Brain stimulation methods for pain treatment

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Abstract. Treatment of pain is one of the most important aims of medicine. Over the past several decades, invasive, semi-invasive and non-invasive brain stimulation methods have been tested and implemented for modulation of the pain. In this review, we bring an overview of those methods including stimulation of both deep brain structures utilizing invasive and semi-invasive techniques and the brain cortex stimulated by non-invasive transcranial magnetic and electrical techniques. Another potentially beneficial method that could modulate pain by stimulating the deep brain with interferential transcranial alternating current is discussed as well.

Key words: Pain — Stimulation — Transcranial — Magnetic — Electrical

Abbreviation: AC, anterior cingulate cortex; CMPf, centromedian intralaminar perifascicular (complex); DBS, deep brain stimulation; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; fNIRS, functional near red stimulation; GABA, gamma-aminobutyric acid; IC, internal capsule; if-tACS, interference transcranial alternating current stimulation; IPG, implanted pulse generator; NAc, nucleus accumbens; NIBS, non-invasive brain stimulation; PVG/PAG, periven-tricular and periaqueductal gray; rTMS, repetitive transcranial magnetic stimulation; tCS, transcranial current stimulation; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nervous stimulation; tES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation; tPCS, transcranial pulsed current stimulation; tRNS, transcranial random noise stimulation; VPL, ventral posterolateral (nucleus); VPM, ventral posteromedial (nucleus).

Introduction

Pain as well as pain treatment methods have accompanied mankind throughout the latter stages of evolution. Early therapies for pain were first seen in China, and then in the Middle East and India. The main approach to pain treatment has been pharmacological, initially in the form of plant-based phytotherapy, with other drugs being added over time (Harrison et al. 2012; Amin and Hosseinzadeh 2015; Finch and Drummond 2015; Mehreen et al. 2016). From antiquity, through the middle ages and into the modern age, each time period was accompanied by discoveries of new painkillers. In ancient times, electric stimulation methods, using shocks from electric catfish (Malapterurus electricus), found in the Nile, were used to treat painful conditions. Even though pharmacotherapy alternatives are becoming more and more effective, pain medication will likely remain the primary method of pain treatment for the foreseeable future, however, in cases where pain is pharmaco-resistant, pharmaceutical alternatives become extremely important (Oakley 2003; Hirayama et al. 2006; Lefaucheur 2008; Eke-Okoro et al. 2018).

Significant scientific study of electrical pain treatment did not really start until 1967, when Wisconsin colleagues Shealy, Mortimer, and Resnik first used electrical stimulation to treat pain (Shealy et al. 1967). Their method involved stimulation of the dorsal spinal cord fasciculi. Electro-
therapy methods for pain after 1967 were mainly invasive, that is, electrodes are applied either to the spinal cord or to brain regions, especially the brain's motor region. Next came methods for deep brain electric stimulation (targeted on areas and paths thought to be associated with pain initiation) and other non-invasive methods, such as stimulation via peripheral, transcutaneous nervous electrical stimulation (TENS), which was one of the first methods developed, and is still used successfully today (Dailey et al. 2013; Rakel et al. 2014; Hazime et al. 2015; Johnson et al. 2017). Since 1997, more non-invasive methods have emerged, notably non-invasive transcranial magnetic stimulation, which is initiated by a magnetic field that is then transformed into an electric field in the brain. This stimulation does not penetrate deeply into the brain, nonetheless the methods are effective in activating areas of the cerebral cortex, and when using today's most modern treatments, can activate areas in the embedded cortex, i.e., the insula (D'Agata et al. 2015). Non-invasive stimulation also uses direct current stimulation (tDCS) methods, and recently, there has been intense experimentation with other methods such as transcranial alternating current (tACS) and transcranial random noise (tRNS) stimulation (Curatolo et al. 2017; O'Connell et al. 2018).

Pain is defined as physical suffering resulting from an injury or disease, experienced through the central nervous system. Pain is a complex phenomenon that is not yet fully understood. Its purpose is to alert the body to damage or danger to its tissues, although scientists do not fully understand what determines the levels and intensity of pain experienced by people. Short-lasting pain that triggers an immediate physical response is known as acute pain (Radnovich et al. 2014). Long-lasting severe pain that persists without diminishment over long periods is known as chronic pain (Crovford 2015a). Additionally, there is a type of pain called psychological pain (Flor 2014; Crovford 2015b). Recent research has shown that the chemicals produced by anxiety are similar to those that are released in response to physical injury. Pain is a complex behavioral paradigm that includes autonomous, neuroendocrine, emotional, and cognitive components that involve distinct neural circuits (Monticone et al. 2015; Peters 2015).

Pain signals travel through the body along billions of specialized nerve cells reserved specifically for transmitting pain messages. These cells are known as nociceptors (Serra et al. 2014). Chemical neurotransmitters that can initiate a pain signal include prostaglandins, bradykinin, and the most potent painful substance known to humans, a chemical known as substance P (the P stands for pain). Prostaglandins are ubiquitous and are manufactured from fatty acids in nearly every tissue of the body (Ma and Eisenach 2002; Schaible et al. 2011). Analgesic pain relievers, such as aspirin and ibuprofen, work by inhibiting prostaglandin production.

