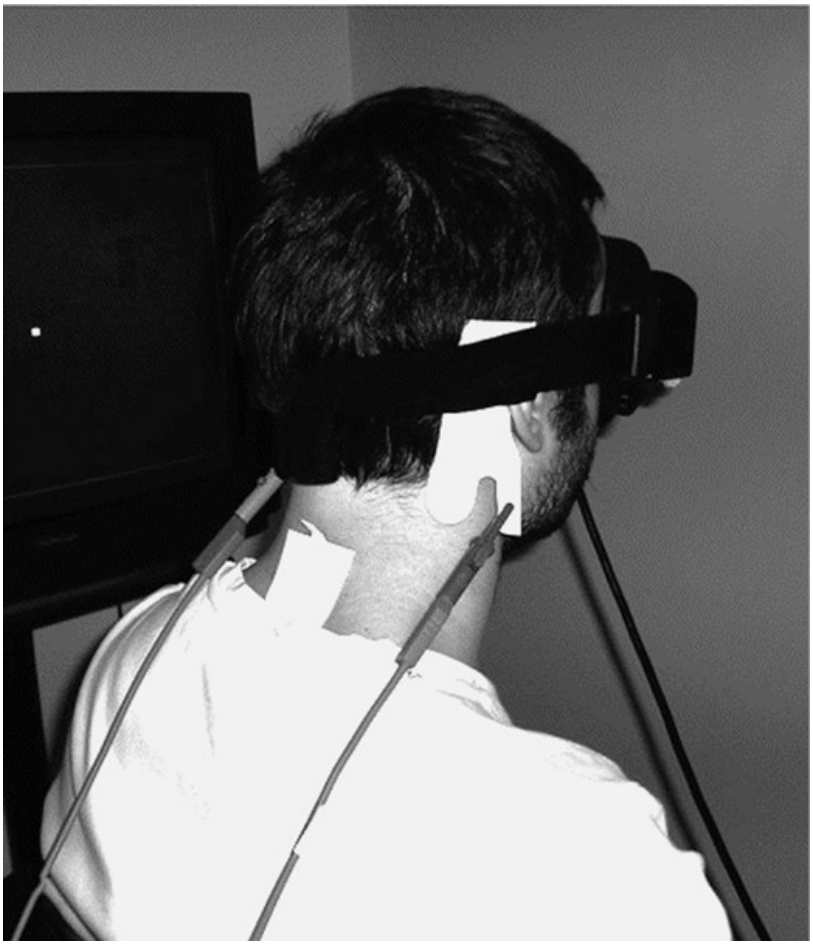

Fig. 41.5 Method of bilateral galvanic stimulation.

GVS is applied through very large surface electrodes (60–90 mm^2) placed over the mastoids, with care to ensure good, clean skin contact. GVS provides a weak current which acts at the spike trigger zone of vestibular afferents, rather than causing membrane depolarization. Maintained GVS generates a series of action potentials (which adapt) during the course of direct current stimulation (Curthoys et al., 2012). GVS produces complex oculomotor, perceptual, and postural responses, dependent on factors such as the stimulus, electrodes, and context and how responses are measured.

Relatively few RCTs have been conducted with GVS, although in one widely noted example, GVS was applied to patients with stroke suffering hemi-spatial neglect (Wilkinson et al., 2014). In this study, 49 patients were

randomized to three treatment arms (one active and nine sham treatments versus five active and five sham treatments versus ten active and zero sham treatments) using bipolar (left anodal, right cathodal) binaural GVS administered at a mean noisy current of 0.5–1.5 mA for 25 minutes. As well as the known benefits of GVS improving performance across a range of visuospatial tasks (such as line bisection, figure copying, and target cancellation), in this study, the authors demonstrated a persisting benefit of GVS on the primary outcome measure [Behavioural Inattention Test (BIT)], between baseline and 4 weeks post-GVS, in all treatment arms. This comparable efficacy of a single versus multiple stimulation sessions is notable.

Applications of neurostimulation to specific neurological disorders

Neurostimulation in neurology has been used for a range of conditions, including migraine, movement disorder, and chronic pain. The list of potential conditions being targeted for possible benefit is ever increasing and now also includes Tourette syndrome, dementia, and disorders of consciousness. There is variable evidence of efficacy in most of these potential conditions, due largely to the lack of reliable trial-based data which include sufficiently large cohorts of patients. The evidence is more compelling for treatment of pain and headache.

