The Effect of Neurostimulation in Depression

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15.1 Historical Overview

There have been reports of the medical use of electricity since the classical antiquity (Fig. 15.1), but only in the second half of the eighteenth century the effects of electricity in animals and humans were systematically studied, establishing the foundations for the electroconvulsive therapy (ECT), magnetic seizure therapy (MST), transcranial direct-current stimulation (tDCS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and repetitive transcranial magnetic stimulation (TMS) (Priori 2003). Luigi Galvani and Giovanni Aldini found that electrical currents, applied through electrodes, could stimulate nerves and produce muscle contractions in frogs and other animals. With the newly developed electric pile, Aldini applied electrical currents through the motor cortex of deceased people and obtained massive facial muscle contractions. In some of the experiments, transcranial electrical stimulation was performed in patients with mental disorders, and this technique was demonstrated effective in the treatment of *melancholy madness* (major depressive disorder—MDD). In this form of stimulation, the intensity of the electrical current was low, the patients remained seated during the procedure, and there were no seizures (Fig. 15.2) (Aldini 1804; Parent 2004). In the following years, there were few studies regarding the treatment with mental disorders with electricity. After more than 100 years of those studies, intensive research on electrical stimulation of the human brain resumed (Priori 2003).

Fig. 15.1 Marbled electric ray—*Torpedo marmorata*. In 43–40 AC, Scribonius Largus used torpedo fish like this to treat headaches. He placed the live ray on the patient's head and it delivered a strong direct electrical current, eliciting a sudden transient stupor and pain relief. Source: By Philippe Guillaume (originally posted to Flickr as fear me) (CC BY 2.0 (http://creativecommons.org/licenses/by/2.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3ATorpedo_marmorata2.jpg

In the first half of the twentieth century, based on observations of patients with epilepsy and psychosis who improved after spontaneous

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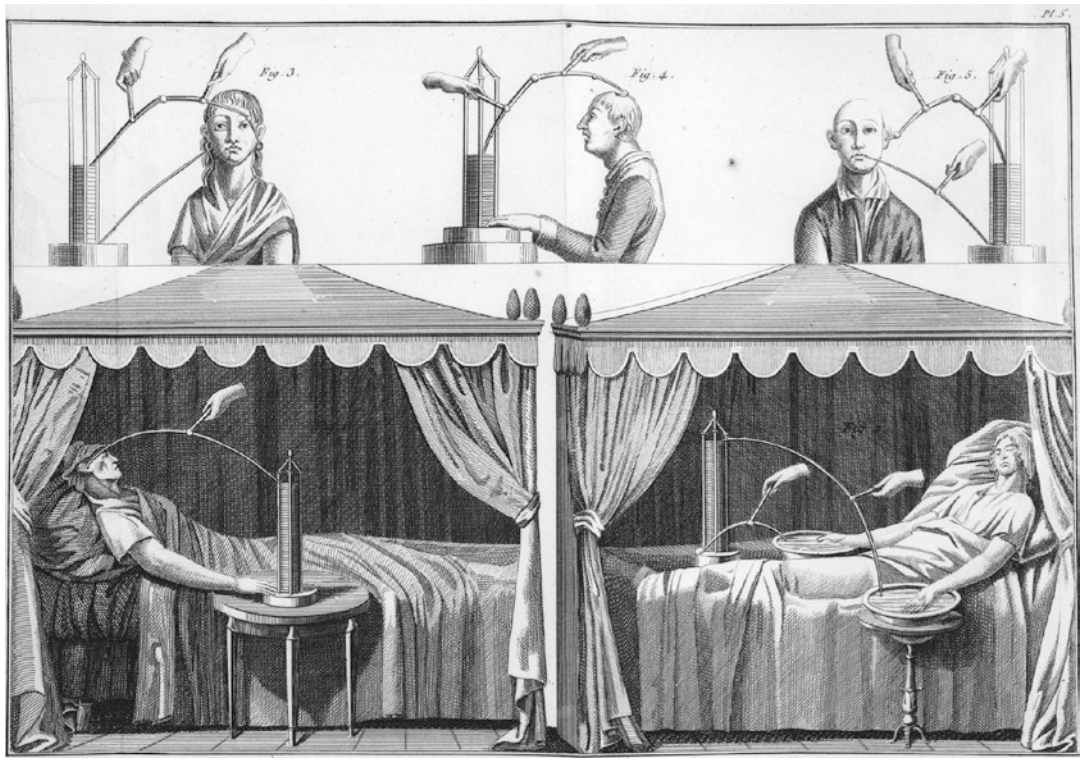