After an injury, cells near the trauma site release the abovementioned chemicals, which activate nociceptors leading to the central nervous system. The pain signal enters the spinal cord via the dorsal root, where it synapses (via interneurons in the dorsal horn) with motor neurons that trigger contraction of the specific muscles needed to pull the injured part of the body away from the source of pain. Additional nociceptors that synapse in the dorsal horn send the signal towards the brain, where they are first processed by the thalamus and then passed to the cerebral cortex (Obara et al. 2013). Here, the brain fully processes the information, locates its source in/on the body, and begins sending signals to relieve the pain (Basbaum et al. 2009).

As the pain signals travel up the spinal cord towards the brain, they are sorted according to severity. The body has two distinct pathways for transmitting pain messages, i.e., epicritic and protopathic. The epicritic system is used to transmit messages of sudden, intense pain, such as that caused by cuts or burns (Bigley 1990). The neurons that transmit such messages are called A fibers, and are capable of transmitting signals very quickly. The protopathic system, which transmits signals over C fibers, is used to transmit less severe pain signals, such as one might experience after strenuous exercise. The C fibers of the protopathic system transmit signals more slowly than the A fibers of the epicritic system (Reddi 1998; Serpell 2006).

The gate theory of pain holds that the nervous system can only process limited amounts of information at a time (Melzack and Wall 1965). This may explain why chronic pain presents its own set of problems. Treating chronic pain is difficult because the pain damages the central nervous system, making it weaker and more susceptible to pain. Similar problems also arise when nerve cells are damaged by chemotherapy, diabetes, shingles, or other diseases. In the case of arthritis and other inflammatory diseases, the body's threshold for pain is lowered, thus producing more pain from fewer pain signals (Andersen et al. 2014; Babatunde et al. 2018; Gijon-Nogueron et al. 2018).

Treatments for pain vary widely. For mild pain, the most common form of treatment is aspirin, a medication discovered in the 19th century and derived from salicin, a chemical found in the bark of the willow tree (Walker et al. 2018). Today, there are several mild painkillers on the market for the relief of minor, inflammatory pain, including ibuprofen and acetaminophen. (Moore et al. 2015). For more severe pain, opiates, which are derived from the opium poppy, a common flowering plant, are often used (Pergolizzi et al. 2008; Wolff et al. 2012). Opiates work by attaching themselves, at the molecular level, to nerve cells that transmit pain signals. Opiates work very well in relieving pain but are quite dangerous and can become addictive.
In the 1970s, scientists began looking for natural opiate-like substances, and found that the body does indeed produce its own painkillers, which have come to be called endogenous opioids. The two most common endogenous opioids are endorphins and enkephalins. These chemicals attach themselves to opiate receptors on nerve cells just as opiates do. Studies have found that the body can be stimulated to release these chemicals using TENS and acupuncture (Levine and Taiwo 1989; Stein et al. 1990; Kalra et al. 2001; Stein et al. 2003; Ibrahim et al. 2005; Ainsworth et al. 2006; Sabino et al. 2008).

**Deep brain structures in pain treatment**

Deep brain structures became a target for pain treatment several decades ago. They are usually activated by electric current stimulating the cerebral motor cortex, which orthodromically stimulates the thalamus. The thalamus is full of gamma-aminobutyric acid (GABA) receptors and produces large amounts of GABA, which influences the ascending thalamo-cortical pathway that leads from the thalamic nuclei (in particular the ventral posterolateral (VPL) and ventral posteromedial (VPM) nuclei to the postcentral gyrus of the cerebral cortex, which is located in Brodmann's Areas 3, 2, and 1 (areas of pain perception). Despite the demand for both safe and easy to use methods for stimulation of deep brain structures, contemporary methods for stimulation of deep brain structures are either effectively strong but invasive or they are non-invasive but ineffectively weak. The inspiration for a potential solution to this problem, i.e., effective but non-invasive stimulation of deep brain structures comes from tACS, which has been previously used experimentally

![Diagram of brain pathways](image-url)