Neurostimulation for pain

Debilitating chronic pain disorders are common in clinical practice across specialties. Such pain is often poorly responsive to treatment in the form of drugs or pain management employing psychological therapies. Neurostimulation has been trialled for chronic conditions such as failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS), as well as for neuropathic pain associated with peripheral neuropathy, post-herpetic neuralgia, and ischaemic pain due to cardiovascular and peripheral vascular disease (Mekhail et al., 2010).

Chronic spinal pain

FBSS is characterized by intractable chronic pain affecting the legs, buttocks, or low back, following spinal surgery that may have successfully corrected the underlying pathology, but without achieving adequate relief. FBSS has been traditionally managed with treatments such as analgesic medication, physiotherapy, nerve root blocks, or epidural steroid injections. Many patients fail to benefit from these approaches, and it is for these that neuromodulation therapy, in the form of spinal cord stimulation (SCS), may offer an alternative way forward. FBSS is now the commonest indication for neurostimulation therapy for chronic spinal pain. The procedure involves placement of one or more multiple contact neurostimulation leads into the posterior epidural space of the spine. The targets for SCS are the dorsal column tracts adjacent to dorsal nerve roots entering the dorsal horn of the spinal cord. When applied, an electric field is created over the cord, resulting in paraesthesiae in the painful regions affected. Pain relief of at least 50% is reported, but efficacy depends on careful selection of patients, spinal levels targeted, the underlying pathology, and the type of pain generator. Unintentional stimulation of spinal roots can lead to side effects such as dysaesthesia and unpleasant motor responses. SCS has been used to treat pain due to lumbar spinal stenosis and intractable pain originating in the cervical spine. Initial costs of SCS can be substantial, hence limiting its use only to carefully selected patients. A device for SCS was first approved by the FDA in 1989.

Neuropathic pain

In chronic neuropathic pain, the cause of the underlying injury may have resolved, but the pain remains. CRPS is a type of neuropathic pain suitable for treatment with neurostimulation. CRPS is divided into CRPS-I, formerly known as reflex sympathetic dystrophy, and CRPS-II, also known as causalgia. CRPS-I is related to the loss of small-diameter nerve fibres C and A-δ. SCS is reported to have positive benefits in CRPS-I (Mekhail et al., 2010). Early treatment (<4 months from failure of conservative management) is advised.

Nerve stimulation for headache syndromes

The World Health Organization (WHO) estimates headache disorders, including migraine and cluster headache, to be one of the most prevalent conditions affecting man. Ten per cent of the world's population are believed to suffer with migraine. Of these, 50% are self-treating. Only 10% have access to neurology (Armitage et al., 2003). In the United States, 40 million people are estimated to suffer with migraine (World Health Organization, 2011). Chronic migraine affects 2% of the general population in the United States. Treatment-refractory migraine and cluster headache affect approximately 5% of patients attending specialist headache clinics.

Headache conditions can be classified as episodic and chronic. Episodic headache is defined as that occurring <15 days a month for >3 months. Chronic headache is headache occurring >15 days a month for >3 months. Chronic headache sufferers amount to 4% of the global population (Miller et al., 2016). Most chronic headaches are chronic migraine or cluster headache.

The commonest type of migraine is characterized by recurrent episodes of head pain, often throbbing and unilateral, sometimes preceded by aura (Dahlem et al., 2013). Chronic migraine is also defined as the occurrence of >15 headache days per month over a 3-month period, with at least eight of these characterized as migrainous, in the absence of medication overuse. Migraine aura symptoms are most often visual field disturbances but can also involve other sensory modalities or cognitive functions.

Cluster headache is characterized by attacks of severe pain localized orbitally, supraorbitally, or temporally, lasting for 15–180 minutes and occurring from once every other day to eight times daily (Walter and Kaube, 2012). The symptoms of cluster headache include conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, and eyelid oedema. The usual pattern of occurrence is with remissions (episodic cluster headache), but one in seven sufferers have chronic cluster headache, i.e. no remission periods lasting 1 month or longer.

