1 Introduction to Brain Stimulation

Irving M. Reti and Andrew D. Chang

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Introduction

Brain stimulation refers to neural modulation of specific brain regions or networks, typically by electric or electromagnetic fields. Stimulation can result in therapeutic seizures or be nonconvulsive. Nonconvulsive stimulation can be accomplished either by direct stimulation of neural pathways through implantation of electrodes or noninvasively. Devices and technologies that deliver brain stimulation have emerged as both tools to probe brain function and as therapeutic options for patients with neuropsychiatric disease who fail to respond to or cannot tolerate medications and other therapies. Interest among researchers in brain stimulation has grown enormously in the past decade for several reasons: our understanding of brain function and circuitry has increased immensely; innovative technology to stimulate the brain focally targeting specific networks has developed in parallel; neuropsychiatric disease makes up an increasingly large proportion of disease and disability worldwide, which oftentimes is resistant to conventional pharmacological treatments. Evidence for the increased interest in the field is revealed by a search on PubMed using the key words “Brain Stimulation”: there were 121 hits in 2000, 625 hits in 2007, and 1500 hits in 2013.

Although electroconvulsive therapy (ECT) dates back to the 1930s, little is known about how it works; likewise for the newer brain stimulating technologies which are also evolving as technology and our understanding of brain function improve. Moreover, brain stimulation is expanding in scope both as a way to probe brain function and as a treatment. Just as there are texts focused on psychopharmacology for students and researchers, the same is required in the field of brain stimulation. We hope to have created such a volume which is an introduction to this rapidly expanding field.

Key to understanding how brain stimulating technologies work is an understanding of brain circuitry that mediates normal and abnormal brain function. As a result of the neuronal activation triggered by brain stimulation, a cascade of molecular events leads to long-lasting neuronal changes especially at the synapse that outlives the initial stimulus and can last hours, days, or longer. Accordingly, the first part of the book focuses on neuronal circuits subserving the motor and limbic systems and the activity dependent changes in neuronal function triggered by brain stimulation (Chapters 2–4). The second part of the book focuses on the brain stimulation technologies themselves that can be categorized as either noninvasive (Chapters 5–13) or invasive (Chapters 14–17). Within the noninvasive category, the technology may be convulsive (Chapters 5–8), relying on therapeutic seizure for efficacy or nonconvulsive (Chapters 9–13) using electromagnetic or electrical stimulation without
seizure induction. Chapter authors are leading experts in their specialized area within the field of brain stimulation.

**A Historical Perspective**

Key milestones in neuroscience discovery have been critical for today’s progress in the field of brain stimulation (Finger 1994; Finger 2000; O’Shea 2013). The field of neuroscience began in earnest when Hippocrates stated that the brain is the seat of intelligence. However, it would not be until 1791 that its electrical nature was elucidated by Luigi Galvani and Alessandro Volta, who used electricity to activate nerves and muscles of the frog. The 19th century saw a boom in discoveries of functional neuroanatomy. For example, Paul Broca and Carl Wernicke described the brain structures responsible for speech and aphasias. In 1889, Sir Victor Horsley published the somatotopic map of the monkey motor cortex, giving rise to the concept of the homunculus. That same year, Santiago Ramon y Cajal posited the "connectionist" theory, according to which the brain functions through complex communication among individual neurons. His work was instrumental in bringing forth the modern era of systems neuroscience, the idea that the nervous system is composed of a series of modular circuits for each brain function. Through the work of Mahlon Delong and others we now recognize a parallel organization of functionally segregated basal ganglia–thalamocortical circuits with each circuit engaging specific regions of the cortex, striatum, pallidum, substantia nigra, and thalamus (Alexander et al. 1986; see Chapters 2 and 3).

In parallel to the advances in understanding the circuits that mediate brain function, there have been equally important discoveries in understanding how neurons function at the cellular level, including how neurons communicate and how memories are formed. Donald Hebb’s formulation of long-term potentiation in his 1949 book *The Organization of Behavior* was a key advance in understanding how neurons adapt in the learning process. He coined the phrase “neurons that fire together, wire together,” which is the basic mechanism underlying synaptic plasticity (see Chapter 4). These and other key neuroscientific discoveries have provided the impetus for understanding and developing brain stimulation modalities.