**Figure 1.** Pathways and brain regions involved in the transmission and modulation of pain signals. Primary afferent neurons, with their cell bodies in the dorsal root ganglia, or trigeminal ganglion (mouth and face), couple with second order neurons in the dorsal horn of the spinal cord, or the spinal nucleus of the trigeminal complex. Axons of the second order neurons cross the midline and project to the thalamus and a variety of other targets in the medulla oblongata, pons, and midbrain, including the rostral ventral medulla (RVM) and the periaqueductal gray (PAG). Third order neurons, with their cell bodies in the thalamus, project to the somatosensory cortex, responsible for the sensory-discriminative aspects (intensity, location and quality) of pain, and to the limbic cortical areas, such as the anterior cingulate, insula, and the prefrontal cortex, which are involved in mediation of the affective / emotional components (aversiveness) of pain. Thalamic neurons also project to the amygdala, which in turn interact with the nucleus accumbens, a region involved in both pain processing and the mediation of reward / motivational behavior. These various brain regions also send input to the PAG, which, via the raphe nuclei in the RVM and the locus coeruleus, send descending pain modulatory projections back to the first synapses in the afferent pathways. (This figure was courteously provided by its author Prof. Ernst Brodin, by the Tidende Journal which the figure published and by illustrator Sole Lätti).
in different setups in an effort to therapeutically influence pain (Angelakis et al. 2013; Bae and Lee 2014; Elnaggar and Elshafey 2016; Gundlach et al. 2016; Hasegawa at al. 2016; Peng and Tang 2016; Albornoz-Cabello et al. 2017; Franco et al. 2017; Ladi-Seyedian et al. 2017). Exploring the capability and suitability of tACS for pain modulation or suppression are tasks for the future.

The analgesic effects of stimulating deep brain structures

The analgesic effects of stimulating deep brain structures (for involved structures see Figure 1) have been known for more than a half-century and date back to experiments by Olds and Milner (1954). Since its first use, deep brain stimulation (DBS) has been tested on several types of pain (e.g., chronic pharmacoresistant orofacial pain, rheumatoid arthritis pain, etc.). Additionally, targets for DBS have also been investigated and include: the internal capsule (IC) (Adam et al. 1974), thalamic structures such as the somatosensory intralaminar thalamus (nucleus centro medianus, centromedian intralaminar perifascicular complex, CMPf) (Hécaen et al. 1949), periventricular and periaqueductal gray (PVG/PAG) (Duncan et al. 1991), nucleus accumbens (NAc) (Mallory et al. 2012), and the anterior cingulate cortex (AC) (Antal et al. 2014; Boccard et al. 2014).

Anterior cingulate stimulation

Anterior cingulate (AC) stimulation in patients with chronic pain with a range of etiologies (failed back surgery syndrome, post stroke pain, brachial plexus injury, cervical spinal cord injury, head injury, and pain of unknown origin, etc.) has resulted in improvement that was also associated with improved subjective analgesic properties relative to PVG stimulation alone (Boccard et al. 2014). Additionally, there was a comprehensive review (Russo and Sheth 2015) of preclinical and clinical studies of AC stimulation as part of pain treatment.

Nucleus accumbens

The nucleus accumbens (NAc) forms an extension of the ventral striatum, which is involved in reward processing. DBS of the NAc has been used to treat depression and obsessive-compulsive disorder (Hauptman et al. 2008; Franzini et al. 2010). NAc also sends inhibitory projections into the medial thalamus (Albe-Fessard et al. 1985) and from there to the dorsal horn neurons, which modulate pain perception (Lorenz et al. 2003). The NAc, together with the prefrontal cortex, insula, and AC have been shown to mediate the affective component of pain (Albe-Fessard et al. 1985; Lorenz et al. 2003). There was also a case of post-stroke pain that was treated, with great effect, using DBS targeted on the NAc and PVG simultaneously (Mallory et al. 2012).

Somatosensory thalamus

The somatosensory thalamus, consisting of the ventro-posterior lateral (VPL) and ventro-posterior medial (VPM) nuclei, has, in the past, been targeted for stimulation to suppress aberrant neuronal firing, which was observed in chronic pain (Gerhart et al. 1983); presumably driven by the absence of normal sensory input (Mazars et al. 1973). The now obsolete gate control theory (Melzack and Wall 1965) postulated that low threshold somatosensory pathways inhibit pain perception and that stimulation of this pathway would reduce neuropathic pain. This idea has been supported using animal models in which VPL stimulation inhibited spinohalamic nociceptive neurons (Gerhart et al. 1983) as well as in modulation of facial anesthesia dolorosa (Hosobuchi et al. 1973), inhibition of the ipsilateral or contralateral VPL (Gerhart et al. 1983), neuropathic pain secondary to brachial plexus injuries, and phantom limb pain (Pereira et al. 2007, 2013).

The peri-ventricular and periaqueductal gray

The peri-ventricular and periaqueductal gray (PVG/PAG) is the most promising target for DBS in the treatment of chronic pain (Bittar et al. 2005). The first descriptions of DBS of human PVG/PAG demonstrated relief of somatoform and nociceptive pain in both acute and chronic settings (Richardson and Akil 1977a, 1977b). This was consistent with descriptions of the PAG-derived descending inhibitory system modulating nociceptive inputs at the spinal level (Mayer and Liebeskind 1974). Recent evidence demonstrates PAG DBS causes a focal reduction of opioid binding in areas of electrostimulation, which is consistent with the release of endogenous opioid peptides (Sims-Williams et al. 2017). The centromedian parafascicular complex (CMPf) has afferents from the ventral posterolateral thalamus (VPL), spinohalamic tract (STT), and trigeminal lemniscus, and efferents to the striatum, cortex, and AC. The CMPf is responsive to nocuous stimuli and sensitive to stimulus intensity but its stimulation has yielded inconsistent results (Davis et al. 1998; Weigel and Krauss 2004). Neuropathic pain in humans corresponds with increased activity of CMPf neurons (Hirato et al. 1991). CMPf stimulation or ablation has been found to be helpful in the treatment of central pain and deafferentation pain (Hariz and Bergenheim 1995; Hollingworth et al. 2017).