In a small case series of seven patients, PNS, using wire lead arrays placed at the base of the supraorbital nerve and/or greater occipital nerve, showed a response rate in treating the pain of occipital neuralgia and cervicogenic headache of approximately 88% and 40–50% for primary migraines and cluster headache, respectively (Reed et al., 2010). Headache with a fronto-temporal distribution appears to be responsive to stimulation of the distant occiput. The authors suggested ONS for occipital pain, supraorbital nerve stimulation (SONS) for frontal pain, and combined ONS-SONS for holocephalic pain. The rationale for combination treatment is suggested by the knowledge that trigeminal and greater occipital nociceptive afferents converge on the same second-order sensory neurones in the trigeminocervical complex, and therefore on a final common pathway to higher structures and nuclei important for pain modulation. (The supraorbital nerve is a branch of the first division of the trigeminal nerve.) Stimulation parameters can be adjusted to control the paraesthesiae achieved.

ONS requires a minor invasive surgical procedure, but this is not widely available and may only be carried out by highly specialized services combining headache and surgical expertise (Miller et al., 2016). The procedure therefore is reserved for those with highly refractory headache syndromes not responsive to all other treatments. ONS has no role in the acute treatment of migraine or cluster headache. When fitted, the occipital

nerve stimulator is left on at all times. Adverse events include lead migration (13%), lead fracture (4%), erosion of an electrode through the skin (4%), infection (10%), painful stimulation (17%), and pain over the battery site (18%) (Miller et al., 2016). Although ONS suggests stimulation of the occipital nerve itself, the use of multiple contact points that can be programmed to function as cathodes or anodes (allowing distribution of the locality and intensity of the stimulation) means that the term 'occipital field stimulation' is a more accurate description (Trentman et al., 2016).

Non-invasive neurostimulation for chronic migraine

Transcutaneous electrical nerve stimulation (TENS) modulates neural activity by non-invasive stimulation of peripheral nerves. In migraine, supraorbital transcutaneous stimulation (STS) has been tested, targeting the ophthalmic division of the trigeminal nerve. Using biphasic rectangular alternating current impulses at 60 Hz, Dahlem et al. (2013) reported a therapeutic gain of 26%, similar in efficacy to preventative drug and non-drug treatments.

TMS and TES have also been applied to migraine. These methods target cortical brain regions, rather than peripheral nerves. Early small-scale studies have suggested that TMS may be effective in disrupting cortical spreading depression (SD) in the aura phase, suggesting potential for aborting migraine attacks, but much larger replicated studies are needed.

Two versions of TES are available. In tDCS, cathodal stimulation inhibits neuronal firing and anodal stimulation increases neuronal firing. With tACS, polarity cyclically changes according to the frequency of the alternating current. There is preliminary evidence for a positive, but delayed, response to tDCS applied to motor (anodal) and orbitofrontal (cathodal) cortices in patients with chronic migraine (Dahlem et al., 2013).

CVS has also recently been reported as a potential beneficial adjuvant treatment for the management of episodic migraine. Researchers tested subjects over 3 months using a parallel-arm, block-randomized, placebo-controlled design, with the primary end-point defined as a change in monthly migraine days from baseline to the third-treatment month. Active arm subjects reported immediate and continued steady declines in migraine frequency over the treatment period, with an overall therapeutic gain of 2.8 fewer migraine days (Wilkinson et al., 2017).

Other neurological disorders

Neurostimulation in memory disorders

Patients with AD and other neurodegenerative conditions are set to exponentially increase in number due to ageing populations worldwide surviving to ever longer average lifespans. In the United States alone, an estimated 5.5 million people of all ages have AD. Of these, around 5.3 million are 65 years and older and 200,000 are younger and have early-onset AD. Treatments for AD and other neurodegenerative conditions are currently limited to symptom control, rather than reversal or cure.

Memory impairment is usually the first cognitive manifestation of neurodegenerative processes. rTMS studies have confirmed the role of the prefrontal cortex in encoding and retrieval of verbal or non-verbal material in healthy subjects. Other research has assessed the effect of rTMS on both left and right dorsolateral prefrontal cortices (DLPFCs) on naming and language performance in AD patients using a two-crossover, sham-controlled, single-session study design. Significantly improved accuracy in both action and object naming was found following high-frequency rTMS, an effect seen in both mild AD [Mini-Mental State Examination (MMSE) scores ≥17/30], and moderate to severe AD (MMSE scores <17/30) (Nardone et al., 2015).

tDCS has also been found to be of benefit when applied to patients with AD. Several studies have reported improvements in mild AD using anodal tDCS, particularly recognition memory, but not working memory (Nardone et al., 2015). The initial findings merit replication in much larger sample groups with RCT design and double blinding to confirm whether the effects are definite, the duration of effect (if any), the most optimal stimulation parameters, and patient inclusion criteria.