Fig. 15.2 Experimental treatment of melancholia with electrical currents. Source: Gionanni Aldini (1804). See page for author (CC BY 4.0 (http://creativecommons.org/licenses/by/4.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3AGiovanni_Aldini%2C_Essai…sur_le_galvanisme…_Wellcome_L0023896.jpg

seizures, Ladislaus von Meduna studied methods to produce seizures in schizophrenic patients. In 1934, this researcher found that camphor injections induced seizures and significant improvements of psychotic symptoms. von Meduna also demonstrated that pentylenetetrazol, a gamma-aminobutyric acid (GABA) receptor inhibitor, also produced seizures and clinical improvements. In 1938, the Italian researchers Luigi Bini and Ugo Cerletti documented the therapeutic effects of electrically induced seizures in humans (Isenberg and Zorumski 2000).

Bini and Cerletti studied the effects of electrical currents in animals and found that a direct-current flow through the heart kills them, but if the current is applied across the head, there are no significant cardiac risks. After several experiments with animals, they began the experiments with humans and demonstrated the efficacy of electrically induced seizures in treating psychotic patients (Fig. 15.3). The induction of seizures with electricity was safer and more reliable than the one produced by drugs. In a few years, ECT was disseminated through the globe. In the 1950s, when few pharmacological treatments for mental disorders were available, ECT was studied in the treatment of many of them and became the most important treatment for MDD. The development of antidepressants and the increased prejudice against ECT led to a decline in its use, although ECT is still considered one of the safest and most effective treatments for mood disorders (Isenberg and Zorumski 2000).

In the last 80 years, ECT techniques were improved, and there was a significant reduction of risks and side effects. The intense muscle contractions induced by the electrical currents provoked bone dislocation and fractures of spine and long bones. However, the use of muscle relaxants resolved these problems. The routine use of

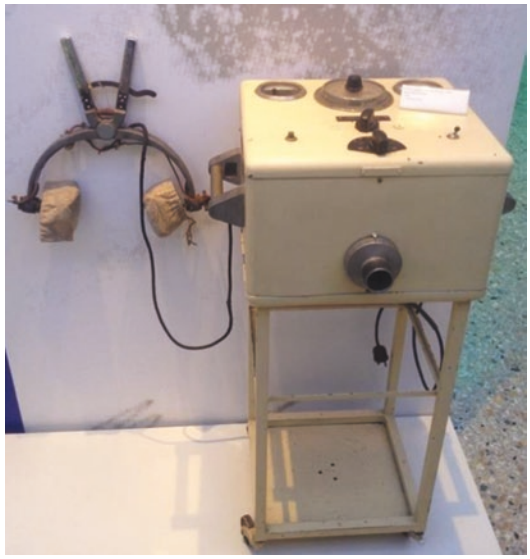

Fig. 15.3 Electroconvulsive machine designed by Bini and Cerletti to treat mental disorders. Source: By Francesca.pallone (Own work) (CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3AMacchina_elettroshock_Ugo_Cerletti.jpg

Fig. 15.4 Repetitive Transcranial Magnetic Stimulation application. Source: By Baburov (Own work) (CC BY-SA 4.0 (http://creativecommons.org/licenses/by-sa/4.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3ANeuro-ms.png

general anesthesia, vigorous oxygenation throughout the procedure, and cardiac and respiratory monitoring resulted in a decreased risk of hypoxia and cardiopulmonary complications. Other techniques such as brief-pulse electrical stimulation and unilateral ECT were developed to reduce the side effects of this treatment even more. For a long time, it was believed that electrical currents could produce therapeutic effects only if they resulted in seizures (Isenberg and Zorumski 2000).