Invasive brain stimulation

Invasive brain stimulation methods, in general, involve situations in which brain structures are in physical contact (“in situ”) with the stimulating microelectrode. In practice it means stimulation of the superficial (cortex) or deep brain structures, which are out of reach of non-invasive stimula-
Brain stimulation methods for pain treatment

Brain stimulation methods for pain treatment is a minimally invasive, targeted neurosurgical intervention that enables structures deep in the brain to be stimulated electrically using implanted electrodes and a pacemaker (see Figure 2). The method was initially developed for and applied to movement disorders in several target areas; such as the thalamus, the pallidum, and the subthalamic nucleus. It is currently being extended to other indications, such as epilepsy (Chan et al. 2018; Hartl et al. 2018; Lobato-Polo et al. 2018; Son et al. 2018), dystonia (Magown et al. 2018; Takeda et al. 2018), tremor (Moldovan et al. 2017; Camalier et al. 2018), cluster headache (Chabardès et al. 2016; Láinez and Guillamón 2017), chronic pain, including pain from stroke (Lempka et al. 2017; Gopalakrishnan et al. 2018), amputation (Pereira et al. 2013; Kuffler 2018), trigeminal neuralgia (Nizard et al. 2012; Yamgoue et al. 2016) and multiple sclerosis (Abboud et al. 2017; Oliveria et al. 2017), and recently to psychiatric disorders, such as obsessive compulsive disorder (Naesström et al. 2017; Winter et al. 2017; Franzini et al. 2018), Tourette’s syndrome (Marceglia et al. 2017; Martínez-Ramírez et al. 2018), and depression (Kringleb 2007b). The mechanism of action will likely turn out to be quite complex, involving cell-firing inhibition, neurotransmitter depletion, jamming and excitation of inhibitory pathways that lead to functional inhibition, and mimicking the effects of lesioning of the stimulated structures (Benabid 2014).

While DBS for Parkinson’s disease is based on 20 years of experience, a standard and widely accepted DBS treatment for chronic pain (even though DBS has been used to treat pain for over 50 years) remains restricted to a handful of experienced, specialist centers (Pereira et al. 2013).

The DBS system consists of three components: an implanted pulse generator (IPG), leads, and an extension. The IPG is a battery-powered neurostimulator, encased in a titanium housing that sends electrical pulses to the brain that interfere with neural activity at the target site. The lead is a coiled wire, insulated with polyurethane, with four platinum-iridium electrodes that are placed in one or two different nuclei of the brain. The lead is connected to the IPG by an extension, which is insulated wire that runs below the skin, from the head, down the side of the neck, behind the ear, to the IPG, which is placed subcutaneously below the clavicle, or in some cases, the abdomen. The IPG can be calibrated to optimize symptom suppression and control side effects. DBS lead placement is done relative to the type of symptoms to be addressed. For non-Parkinsonian essential tremor, the lead is placed in either the ventral intermediate nucleus of the thalamus or the zona incerta (Holstlag 2018); for dystonia and symptoms associated with Parkinson disease, the lead can be placed in either the globus pallidus internus or the subthalamic nucleus. The leads are placed in the NAc for obsessive compulsive disorder and depression, the posterior thalamic region or periaqueductal gray for incessant pain, and in the anterior thalamic nucleus for epilepsy. All three components of the system are surgically implanted inside the body. Lead implantation can take place under local or general anesthesia.

![Figure 2. Arrangement of deep brain stimulation (DBS) technique.](image)

![Figure 3. Scheme of interferential transcranial alternating current stimulation (if-tACS) with potential use to modulate pain associated with deep brain structures. In principle, if-tACS is to produce low frequency effects at sufficient intensity and depth to avoid patient discomfort in the superficial tissues (i.e., the skin). Two AC currents with slightly different frequencies are used in crossed arrangement. The result frequency affecting tissue in the crossed section (in deep structures) is equal to the difference between original AC frequencies. For more details, see text.](image)
Semi-invasive brain stimulation

Semi-invasive brain stimulation methods, contrary to the DBS methods, do not need a permanently implanted wire or optical fiber. They need just nanoparticles incorporated into neural tissue and activated by an external non-invasive stimulus. Thus, cellular signaling deep inside the brain can be controlled remotely without permanent implants. In this context, the term “semi-invasive” is related to how nanoparticles are introduced into the body. In general, it can be injection, ingestion, and inhalation or via skin or wounds; currently, injection is only used for experimentation.