GVS has also been investigated for effects on cognitive function. In healthy subjects, subsensory anodal stimulation over the left mastoid was found to improve (speed up) visual memory recall of faces (Wilkinson et al., 2008).

Non-invasive neurostimulation for traumatic brain injury

Traumatic brain injury (TBI) is temporary or permanent impairment of brain function, following physical trauma, usually an external force, to the brain. The annual incidence of TBI in the United States is approximately 2000 per million, with an estimated 1.5 million US individuals experiencing a TBI each year (Dhaliwal et al., 2015). There is huge heterogeneity in the type of TBIs suffered, but common themes occur in sufferers' post-TBI neuropsychiatric symptoms such as affective disorder (particularly depression), sleep disturbance, fatigue, anxiety, and varying degrees of cognitive dysfunction (working and episodic memory, cognitive processing speed, executive function, and attentional and concentration difficulties).

After TBI, the side effects of psychotropic medications are less well tolerated and symptoms are more resistant to eradication, leading to chronic disability and societal burden. It is not surprising that, in relation to treatment of any neuropsychiatric consequence of TBI, no medication has to date received approval by the US FDA. Treatments tend to be largely based on clinicians' experience, preferences, and anecdote. This demonstrates the necessity of exploring novel methods of treatment, including NIBS.

A systematic review of studies using NIBS in TBI found evidence in relation to rTMS and tDCS (Dhaliwal et al., 2015). rTMS has been reported mildly beneficial when given to post-TBI inpatients suffering with suicidal thoughts using a protocol of high-frequency rTMS over the left prefrontal cortex administered three times a day (6000 pulses over 30 minutes at 10 Hz and 5-s train duration) for 3 days. The authors (George et al., 2014) found a more rapid rate of recovery in those subjects treated actively, compared to sham, but no other differences between the groups. Case reports have documented improvements in a range of post-TBI symptoms such as hemi-spatial neglect, depression, and executive function, but definite evidence of efficacy remains enigmatic. Similarly, tDCS provides limited evidence of benefit in improvement of various aspects of brain function such as cognition and attention, but studies need to be replicated. The main risk of NIBS in TBI is seizure generation due to increased neural excitability.

Non-invasive neurostimulation for sleep

The sensation of rocking, as in putting a baby to sleep, can also be created by electrical stimulation of the vestibular system, raising the intriguing possibility of vestibular stimulation as a means of addressing disorders of sleep such as insomnia. Physiological evidence of a neuronal basis for connectivity of the vestibular system to sleep mechanisms is suggested by labyrinthine inputs to the pontine reticular formation neurones involved in mediating switching between sleep states, and medial vestibular projections to regions mediating arousal such as the lateral hypothalamus (Krystal et al., 2010).

In a model of transient healthy volunteers measuring polysomnographic latency to persistent sleep in a 4-hour phase advance protocol in normal sleepers, Krystal et al. found that after bilateral electrical stimulation of the vestibular apparatus via electrodes on the skin of the mastoid process at 0.5 Hz (sham-controlled), only a small effect on shortening sleep-onset latency occurred, as compared to sham. More persuasive evidence, however, of

an effect of NIBS on sleep architecture has been provided by experiments with TMS which showed that, with appropriate stimulation parameters, TMS pulses at <1 Hz during NREM sleep can evoke slow waves and spindles in sleeping subjects. Evoked slow waves have been shown to lead to a deepening of sleep and an increase in EEG slow-wave activity (0.5–4.5 Hz), which may be associated with 'brain restoration' and memory consolidation (Massimini et al., 2007). The effect has also been reported with tDCS (Bellesi et al., 2014)).