Research with low-current stimulation of the cortex was resumed in the 1980s. Merton et al. (1982) found that short electrical pulses applied to the motor cortex produced a synchronous muscle action potential and a twitch in the adductor of the thumb and other muscles. At the same time, experiments with magnetic stimulation carried out by Barker et al. (1985) indicated that rapid time-varying magnetic fields could produce electrical currents in the cerebral cortex. They also found that each magnetic pulse on the motor cortex produced a muscle action potential and a twitch in the muscle. The major advantage of the magnetic stimulation over the electrical stimulation is that the first is pain-free, while the last may produce pain in the scalp. Both methods were effective to stimulate superficial cortex but did not reach deep brain regions. In the last 30 years, several techniques and protocols were developed to increase the efficacy of the transcranial magnetic stimulation, including the use of repetitive pulses, neuronavigation systems, and several models of magnetic stimulators and coils. TMS has been studied in many different medical conditions, and it demonstrated efficacy in the treatment of mood disorders, schizophrenia, chronic pain, stroke rehabilitation, and others (Fig. 15.4) (Ziemann 2017). Since 1995, TMS has been studied as a treatment for MDD, including the treatment-resistant clinical presentation (Anderson et al. 2016).

There is a risk of seizure in TMS applications, especially if a larger dose of magnetic stimulation is administered. This evidence made researchers question if seizures induced by magnetic stimulation would produce the same therapeutical effects as ECT, without the side effects of this technique (Engel and Kayser 2016). In 1998, Lisanby et al. (2001a, 2001b) started experiments with magnetically induced seizures in nonhuman primates and later in humans. New devices were available in the 2000s, and they were capable of stimulating continuously for up to 10 s at a 100 Hz frequency, inducing seizures reliably. As in ECT, general anesthetics and

muscle relaxants are administered before MST sessions to prevent muscle contractions (Engel and Kayser 2016).

The belief that electrical currents had to induce seizures to produce therapeutic effects led to a loss of interest in nonconvulsive electrical stimulation methods in the first half of the twentieth century. However, recently there has been a resurgence of interest in tDCS. Since the 1960s, systematic studies on tDCS and depression have been made, and most of them indicate that this form of neurostimulation is effective. It was found that direct currents induce polarization, modulating spontaneous neuronal firing, unlike ECT that excites neurons, inducing convulsive activity. tDCS does not produce seizures, loss of consciousness, and memory deficits as ECT does. In addition, the use of sedatives and muscle relaxants are not needed for tDCS (Priori 2003).

The cortical effects of the vagus nerve electrical stimulation have been a subject of interest to scientists since the late 1930s. Studies with cats, dogs, and monkeys indicated that VNS could produce neuronal activity in the orbital gyrus, lateral frontal cortex, anterior rhinal sulcus, and amygdala. Studies with experimental epilepsy in dogs indicated that VNS has anticonvulsant properties; subsequent studies demonstrated the efficacy of this technique in humans too. In 1997, the American FDA approved VNS for the treatment of epilepsy. Currently, the stimulation of the left cervical vagus nerve is made with implantable, bipolar pulse generators. The efficacy of VNS in the treatment of epilepsy and depressive disorders was demonstrated in recent studies (Chae et al. 2001).

The electrical stimulation of deep brain regions with implanted electrodes has been studied in the last 30 years. It is well established that the stimulation at different targets within the basal ganglia is effective in the treatment of Parkinson's disease (Chae et al. 2001). Recent studies also indicate that DBS may be effective in the treatment of treatment-resistant depression (Morishita et al. 2014). Both VNS and DBS are neurostimulation methods that require surgery, an obvious disadvantage compared to ECT, tDCS, and TMS, which are not invasive (Akhtar et al. 2016).

All forms of neurostimulation have acute effects, which occur during the stimulation, and aftereffects, which occur in a period of time from a few minutes to several months. In treatments administered in sessions, such as ECT, MST, TMS, and tDCS, the acute effects and the aftereffects are unambiguous. In methods with continuous stimulation, such as DBS and VNS, it is hard to distinguish between acute effects and aftereffects. Evidence indicates that the therapeutic benefits of neurostimulation are due to these lasting effects, which include changes in neuronal excitability, neurogenesis, changes in glial function, gene activation/regulation, de novo protein synthesis, morphological changes, homeostatic processes, neuroendocrine changes, and changes in neurotransmitters (Bolwig 2011; Cirillo et al. 2017; Isenberg and Zorumski 2000; Martinotti et al. 2011; Nordanskog et al. 2010; Walker et al. 1999).