Protocols for nanomaterial-enabled neural stimulation differ according to the site where the nanoparticles are finally distributed, and what kind of primary and secondary stimuli are utilized. The nanomaterials can be dispersed or immobilized in the extracellular environment, attached to the membrane, bound to ion channels or internalized into the cytoplasm (Wang and Guo 2016). Then, a wirelessly (non-invasively) transmitted primary stimulus (light, magnetic fields or ultrasound) penetrates through the tissues and is converted by the nanomaterial into a localized secondary stimulus, primarily electric fields or heat, at the nanomaterial-neuron interface, to stimulate the neuron (Wang and Guo 2016). Depending on to the primary and secondary stimuli, nanomaterial-enabled neural stimulation techniques can be classified into opto-electric stimulation (Lugo et al. 2012), opto-thermal stimulation (Eom et al. 2014), magneto-electric stimulation (Yue et al. 2012), magneto-thermal stimulation (Huang et al. 2010), and acousto-electric stimulation (Ciofani et al. 2010). The main benefits of nanomaterial-enabled neural stimulation technique are the significant improvement of spatial resolution and that nanomaterials can be surface-modified and bio-conjugated for cell-specific targeting, can be delivered by injection, and can be matched to the dimensions of subcellular components, such as those of the neuronal membrane and ion channels (Winter et al. 2005; Lugo et al. 2012). For example, wireless magneto-thermal deep brain stimulation, developed and tested on mice (Chen et al. 2015), works through heat-sensitive capsaicin receptors in nerve cells and the injection of magnetic nanoparticles into specific brain regions (nanoparticles heated by external alternating magnetic fields activate ion channel-expressing neurons).

Even those semi-invasive brain stimulation methods are not used for pain treatment yet; there is no principal obstacle to doing that.

Non-invasive brain stimulation

New technological developments in non-invasive brain stimulation (NIBS) have boosted research in the fields of both therapeutic and neuroimaging. The growing use of NIBS in basic research and in clinical applications reflects its capabilities to modulate brain function in ways not feasible with other techniques. NIBS have continuously provided innovative insights into the functional relevance and plasticity of brain networks.

Experiments using an electro-magnetic field to influence disease processes have been reported many times over the last fifty years. Ziskin and colleagues (Radzievsky et al. 2004; Ziskin 2013) successfully demonstrated that local exposure of skin to low intensity millimeter-length waves caused the release of endogenous opioids, and the transport of these agents by the blood to all parts of the body resulted in pain relief and other beneficial effects.

Relative to the underlying physical principle, NIBS is based on transcranial stimulation either by magnetic field or by electric current. Both transcranial magnetic stimulation (TMS, which includes repetitive TMS, rTMS) and transcranial electrical stimulation (tES, sometimes called transcranial current stimulation, tCS) are utilized in neuroscience and clinical research, as well as in the diagnosis and treatment of neuropsychological disorders. TMS and tES can also be combined with EEG, fMRI, fNIRS, or guided navigation to improve clinical outcomes.

Transcranial stimulation using electromagnetic fields is used to modulate neuronal activity of the brain by applying external electric and magnetic fields to the surface of the scalp. Fields act on the tissues non-invasively up to a distance of a few centimeters below the surface of the skull; thus, the fields can reach the gyri of the cortex and to a more limited extent the sulci in between the gyri. Fields affect brain tissue by inducing depolarization or hyperpolarization of neuronal membranes, which is accompanied by a change in neuron excitability; when used at sufficiently high intensities, it can also lead to action potentials.

From a physiological point of view, TMS activates axons via short-pulsed stimulation that leads to new action potentials, whereas tES has the potential to manipulate the
membrane potential of neurons and modulate spontaneous firing rates, but is insufficient, on its own, to induce action potentials in resting neurons. Despite the very different modes of action between TMS and tES, prolonged application of either technique can cause changes in the excitability of neurons and networks that outlast the actual stimulus application by minutes or even hours.

Both techniques produce a combination of excitatory and inhibitory effects at the neuronal level. The polarization of neurons is changed and, depending on the stimulation parameters, regional cortical excitability either increases or decreases. Many different stimulation protocols have been developed over the years and it is common practice to label protocols as either inhibitory or excitatory. Even so, the effects on cortical excitability continue to be investigated with the goal of defining protocols as definitively inducing neuro-enhancement or neuro-plasticity within a specified neuronal population; frankly, there is still a long way to go. On the other hand, there are certain NIBS protocols that have become well established.

Whether there will be enhanced or impaired effects at the perceptual, cognitive, or behavioral level depends not only on excitability changes but also on the functional properties and underlying mechanisms of all brain areas involved, as well as the interactions between them. This is exactly why both neuro-disruptive and neuro-enhancement effects are scientifically valuable, i.e., in the proper theoretical framework, they allow us to begin teasing apart the affected functional neuronal architecture (Duecker et al. 2014).