Applications of neurostimulation in psychiatric disorders

An expanding range of psychiatric conditions have been targeted for exploratory 'treatment' with non-invasive neurostimulation methods. These include depression, schizophrenia, anxiety disorders, OCD, addiction, autism, and attention-deficit/hyperactivity disorder (ADHD) (Baeken et al., 2015; De Melo et al., 2016; Fitzgerald et al., 2012; Hizli et al., 2013; Rajapakse et al., 2013). Possible application to a range of other disorders has also been suggested, including dyslexia, Tourette syndrome, dementia, post-traumatic stress disorder (PTSD), neuroenhancement (i.e. improving cognition in healthy normals), and low awareness states. The evidence for efficacy, however, is often limited to case studies or studies with small samples. Few double-blind, well-powered RCTs have been done, making the case for efficacy of neurostimulation in such a vastly different set of disorders difficult, with as yet no confirmed theory of biological effect at the neuronal level, although various speculative hypotheses are stated.

Depression

That being said, there is still a significant evidence base for the use of tDCS in depressive disorders (e.g. Holtzheimer et al., 2017). The current approach is for enhancement of neural activity in the left DLPFC with anodal stimulation and/or reduction in neural activity in the right DLPFC with cathodal stimulation. tDCS applied in this way also affects deeper brain structures such as the amygdala, hippocampus, and subgenual cortex. The precise changes in resting-state brain networks that produce the antidepressant effects of tDCS remain unknown.

Meta-analyses have suggested that active tDCS is superior to sham treatment and the combination of antidepressant + tDCS is more effective than either alone, suggesting an additive interaction. The possibility of the effect of tDCS being mediated by pharmacological modulation of serotonergic and noradrenergic neurones located in deep brain structures, even though these might not be directly affected by superficial current flow generated by tDCS, has been suggested (Brunoni et al., 2014b, cited in Tortella et al., 2015). Alternatively, or additionally, serotonergic enhancement may boost the neuroplastic effects of anodal tDCS, thus resulting in synergistic effects.

Much research has also investigated the effects of rTMS in depression. Treatment protocols for depression have consisted mostly of 5–25 sessions of high-frequency rTMS to the left DLPFC or low-frequency rTMS applied to the right DLPFC. A meta-analysis of 34 studies comparing rTMS with sham treatment showed a moderate effect size on depressive symptoms, comparable to psychotherapy and pharmacotherapy (de Raedt et al., 2014).

Schizophrenia

Some of the most treatment-resistant symptoms of schizophrenia include persistent auditory hallucinations and negative symptoms such as blunting of affect, poverty of speech and thought, apathy, anhedonia, reduced social drive, loss of motivation, lack of social interest, and inattention to social or cognitive input.

The Repetitive Transcranial Magnetic Stimulation for the Treatment of Negative Symptoms in Schizophrenia (RESIS) trial was conducted from 2007 to 2011. A total of 175 patients were enrolled and randomized to either

10–20 Hz active or sham rTMS applied for 15 sessions to the left DLPFC. Unfortunately, a beneficial effect of active stimulation was not found. However, other treatment studies with different treatment parameters, less strict methodology, and smaller sample sizes have shown positive effects (Hasan et al., 2016).

For the management of auditory hallucinations, inhibitory 1-Hz rTMS applied to the left temporal lobe for 5–20 sessions was found to have been used in 393 patients who had received this protocol in sham-controlled studies, but only half of the studies showed a beneficial effect of the intervention. A significant placebo effect has been reported in one meta-analysis (Hasan et al., 2016). Hence the evidence is equivocal for benefit.

tDCS for persistent auditory hallucinations in schizophrenia has also been studied using a protocol involving stimulation twice a day on five consecutive days, administering 20 minutes of active 2-mA tDCS or sham stimulation to the left temporo-parietal junction (inhibitory cathode), with the excitatory anode placed over the left DLPFC. Active stimulation was found superior to sham stimulation, with a reduction in auditory verbal hallucinations of 31% in a sample of 30 patients with medication-refractory auditory hallucinations. Negative studies, however, have also been reported (Hasan et al., 2016). Hence, in clinical practice, neither tCDS nor rTMS can be recommended, although the evidence for benefit is intriguing. Many other techniques such as tRNS and tACS are also being investigated, but theoretically an infinite number of protocols is possible and there is no consensus yet on what the best parameters or protocol might be. There are also a number of modulating variables, such as cortical architecture, skull thickness, age, sex, genetic factors, and medication in use, which add complexity. The optimal ‘therapeutic’ dose of stimulation remains uncertain. The underlying physiology of effect (if present) is also unknown.