15.2 Electroconvulsive Therapy

The goal of an ECT session is to induce a generalized seizure of adequate duration in the central nervous system. Electrical stimuli that do not induce seizures, or produce only partial seizures, or produce seizures with short duration are not considered effective (Isenberg and Zorumski 2000). A significant difference between ECT and the other neurostimulation methods is that, in the former, the electrical current affects the whole brain; it is not targeted to a specific area or brain structure.

There are two types of ECT devices, the constant-current stimulators and the constant-voltage stimulators. It is easier to calculate the charge administered (charge = current × time) in the constant-current stimulators, compared to constant-voltage stimulators, in which information about impedance is needed to calculate the administered charge. Older ECT devices are alternating current sine-wave generators. These waves have a frequency of 60 cycles per second, and each half sine wave has an 8.3 ms duration. Neuronal cells fire after a few milliseconds, but they remain refractory for several milliseconds

(ms) after that. As a result, much of the current flow occurs during inexcitable periods in the sine-wave stimulus. Modern ECT devices administer repeated brief square-wave pulses with a duration from 0.5 to 2.0 ms, which are much more effective than old devices to produce generalized seizures. In current devices, there may be only positive pulses or alternating positive and negative pulses, and the usual frequency is between 30 and 100 Hz. The total charge of an ECT session can be calculated by multiplying the duration of each pulse by the number of pulses by the total train duration (Isenberg and Zorumski 2000).

If ECT electrodes are placed bitemporally and a minimally suprathreshold electrical dose is administered, the treatment produces significant clinical benefits. When the electrodes are placed unilaterally in the non-dominant hemisphere, a charge as high as 2.5 times the seizure threshold is needed to produce clinical improvement. An adequate seizure should last for about 25 s. Many patient characteristics influence the seizure threshold, including age, gender, and medications in use. Compared to brief-pulse stimulus, sine-wave stimulus is ineffective and yields higher seizure thresholds. Electrical dosing schedules begin with a low electrical charge, which is increased until a generalized seizure is obtained (Isenberg and Zorumski 2000).

The efficacy of ECT in the treatment of mood disorders is unquestionable. However, it is still not entirely clear how it works. There are three main theories to explain how ECT works: (1) the generalized seizure theory, (2) the normalization of neuroendocrine dysfunctions theory, and (3) the hippocampal neurogenesis and synaptogenesis theory (Bolwig 2011).

The first hypothesis is based on the effect of generalized seizures produced by the ECT. Evidence indicates that actual ECT is more effective than nonconvulsive electrical stimulation methods such as tDCS and TMS in patients with severe mental disorders (Ren et al. 2014). In addition, unilateral ECT induces seizures, which are not as generalized as the seizures induced by bilateral ECT. Consequently, unilateral ECT is not as effective as bilateral ECT. The seizure is important for ECT to take effect, and the greater the generalization, the stronger the brainstem is activated. However, the presence of generalized seizures does not guarantee the efficacy of ECT because in some cases, even when generalized seizures are produced, this technique is ineffective (Bolwig 2011). Over the course of treatment, there is a decrease in the seizure threshold and duration, producing an anticonvulsive effect. Studies indicate that the GABA, endogenous opioids, adenosine, and glutamate may play a role in both clinical and anticonvulsive effects of ECT. This therapy also seems to have important actions on the transmission of monoamines, such as serotonin, dopamine, and noradrenaline, contributing to the antidepressant effect of ECT (Isenberg and Zorumski 2000).

The neuroendocrine theory explains only the effect of ECT in MDD. This theory states that ECT works to restore neuroendocrine dysfunction associated with this condition. Several studies indicate that severe depression of the melancholic subtype is associated with extensive neuroendocrine dysfunction, including abnormalities in the hypothalamic-pituitary-adrenal axis, increased corticotrophin-releasing hormone (CRH), cortisol hypersecretion, and blunted response to the dexamethasone test. Supporting this theory, there is abundant evidence demonstrating that ECT corrects these dysfunctions in humans by stimulating the diencephalon and inducing extensive release of several hormones and neuropeptides, such as adrenocorticotrophin (ACTH), prolactin, vasopressin, and neuropeptide Y (Bolwig 2011).