Despite the current level of knowledge, many questions about the mechanisms of neuromodulation via NIBS remain open. There are basic physical facts, for instance, everyone agrees that NIBS affects neural activity and ultimately behavior through the generation of electric fields and the associated electric currents (Basser and Roth 2000; Wagner et al. 2007) or via magnetic fields (Oliviero et al. 2011), so it makes sense to refer to NIBS as having an electric component and a magnetic component. The biologic effects of all transcranial electromagnetic stimulation techniques are mediated by exogenously generated electromagnetic fields. It is the spatial and temporal field characteristics that distinguish each stimulation modality. The problem of how transcranial electromagnetic stimulation affects brain function is generally parsed into a consideration of the characteristics of the electromagnetic fields generated in the brain during stimulation and how the fields modulate brain function to ultimately effect cognitive/behavioral changes (Hallett 2007; Peterchev et al. 2012).

**NIBS: transcranial magnetic stimulation**

In transcranial magnetic stimulation (TMS), the magnetic field is produced by passing a strong current through an electromagnetic coil placed on the scalp, which in turn induces an electric field and eddy-currents in the underlying cortical tissue, where it produces localized axonal depolarization. TMS has become a major tool in brain research and the treatment of various psychiatric and neurological disorders such as depression, schizophrenia, Parkinson’s disease, Alzheimer’s disease, and various addictions (McNamara et al. 2001; Ferreri et al. 2003; Fregni et al. 2005; George and Belmaker 2007; Politi et al. 2008; Prikryl et al. 2013; Holtzheimer and McDonald 2014; Li et al. 2013; Shen et al. 2016, 2017). However, deeper structures such as the nucleus accumbens (NAc), ventral tegmental area (VTA), amygdala, medial prefrontal cortex, and cingulate lie too deep inside the brain (6–7 cm) to be reached by the magnetic fields generated through standard TMS. Deep TMS (dTMS), which uses a novel coil design suitable for direct stimulation of deeper brain regions (by significantly reducing the decay rates), has recently been demonstrated (Lu and Ueno 2017).

TMS involves administration of magnetic pulses to localized brain areas. The effects of a single TMS pulse are brief and can affect ongoing neuronal processes. Rhythmic pulse sequences, on the other hand, can yield longer-lasting effects on the human brain (Hallett 2007). The effectiveness of different frequencies of repetitive TMS (rTMS) in the treatment of orofacial pain has been tested (Rokyta and Fricova 2012; Fricová et al. 2013; Kohútová et al. 2017). Beside TMS and rTMS, low-field magnetic stimulation (LFMS) and magnetic seizure therapy (MST) are also available. Another, lesser used method, is transcranial static magnetic stimulation (tSMS), which exposes the brain to a static magnetic field by positioning a magnet on the head (Oliviero et al. 2011; Paulus 2011a). Pulsed magnetic fields have also been successfully used, to affect pain processing (Robertson et al. 2010), in the treatment of musculoskeletal chronic pain (Thomas et al. 2007), rheumatoid arthritis, and fibromyalgia (Thomas et al. 2001; Shupak et al. 2006).

**NIBS: transcranial electrical stimulation**

The history of transcranial electrical stimulation (tES) of the human brain is quite long. In ancient Rome, patients with unbearable head pain were sometimes treated with jolts from the electricity-producing black torpedo fish, or an electric ray. After Alessandro Volta’s invention (in 1800) of the electric battery (i.e., the “voltaic pile,” which was capable of producing a steady electric current), researchers began to investigate the application of direct current (DC) in a variety of neurological diseases. These early efforts were abandoned mainly because of a lack of sufficiently reliable evaluation methods.

Priori (1998) was among the first to measure the effects of direct current application on the human cortex via changes
In evoked motor potentials. To get the electrical current to pass through brain matter, tES is applied over larger areas of the cortex compared to TMS (Paulus 2011b). tES uses a weak electric current (0.1–2 mA) applied via electrodes placed on the scalp. The current field, due to inhomogeneity and anisotropy of the skull and tissues, is inhomogeneous, which leads to variance. Most of the electric current enters the surface layers (skin, etc.) and only a small portion enters the cerebral cortex, where it affects the membrane potential of neurons.

TDCS

TDCS uses a uniform electric current intensity of 0.4–2 mA for 5–30 minutes and is applied across surface electrodes placed on the head. Current changes are largest directly beneath the electrodes: the area under the cathode is targeted to reduce excitability of cortical neurons and the area under the anode is targeted to have the opposite effect. By changing the surface area of the electrodes, it is possible to vary the current density and thus the effect at both electrodes. Changes can persist for several hours after application. TDCS is reliable in terms of parameters such as stimulation intensity and duration, and validation of its plastic after-effects (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003, 2008). In order to achieve after-effects, stimulation needs to last for at least three minutes with an intensity of at least 0.6 mA (Nitsche and Paulus 2000). Not surprisingly, the direction of electrode polarization is critical in terms of the after-effects. Through stimulation of the motor cortex, tDCS can be used for: chronic pain (Deer et al. 2014; Souto et al. 2014; Hodaj et al. 2016), pain after stroke (Schjetnan et al. 2016; Chhabar et al. 2016; Russo et al. 2017) and tinnitus (Garin et al. 2011; Teismann et al. 2014).