Anxiety disorders

Anxiety may be a component of a number of common psychiatric disorders such as panic disorder, generalized anxiety, agoraphobia, PTSD, OCD, and others. Herein lies the problem, common to many studies on the efficacy of methods of NIBS in psychiatry, of variable phenomenology and the heterogeneity of psychiatric disorders. There is also the difficulty of providing adequate sham conditions in a population that is difficult to homogenize because of differences in concurrent treatments with psychotropics (e.g. anxiolytics and antidepressants) and behavioural therapies. Hence evidence in this area can, at best, be described as anecdotal, with few systematic, randomized, and blinded controlled trials.

TES is similar in nature to tDCS in that an electrical source is used to stimulate cortical neurones. (Note that TES is also sometimes referred to in the literature as a general term for all modalities of electrostimulation used transcranially with electrodes, with the electrical stimulus often generated by batteries.) When not used as a term in this general way, TES differs from tDCS in the electrodes applied, the current sources used, and the desired effect. TES employs smaller electrodes than tDCS scalp electrodes, leading to much larger stimulating current densities, compared to tDCS. TES actively evokes action potentials from the underlying neural substrate, whereas the effects of tDCS alter the overall excitability of the neural response. Use of TES in awake human subjects is limited due to induced pain from strong activation of skin and scalp pain receptors (Wagner et al., 2007).

TES has been reported (Bystritsky et al., 2008) as effective in generalized anxiety disorder (GAD) using electrical stimulation at 0.5 Hz and 300-μA intensity over 6 weeks (cited by Kumar et al., 2016). The evidence regarding the efficacy of tDCS in GAD, however, is limited.

The evidence supporting the efficacy of NIBS in OCD is more hopeful, with studies using tDCS and rTMS showing benefits. tDCS applied to the DLPFC (anodal left DLPFC, and cathodal right DLPFC) in healthy volunteers reduced anxiety responses to threatening stimuli (Kumar et al., 2016). Meta-analyses of RCTs of rTMS in patients with OCD found active rTMS to be more efficacious than sham rTMS. There is speculation regarding the mechanism of effect, including the possibility that rTMS has a modulating effect on amygdala

activity through prefrontal cortical circuitry. Low-frequency rTMS and high-frequency rTMS targeting the right and left medial prefrontal cortices, respectively, for 4 weeks have been reported as effective in social anxiety disorder. It is possible that rTMS in PTSD may be beneficial, but rigorous replicated studies are lacking; hence definite conclusions cannot be drawn. Notably, it has been reported that rTMS at 1 Hz over the right DLPFC, over ten sessions, was better than sham rTMS in improving symptoms of PTSD. A possible mechanism of effect of improvement in PTSD may be disruption of episodic memory recall (of the traumatic memory).

Substance misuse

Substance dependence, whether due to alcohol or other drugs of abuse (e.g. methamphetamines, nicotine, cocaine), represents a significant global burden of disease. Repeated drug or alcohol use is known to lead to neuro-adaptations in the ventral striatum and ventral tegmental areas, which, in turn, results in decreased dopamine secretion (Jansen et al., 2013). Diminished functioning of the DLPFC and anterior cingulate cortex is also noted to be present in addictive disorders, possibly indicating diminished inhibitory control affecting cognitive and behavioural processes. Craving often accompanies addictive behaviours, whether due to food (as in obesity) or substances. Neuroimaging studies have linked craving to reduced prefrontal activation and lower D2 dopamine receptor density in the striatum.

Reducing craving therefore has been seen as an approach suitable for trials of TMS and tDCS. A number of studies have targeted the DLPFC as a stimulation site. The outcomes, though failing replication in other studies with similar study populations, nonetheless, as part of a meta-analysis of only double-blind RCTs, comparing real rTMS/tDCS with sham rTMS/tDCS, suggest a medium effect size favouring non-invasive high-frequency neurostimulation over sham stimulation on craving levels for food and drugs/substances (Jansen et al., 2013). Further research is needed to determine whether these effects are beneficial as stand-alone treatment or should supplement existing treatments.

Neuroenhancement in health

Neuroenhancement describes the use of neuroscience-based techniques for enhancing cognitive function in individuals without a neurological or psychiatric diagnosis. A number of studies have explored direct current stimulation of the brain in healthy adults to enhance attention, learning, and memory (Clark et al., 2014). The results broadly showed reduced performance with cathodal stimulation and increased performance arising from anodal stimulation, but the effect sizes are small. An advantage of tDCS in this setting is that electrode placement may need to be less precise for anatomical targeting, but comparisons between studies is made difficult by the lack of common protocols, common reporting measures of cognitive enhancement, and lack of control conditions.