Finally, the neurogenesis theory states that ictal activity induces neurotrophic effects in the limbic system, which would be crucial for the therapeutic efficacy of ECT. On the one hand, recent evidences indicate that untreated depression is correlated to impaired hippocampal neurogenesis and hippocampus volume decrease in humans. On the other hand, animal studies demonstrated increased hippocampal volume and increased levels of BDNF and synaptogenesis in this region after serial electroconvulsive stimulation. Neuronal activation is correlated to increased endothelial cell proliferation in the hippocampus

too (Bolwig 2011). In humans, ECT series also induce significant increases in hippocampal volume and in brain-derived neurotrophic factor (BDNF) (Martinotti et al. 2011; Nordanskog et al. 2010). Both in humans and animals, there seems to be a correlation between the number of sessions and the neurotrophic effect of ECT (Bolwig 2011). Electroconvulsive stimulation induces a rapid increase of tissue plasminogen activator (tPA) in the plasma and in the central nervous system, which activates matrix metalloproteinases. These endopeptidases are essential in central nervous system regeneration and repair processes, such as neurogenesis, angiogenesis, and vascular remodeling. According to this hypothesis, tPA also participates in additional mechanisms implicated in neurogenesis that include activation of BDNF, activation of vascular endothelial growth factor, and increased bioavailability of zinc, indicating that tPA may play a crucial role in ECT-induced neurogenesis (Hoirisch-Clapauch et al. 2014).

15.3 Repetitive Transcranial Magnetic Stimulation

TMS devices produce magnetic fields and deliver magnetic pulses to the cortex. These pulses induce electrical currents in the brain tissue, depolarizing target neurons. High-frequency TMS, with more than one pulse per second, activates the stimulated regions, while low-frequency TMS, with one or less pulse per second, inhibits the target cortical areas. The position of the stimulator is critical for an effective TMS treatment. The motor cortex is the target area for motor localization and motor thresholding, while the prefrontal cortex is the main target in the treatment of MDD. Excitatory TMS over the left prefrontal cortex has been well studied and demonstrated to have an antidepressant effect. On the other hand, inhibitory rTMS is still under investigation, and a functional correlation has been found for inhibition of the right prefrontal cortex with depression. Both excitation and inhibition of cortical areas by TMS seem to be effective for the treatment of MDD (Akhtar et al. 2016).

In addition to acute changes in neural excitability, recent evidence indicate that several other mechanisms may contribute to the lasting effects of TMS. These effects are probably explained by changes in cortical synaptic transmission, resembling the long-term potentiation/long-term depression (LTP/LTD) process, and additional regulatory mechanisms from cellular to brain networks level. However, the cellular processes directly influenced by TMS are not entirely clarified (Cirillo et al. 2017).

In standard TMS protocols, the frequency ranges from 5 to 20 Hz; the stimulation is delivered in trains from 2 to 10 s, with intervals from 10 to 60 s; and the sessions last from 15 to 45 min. In theta-burst stimulation (TBS) protocols, bursts of three pulses at 50 Hz repeated at 200 ms intervals are delivered in a 1–6 min session. Despite the short session duration, TBS induces aftereffects with the same or longer duration than conventional TMS. In continuous TBS, a single train of burst lasting 20–40 s is delivered, and it has inhibitory effect in the cortex. Intermittent TBS, which consists of the same burst train split into twenty 2 s sequences, repeated every 10 s, has an excitatory effect. Two pulses delivered at 1.5 or 2 ms interstimulus intervals, repeated every 5 s, (I-wave TMS) produces bidirectional changes in excitability with high temporal fidelity. Studies also indicate that the delivery of four subthreshold pulses (quadripulse stimulation) at 1.5 ms or longer intervals could induce bidirectional plastic changes on a broader temporal scale (Cirillo et al. 2017; Milev et al. 2016).