TRNS

TRNS has a frequency spectrum that is typically divided into low frequency (0.1–100 Hz) stimulation and high frequency (100–640 Hz) stimulation. This is an effective method of avoiding directional sensitivity associated with standard TDCS and sinusoidal tACS. To screen for the most efficient frequencies, within a physiological range, random noise frequency patterns are used (Terney et al. 2008), which have the potential to desynchronize (pathological) rhythms.

TACS

TACS, which uses non-uniform flow for non-invasive transcranial stimulation, is still poorly understood. The simplest case involves stimulation using a single frequency harmonic signal in the range of 0.1–5000 Hz. TACS appears to interact with ongoing rhythms in the cortex from 0.1 Hz (delta waves) up to over 60 Hz (gamma waves) on an EEG. Sinusoidal tACS allows manipulation of intrinsic cortical oscillations with externally applied electrical frequencies. Of course, combinations using any frequency are possible, the more frequencies involved, the closer the results approach the effects of TRNS. Evidence for a relationship between alpha EEG activity (8–12 Hz) and pain has also been investigated. TACS at alpha frequencies (alpha TACS) permits direct manipulation of brain alpha activity and therefore an examination of the potential causal relationship between alpha activity and pain (Arendsen et al. 2018). While somatosensory alpha TACS can reduce pain (Gundlach et al. 2016), inter-regional phase synchronization with dual-site tACS could be beneficial for modulation of specific cognitive processes in the human brain (Saturnino et al. 2017). TACS has also been found to be a promising method for boosting memory (Marshall et al. 2006). The intensity of tACS applied frontally is usually limited to 400 mA to avoid retinal phosphenes, which can occur at higher intensities (Antal and Paulus 2008, 2016). Other evidence for the influence of TACS can be seen in the motor cortex, where 20 Hz has been shown to slow down voluntary movements (Pogosyan et al. 2009). Also, it is possible to increase alpha power, via stimulation, by using a TACS frequency within the individual's EEG range (Zaehle et al. 2017). TACS seems set to open a new era of directly interfering with cortical rhythms and actively synchronizing cortical rhythms, although at present interference with phosphenes in the frequency range of about 10–40 Hz is a problem. This problem does not occur when TACS is used in the "ripple" frequency range (Moliadze et al. 2010). Ripples
### Table 1. Overview of brain stimulation methods

| Stimulation method                  | Treatment                                                                 | References                                                                 | Advantages                                                                                                                                         | Disadvantages                                                                                           |
|-------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| DBS with implanted electrodes       | Parkinson’s disease, epilepsy, dystonia, tremor, cluster headache, chronic pain, pain from stroke, amputation, trigeminal neuralgia, multiple sclerosis, obsessive–compulsive disorder, Tourette's syndrome depression | Kringlebachi et al. 2007; Pereira et al. 2007, 2013; Holslag 2018; Johnson et al. 2008 | Strong effect, precise targeting, personalized tuning and targeting for intended structure                                                                 | Invasive electrode placement, pacemaker implanted under the patient’s skin                                  |
| Wireless magneto-thermal DBS        |                                                                             | Chen et al. 2015                                                           | Non-invasive application of the magnetic field                                                                                                       | Invasive application of magneto thermal particles                                                        |
| TMS                                 | Depression, schizophrenia, Parkinson’s disease, Alzheimer’s disease, various addictions | Holtzheimer and McDonald 2014; McNamara et al. 2001; George and Belmaker 2007; Prikryl et al. 2013; Fregni et al. 2005; Ferreri et al. 2003; Li et al. 2013; Politi et al. 2008; Shen et al. 2016, 2017 | Non-invasive                                                                                                                                       | Low spatial targeting compared to DBS, higher cost compared to other non-invasive methods                  |
| rTMS                                | pain                                                                      | Rokyta and Fricová 2012; Fricová et al. 2013; Kohútová et al. 2017; Robertson et al. 2010; Thomas et al. 2007, 2006; Thomas et al. 2001 | Non-invasive, low cost                                                                                                                                | Less pronounced effect compared to rTMS                                                                     |
| tDCS                                | chronic pain, trigeminal pain including refractory oro-facial pain, fibromyalgia, major depression, bipolar disorder, schizophrenia, Alzheimer’s disease associative learning, Parkinson’s disease, pain after stroke, tinnitus | Souto et al. 2014; Hodaj et al. 2016; Borckardt et al. 2011; Antal et al. 2010; Hansen et al. 2011; DosSantos et al. 2012; Hagenacker et al. 2014; Kreuzer et al. 2017; Fricova et al. 2016; Castillo-Saavedra et al. 2018; Valle et al. 2010; Tortella et al. 2015; Liu et al. 2017; Vigod et al. 2014; Brunoni et al. 2016; Pereira-Junior et al. 2015; Tortella et al. 2015; Bersani et al. 2015; Palm et al. 2016; Gögler et al. 2017; Agarwal et al. 2013; Nardone et al. 2012; Narita and Yokoi 2017; Bystad et al. 2016; Branscheidt et al. 2017; Hendy et al. 2016; Schabrun et al. 2016; Benninger et al. 2010; Schietnan et al. 2013; Russo et al. 2017; Teismann et al. 2014; Garin et al. 2011 | Non-invasive, low cost                                                                                     | Less pronounced effect compared to rTMS                                                                     |
| tRNS                                | chronic pain, pain after stroke, tinnitus                                | Terney et al. 2008                                                        | Non-invasive, low cost                                                                                                                                | Less pronounced effect compared to rTMS                                                                     |
| tACS                                | Pain, modulation of cognitive processes                                   | Gundlach et al. 2016; Saturnino et al. 2017; Arendsen et al. 2018; Marshall et al. 2006; Antal et al. 2008 | Non-invasive, low cost promising                                                                                                                     | Less pronounced effect compared to rTMS                                                                     |