There are now numerous ‘commercial’ devices (marketed from a few dollars to several hundreds of dollars), widely available to the public via the Internet, for non-invasive neurostimulation. Sales are not regulated by current legislation which applies to all medical devices, owing to a legal loophole, frequently used in such sales, which often takes the form of a disclaimer to the effect:

> ‘The information and devices displayed on this site are not intended to treat, cure, or prevent any medical disease, and this article is not considered to be medical advice. If a reader decides to purchase and use a tDCS machine, it is his or her responsibility to use it correctly and safely and ensure that it works correctly.’

The number of devices actually approved for medical use, e.g. by the US FDA and the Centre for Devices and Radiological Health (CDRH), are, by comparison, very few and usually for indications such as DBS for

Parkinson's disease and neurostimulation for epilepsy. Clinical trials that provide data for approval are often restricted in scope and time-limited.

Devices are also undergoing testing in significant numbers in pre-clinical animal work, but with results not always leading to publication, and therefore not available for scrutiny. Researchers have used publicly available US FDA databases to identify pre-market approval (PMA) studies of this type. The results showed that a variety of animals are used in research of this type (e.g. sheep, monkey, dog), with wide variations in stimulation durations (from hours to years) and frequencies of stimulation (from 10 to 10,000 Hz) (Kumsa et al., 2018). The translational value of this research to human subjects is unclear.

Devices used in human trials to study potential for therapeutic benefit, e.g. tDCS for recovery of speech and language after stroke, pain mitigation, etc., also often face the difficulty that, at the end of the trial, patients who have been highly responsive to the intervention may not be able to continue treatment outside of the trial, leading to some patients then seeking alternative 'do-it-yourself' (DIY) devices (Bikson et al., 2016), usually used without any medical supervision.

Putative mechanisms of effect

A variety of putative mechanisms (e.g. Deisseroth et al., 2015; Fertonani et al., 2017; Remue et al., 2016; Tye et al., 2009) have been proposed for the many different stimulation techniques outlined previously, but it is beyond the remit of this chapter to review them in any detail. Instead we comment on just two mechanisms that, partly by virtue of their operation at the systems-level and potential ease of induction, are receiving increasing attention.

Neural stimulation and the immune system

There is increasing evidence of a dynamic and interactive relationship between the nervous system and the immune system. It is only relatively recently that microglial cells, which account for 0.5–16.6% of the total number of cells in the human brain and are a key cellular component of the immune system, have been recognized as having many potentially important functions in the normal development, function, and repair of the central nervous system (CNS) (Gomez-Nicola et al., 2015). Microglia actively 'sense' the microenvironment and activation occurs in response to any disturbance of CNS homeostasis, ranging from infection to acute or chronic brain injury. In neurodegenerative diseases, microglial activation is considered to be a response to inflammation due to disease. Neurones partner with immune cells in the regulation of inflammation. Neurones sense inflammatory products and can mount fast and directed responses to regulate immune function and inflammation (Pavlov and Tracey, 2015). Peripheral immune cell activation, with the release of cytokines and other immune molecules, is communicated to the brain through neural and humoral mechanisms, e.g. via afferent vagus nerve fibres.

Koopman et al. (2016) use the term 'inflammatory reflex' to define the signals that travel in the vagus nerve to inhibit monocyte and macrophage production of tumour necrosis factor (TNF) and other cytokines. Inflammatory reflex signalling, enhanced by electrically stimulating the vagus nerve, significantly reduces cytokine production and attenuates disease severity in experimental models of endotoxaemia, sepsis, colitis, and other models of inflammatory syndromes. Koopman et al. have also shown that VNS delivered once daily for 60 s to a group of rheumatoid arthritis patients with an implanted device could attenuate joint swelling, inhibit cytokine production, and confer significant protection against synovitis and periarticular bone erosions.

In addition to pharmacological interventions, device-generated brain modulation (e.g. tDCS, TMS) not only may have a role in neural modulation, but also could, via this route, influence anti-inflammatory activity in the brain, as a potential mechanism of action for the outcomes being seen in the various disorders in which neuromodulation is being tested.