Therapeutic neurostimulation application requires the induction of long-lasting changes. In humans, modifications dependent to N-methyl-D-aspartate receptor (NMDAR) and Ca^{2+} channels induced by TMS protocols point to long-term synaptic changes similar to the synaptic plasticity demonstrated in cellular and animal studies. Nevertheless, early modifications of synaptic function are needed, and they are produced by: (1) changes in Ca^{2+} dynamics and activation of Ca^{2+}-dependent enzymes, modulation of the glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)/NMDAR expression, and induction of immediate-early genes; (2) modulation of neu-

rotransmitters release; (3) effects on neurotrophic factors; (4) effects on neuroendocrine systems; and (5) effects on the glial network, inflammation, oxidative stress, and prevention of neuronal cell death (Cirillo et al. 2017).

15.3.1 Intracellular

Changes in the level of neural excitability and initiation of action potential are produced by TMS. It also alters channel/receptor properties and membrane resting potentials and thresholds, consequently changing spontaneous activity, synaptic connectivity, and/or timing dynamics of cellular gating components (Cirillo et al. 2017).

Animal studies also demonstrated morphologic changes with magnetic stimulation. On the one hand, 1 T low-frequency stimulation produced extensive dendritic/axonal arborization, increased synapses density, and other modifications in hippocampal neurons. On the other hand, the same kind of stimulation, but with a stronger magnetic field (1.55 T), reduced the axonal and dendritic arborization, consequently decreasing the number of synapses (Ma et al. 2013). In vitro studies demonstrated that high-frequency magnetic stimulation could produce changes in dendritic spines morphology (Cirillo et al. 2017).

Magnetic stimulation produces increases in glutamatergic transmission, MNDAR activation and sensitization, changes in the AMPAR, and increased conductance of Ca^{2+} channels. There is an activation of immediate-early genes, which, in turn, activate other genes. The downstream genes modulate the expression of several proteins, producing functional and structural modifications in the neurons. These changes include the expression of second messengers and membrane receptors. Immediate effects of neurostimulation become long-lasting effects through the activation of immediate-early genes. It was also demonstrated that TMS may modulate histone H3 and H4 acetylation, changing the expression of genes associated with neuronal function and structure (Cirillo et al. 2017).

15.3.2 Neurotransmission

Studies demonstrated that TMS can interfere with 5-hydroxytryptamine (5-HT) receptors, including 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A}. Changes in these receptors could produce increased serotonergic transmission, explaining the antidepressant effect of TMS. Magnetic stimulation also alters dopaminergic neurotransmission. Acute stimulation increases dopamine in several brain areas, while repeated stimulation modulates the expression and activity of monoamine transporters. GABA modulates cortical excitability, which is also influenced by TMS. Depending on the stimulation protocol, the cortical excitability could be increased or decreased, probably producing opposite effects in GABAergic neurotransmission. Currently, it is not entirely clear how magnetic stimulation affects the (inhibitory) GABA system, but it has been established that this kind of stimulation increases the (excitatory) glutamate neurotransmission. Acetylcholine has an important role in the central nervous system neuroplasticity and seems to mediate the long-term effects of neurostimulation (Cirillo et al. 2017).

15.3.3 Neurotrophins

Neurotrophins play a major role in synaptic plasticity and neuronal survival and differentiation. In vivo animal studies demonstrated that TMS may increase brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and other neurotrophins (Cirillo et al. 2017).

15.3.4 Neuroendocrine

The activation of the hypothalamo-pituitary-adrenal (HPA) and the sympathoadrenal systems is an important element of the physiological response to stress. The glucocorticoids, which are the end-products of the HPA axis activation, are also involved in synaptic plasticity. Studies with TMS indicate that this neurostimulation method probably modulates the HPA axis,

decreasing the cortisol levels in resting state and in response to stress as well (Cirillo et al. 2017).