DBS, deep brain stimulation; TMS, transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; tRNS, transcranial random noise stimulation.
are short hippocampal oscillations with a frequency between 100–250 Hz, which are associated with memory encoding.

**Interference tACS**

Interference tACS (if-tACS), as an analog of interferential therapy used in physiotherapy for significant physiological effects, may have the potential to modulate pain associated with deep brain structures. The goal of interferential therapy is to produce low frequency effects at sufficient intensity and at sufficient depth to avoid patient discomfort in the superficial tissues (i.e., the skin). Skin discomfort is related to the impedance of the skin being inversely proportional to the frequency of stimulation. The lower the stimulation frequency, the greater the impedance to the passage of the current and the greater the discomfort as current is ‘pushed’ into the tissues against this barrier. Skin, under normal conditions, (i.e., intact, room temperature, humidity 40–50%) at 50 Hz has an impedance of approximately 3200 Ohms, while at 4000 Hz it drops to approximately 40 Ohms. The result of applying a higher frequency is that it will pass more easily through the skin and requires less electrical energy input to reach the deeper tissues, thereby causing less discomfort.

The clinical application of interferential therapy is based on peripheral nerve stimulation (frequency) data. Above 250 Hz, electrical stimulation is without associated painful or unpleasant side effects. There are four main clinical applications of interferential therapy: pain relief (Johnson and Tabasam 2003; Hurley et al. 2004; Jorge et al. 2006; McManus et al. 2006; Walker et al. 2006; Atamaz et al. 2012; Gundog et al. 2012; Rocha 2012), muscle stimulation (Bircan et al. 2002; Bellew et al. 2012), increased local blood flow (Noble et al. 2000), and reduction of edema (Christie and Willoughby 1990; Jarit et al. 2003).

The physiological effects of tissue stimulation with medium frequency currents (1–100 kHz) are not completely understood. When two of these medium frequency currents pass through the tissues simultaneously and in a direction such that their paths cross, they literally interfere with each other. This interaction gives rise to an interference current that has the characteristics of low frequency stimulation (in effect the interference mimics low frequency stimulation). The exact frequency of the resultant interference frequency can be controlled by the input frequencies. If, for example, one current is 5000 Hz and its companion current is 5020 Hz, the resultant frequency would be at 20 Hz, carried by median frequency (5010 Hz) amplitude modulated current (see Figure 3). The magnitude of the low frequency interference current is approximately equivalent to the sum of the input amplitudes. Low frequency currents are physiologically effective for nerve stimulation.

Although the theoretical basis for interferential therapy is incomplete, the positive effects have been convincingly documented. Proven physiological effects include local blood flow increase, local stimulation of neurons, and local muscle stimulation. Application of current interference to the brain (i.e., if-tACS) should be expected to produce effects in the brain similar to those seen in body tissues. Except for muscle stimulation, the potential should exist for increased local blood flow and local stimulation of neurons. Based on calculations of technical parameters, there is promising potential for if-tACS to reach, with proper electrode configurations, deep brain structures involved in pain generation and transmission. Therefore, if-tACS may be capable of modulating pain associated with specialized thalamic nuclei. Compared to standard invasive DBS, the if-tACS has substantially higher respect to the brain tissue, thus a significant benefit for patients. Once tACS testing is successfully completed, if-tACS will compete with other non-invasive neuro-modulatory methods (TMS, rTMS, tDCS, and tACS). A brief overview of brain stimulation methods discussed above can be found in Table 1.

**Conclusion**

Contemporary methods of transcranial stimulation utilized in pain treatment are widely accepted in everyday clinical practice and there is an abundance of experimental experience indicating their most appropriate uses, limits, application protocols, etc.

Invasive and non-invasive brain stimulation methods have been used, for more than two decades, as an alternative to pain pharmacotherapy or as the last choice in pharmaco-resistant pain. Even though the better-established techniques continue to evolve, there is still plenty of room for new approaches and new combinations of formerly verified methods. Because of the emergence of new techniques and technologies, future expansion can be expected in semi-invasive and non-invasive methods since they are safe and comfortable for the patient, are easy to apply, and are effective, i.e., affordable in routine use.

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