Brain oscillatory activity and entrainment

A second and important theory of how neuromodulation may be having its effects is via studies of brain EEG activity. The most immediate effect of rTMS on brain function appears to be alterations of the oscillations of the underlying brain tissue. High-frequency stimulation (>5 Hz) leads to synchronization of EEG activity in the alpha and beta bands. Studies have demonstrated that high-frequency rTMS leads to alterations of cortical oscillations not only at the site of stimulation, but also in more distant areas as well, consistent with the idea of linkage of brain regions through corticocortical and thalamocortical loops (Leuchter et al., 2013). rTMS pulses appear to trigger and reset oscillatory mechanisms marked by 'event-related synchronization' (ERS) at the frequency of stimulation in the area stimulated, followed by 'event-related desynchronization' (ERD) and re-emergence of endogenous rhythms. Low-frequency (1 or 5 Hz) stimulation may facilitate emergence of local endogenous rhythms by disrupting persistent low-frequency thalamocortical resonance phenomena. Regardless of frequency of stimulation, enhancement of the re-emergence of endogenous local cortical and thalamocortical rhythms may be central to the mechanism of action of rTMS and other forms of neurostimulation, which can also deliver an entraining stimulus.

Conclusion

In this chapter, a number of neurostimulation technologies, their principles of operation, and potential therapeutic applications have been considered, along with the evidence available for benefit. The technologies continue to evolve and develop. There are emerging theories of how the technologies may be interacting with the nervous and immune systems and the brain's innate oscillatory rhythms. More research is needed to better understand how the technologies work, but also whether the potential therapeutic benefits in neurological, neuropsychiatric, and psychiatric disorders are reproducible in larger, well-designed studies. The twenty-first century is predicted to greatly enhance our understanding of brain systems, brain diseases, and the methods of intervention in health and disease, which may have profound impact on future therapeutic management of neurological and psychiatric conditions. Advanced knowledge of neurophysiology, brain networks, neuroimaging, neuroimmunology, neuroplasticity, and neurogenetics seem certain to be key to enable currently practising and future generations of neuropsychiatrists and neurologists to make the best and most informed use of emergent novel neurotechnologies. There is optimism that these technologies, in due course, will take their deserved place alongside medical approaches based on pharmacotherapy, neurosurgery, and psychological therapy.

> **Key learning points**
>
> - Current evidence regarding invasive novel neurostimulation technologies favours neurological applications more than psychiatric indications. Invasive technologies are more prone to risk and expense at initiation but are also not without side effects, adverse effects, and limitations. Treatment resistance as an indication, careful patient selection, and multidisciplinary specialist teams are necessary to optimize good outcomes of intervention.

- There are an expanding range of neurotechnologies for non-invasively stimulating the brain for use in neurological, neuropsychiatric, and psychiatric disorders. Research into the clinical efficacy of these technologies has expanded rapidly, particularly in the last decade. Some modalities (e.g. tDCS, TMS, CVS/GVS) have potential to induce clinically relevant improvements in difficult-to-treat patient populations and thus represent possible new tools for intervention in a range of mental disorders. The use of these 'tools' remains in its infancy and much further evidence of efficacy, based on large-scale multi-centre RCTs, is required to progress from research laboratory tools to the clinic.
- The challenges facing researchers include highly variable patient characteristics, differences in concomitant therapies, choice of stimulation parameters and protocols, and study designs. To address these difficulties, sample variability needs to be controlled, and reproducible stimulation parameters defined, to help resolve discrepancies in research findings (Kekic et al., 2016).
- Some neurostimulation technologies have progressed to regulatory approval (e.g. tDCS and rTMS for depression) in clinical populations, but actual provision, particularly in UK-based NHS services, is minimal to nil. Clinical provision is largely via private fee-paying clinics in the UK. This is likely to change as more awareness of these neurotechnologies takes place among clinicians, patients, service commissioners, and other relevant stakeholders.
- The long-term effects of neurostimulation are largely unknown. As commercial 'DIY' devices become increasingly available in larger numbers, at low cost (particularly tDCS stimulators), the perils, as well as the promises, of neurostimulation may become more apparent, with the need to introduce better regulatory protection of consumers.
- There is great need for more translational expertise to move these new technologies from bench to bedside. Grant funders need to show greater willingness to support proof-of-concept studies, where safety risk is lower, as well as mechanism-of-effect studies, which require larger cohorts.

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