15.3.5 Neuroinflammation and Glial Network

Neuroinflammation is a response to external stressors, and it is characterized by the activation of astrocytes and microglia. Consequently, pro-inflammatory mediators are released, and free radicals are produced, including reactive oxygen species, which lengthen the inflammatory state. This state induces maladaptive synaptic plasticity and imbalanced neurotransmitter homeostasis. Magnetic stimulation leads to the release of pro-inflammatory mediators and produces a pro-oxidative state, which, in turn, activates the anti-inflammatory/antioxidant systems. The activation of these systems restores the balance of anti-/pro-inflammatory mediators and protects the central nervous system. TMS modulates the activation of astrocytes and microglial cells (Cirillo et al. 2017).

15.4 Other Neurostimulation Methods

The short-term and long-term changes produced by ECT and TMS have been extensively studied, although studies on modifications induced by newer neurostimulation techniques such as MST, tDCS, DBS, and VNS are still scarce. One may hypothesize that many of these effects obtained with ECT and TMS could also be achieved with MST, tDCS, DBS, and VNS.

15.4.1 Magnetic Seizure Therapy

One of the main technical problems with ECT is that high-skull impedance shunts most of the electrical stimulus through the scalp and cerebrospinal fluid, and away from the brain, reducing the control over the spatial distribution and magnitude of intracerebral current density. This limitation precludes refining convulsive therapy and reducing its side effects, especially cognitive deficits. In ECT, there is a widespread stimulation of cortical and subcortical regions. Bitemporal ECT, which is associated with higher shunting and deeper brain stimulation, is also associated with more severe cognitive side effects (Cretaz et al. 2015).

Noninvasive stimulation of specific areas in the cerebral cortex through nonconvulsive magnetic stimulation has some advantages and disadvantages over ECT. TMS is more focal than electrical stimulation because it avoids the impedance of the scalp and skull and results in an induced electric field confined to superficial cortex. Therefore, the current path and density are more controlled. The high safety and few side effects of TMS may be explained by the high control over electrical currents. Despite the demonstrated antidepressant effect, TMS is not as effective as ECT in the treatment of treatment-resistant depression and suicidality (Cretaz et al. 2015).

In TMS, seizures are considered side effects and are avoided by decreasing the intensity of the stimulation. In MST, an intense magnetic stimulation is administered to produce seizures, aiming at the same antidepressant effect produced by ECT. Although, more accurate and focal seizures triggered by magnetic stimulation could lead to fewer adverse effects than seizures induced by ECT. Commercially available coils permit targeting specific brain areas, and the magnetic pulses penetrate only a few centimeters deep. These pulses induce seizures, which are originated in superficial cortex, and there is no direct electrical stimulation of temporal lobe structures, such as the hippocampus, which are implicated in ECT-related memory impairment. Actually, clinical studies demonstrated the superiority of MST over ECT regarding cognitive side effects, but the former was not as effective as the later in the treatment of treatment-resistant depression (Cretaz et al. 2015). The long-term effects of MST were not adequately studied yet, but one could infer that it could produce the same neurobiological changes produced by ECT, including neurogenesis/synaptogenesis, neuroendocrine modifications, and changes in GABA, endogenous opioids, adenosine, glutamate, and monoamines.

15.4.2 Transcranial Direct-Current Stimulation

In tDCS, a weak constant current (1–2 mA) is applied to the brain for 5–20 min using a pair of saline-sponged electrodes, inducing changes in cortical excitability. One of the electrodes is placed on the scalp, above the cortical area to be modulated, while the other electrode is placed distantly. Changing the polarity of the current produces opposite effects on cortical excitability. Depolarization of neuronal compartments closer to the electrode and consequent increased cortical excitability can be achieved by anodal tDCS. Neuronal hyperpolarization and decreased cortical excitability may be produced by cathodal tDCS. The polarity, duration, and intensity of tDCS vary according to the protocol in use. This neurostimulation technique produces polarity-dependent changes of cortical excitability, but the membrane depolarization is not sufficient to elicit action potentials (Cirillo et al. 2017).

It was demonstrated that tDCS may induce long-term potentiation in mouse motor cortex and rat hippocampus. The long-term potentiation may produce several changes in the central nervous system, including promoting synaptic plasticity and activating immediate-early genes. Unlike TMS, tDCS does not increase the levels of BDNF, NGF, and other neurotrophins. However, it was demonstrated that tDCS decreases the activation of HPA and sympathoadrenal systems, leading to a cortisol reduction and a heart rate variability increase. Like TMS, tDCS also modulates glial cell functions (Cirillo et al. 2017).

15.4.3 Deep Brain Stimulation

The most invasive and precise neurostimulation method is the DBS. The neurostimulator is implanted under the skin, and a thin electrode is inserted directly into a specific brain structure. Then, different currents are applied at varying intensities until the desired effect is produced. On the one hand, high-frequency (>50 Hz) stimulation creates a transient functional lesion and inhibits a brain region from normal participation in brain activity. On the other hand, low-frequency stimulation may intermittently activate a region. DBS in subthalamic nucleus has been reported to produce acute depression, laughter, imaginative associations, and feelings of well-being. However, the neuronal network associated with affective symptoms has not yet been identified, and it remains to be determined if stimulation of this network has therapeutic potential in treating mood disorders (Chae et al. 2001).

15.4.4 Vagal Nerve Stimulation

An implantable, multiprogrammable, bipolar pulse generator is implanted in the left chest wall to deliver electrical signals to the left vagus nerve through a bipolar lead. This bipolar lead is wrapped around the left vagus nerve near the carotid artery through a separate incision at surgery and is connected to the generator. There is an external programming system, which includes a programming wand, a software, and a computer. The clinician can identify, read, and change device settings through this system (Chae et al. 2001).

The vagus nerve is composed of about 20% efferent fibers and about 80% afferent sensory fibers, carrying information to the brain from the head, neck, thorax, and abdomen. These fibers relay information to the nucleus tractus solitarius and then to many areas of the brain. This brain structure passes along incoming sensory information to higher brain regions such as the reticular formation in the medulla and ascending projections to the forebrain. These projections include connections with the parabrachial nucleus, hypothalamus, locus coeruleus, thalamus, amygdala, insula, bed nucleus of stria terminalis, and prefrontal cortex. Positron emission tomography studies indicate that VNS acutely increases synaptic activity in structures directly innervated by central vagus structures and areas that process left-sided somatosensory information. In addition, VNS acutely alters synaptic activity in multiple limbic system structures bilaterally, such as amygdala, hippocampus, and cingulate gyrus. It

seems that the brain undergoes substantial changes over the course of treatment with VNS. Functional magnetic resonance imaging studies in depressed patients implanted with VNS generators show that VNS activates many anterior paralimbic regions. Animal and clinical studies demonstrated that treatment with VNS also produces changes in serotonin, noradrenaline, GABA, and glutamate, which are neurotransmitters associated with the pathophysiology of depressive disorders. Mood improvements were observed in patients with epilepsy treated with VNS, indicating that the indirect stimulation of limbic structures could improve mood regulation (George et al. 2000; Walker et al. 1999).

Conclusions

The neurostimulation methods are diverse. The most important difference between these methods is that ECT and MST induce seizures, while the other methods produce more subtle acute effects. Magnetic stimulation methods seem to produce an effect that is similar to the one induced by direct electrical stimulation. Nevertheless, all techniques induce electrical currents in the brain, producing functional and structural modifications. Clearly, the immediate target of these neurostimulation methods is the polarity of the neuron. Calcium channels, NMDAR, AMPAR, and other receptors/channels in the cellular membrane are affected by neurostimulation by means of neuronal depolarization and increase or decrease of neuron excitability. These immediate effects are followed by a cascade of changes within the neuron, including changes in gene expression and second messengers. Neurostimulation modulates glutamatergic, serotonergic, dopaminergic, GABAergic, and cholinergic neurotransmission. The HPA and sympathoadrenal systems are also modulated by neurostimulation, which reduces the release of corticotrophins and cortisol. These techniques also play a significant role in the regulation of glial cell activity, neuroinflammation, and oxidative stress.

Recent studies demonstrated that neurostimulation produces several neurobiological changes in the brain, but it is still not entirely clear which of these mechanisms produce the improvement of depressive symptoms. Both antidepressants and neurostimulation techniques, which are effective in the treatment of MDD, play a major role in the modulation of several neurotransmitter systems. This is probably the most promising mechanism to explain the antidepressant effect of neurostimulation.

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