Although brain stimulation is an evolving field, the “gold standard” brain stimulating treatment for depression, ECT, dates back more than 70 years. During the subsequent decades, pharmacologic treatments for neuropsychiatric disease dominated. Most novel brain stimulation methodologies have emerged only in recent years following advances in technology, improved understanding of brain pathways subserving neuropsychiatric disease and treatment response, and as a response to medication ineffectiveness or intolerance. Some of these brain stimulation technologies began as research tools for scientists trying to noninvasively probe brain function, for example, transcranial magnetic stimulation (TMS), and were later co-opted by psychiatrists and neurologists as potential treatments. However, deep brain stimulation (DBS) is an example of a treatment modality that has emerged out of our increasing knowledge about brain pathways subserving neuropsychiatric disease.

The burden of neuropsychiatric disease is increasing rapidly and worldwide. According to the World Health Organization, depression is now the leading cause of disability in the world and four of the six leading causes of years lived with disability are due to neuropsychiatric disorders namely depression, alcohol-use disorders, schizophrenia and bipolar disorder. It is estimated that the cost of mental health problems in developed countries is between 3% and 4% of GDP. Unfortunately, medication is ineffective or insufficient for many patients with neuropsychiatric disease. For example, about 30 percent of patients with major depression do not respond to currently available medications or experience intolerable side effects (Rush et al. 2006). Accordingly, there is increased focus on alternative treatment modalities such as brain stimulation as evidenced by the steep rise in research interest in the field, recent clinical trials, and
regulatory approval of several brain stimulating technologies in the past two decades, for example, DBS for Parkinson’s disease, vagus nerve stimulation (VNS) for epilepsy and depression, and TMS for depression.

**Focal Activation**

A major goal of brain stimulating devices is to focally stimulate neural circuits leaving nearby brain regions unaffected. This feature is critical for using these devices as tools to study specific pathways and plasticity within them, and for developing treatments for neuropsychiatric disorders that minimize side effects especially compared with pharmaceuticals. Taking medication has the advantages of convenience and typically being cheaper. However, it may elicit unpleasant or dangerous side effects and must cross the blood-brain barrier, resulting in inadequate or variable levels in the brain. On the other hand, brain stimulating techniques can target key brain regions directly, focally and quickly, facilitating accelerated responses and greater efficacy compared with pharmaceuticals, without producing systemic and local side effects.

**Convulsive Stimulation**

Long before electricity could be harnessed by man, Hippocrates observed that high fever brought on by malaria could trigger convulsions in mentally disturbed people yielding a therapeutic benefit. In the late 1700s, physicians began using chemical agents to trigger seizures, and in the 1930s, electricity would replace chemical agents as a more predictable method for inducing a seizure. See Chapter 5 for a very thorough introduction to convulsive therapy, including its history. To this day, ECT remains the “gold standard” treatment for medication-resistant depression, and in many developing countries it is the first line treatment for mania and other psychoses as well (Gallegos et al. 2012, Tripathi et al. 2014). Since the introduction of ECT, there have been major advances in how it is delivered, for example, the use of brief rather than sine wave pulses, which significantly reduced cognitive side effects. In recent years, even narrower, so-called ultrabrief pulses have been investigated, which are associated with even less cognitive disturbance. It is thought that narrower pulses reduce the volume of neural tissue being stimulated resulting in fewer cognitive side effects. See Chapter 6 for a comprehensive review of efforts to enhance the efficacy of ECT and decrease its cognitive side effects.

Because ECT is such an effective treatment for major mental illness, and yet is associated with memory loss, there is considerable interest in learning more about how it works, in order to optimize its efficacy, minimize cognitive side effects, and guide the development of other potentially efficacious pharmacologic and somatic treatments. Such alternative treatments ideally would not trigger the cognitive side effects of ECT or require anesthesia but would yield similar therapeutic outcomes. Endeavors to understand how ECT works have focused on changes it triggers in the hippocampus and prefrontal cortex, brain regions implicated in the antidepressant efficacy of other modalities. The hippocampus is critical for learning both neutral and emotionally charged information. Hippocampal plasticity, including expression of neurotrophic factors, neurogenesis, and neuritic outgrowth is particularly sensitive to ECT. Connectivity in the prefrontal cortex disrupted by depression is likewise sensitive to the effects of ECT. Emerging data from human, nonhuman primate and theoretical head modeling is teaching us more about how electrode placement and ECT stimulus parameters affect prefrontal and hippocampal plasticity as well as the therapeutic outcome. For a thorough review of this topic see Chapter 7.

The search for convulsive therapy focality, in order to reduce cognitive side effects while maintaining efficacy, first led to the development of right unilateral (RUL) electrode placement in the late 1940s as an
alternative to bitemporal placement. RUL placement avoids direct stimulation over the language centers of the dominant hemisphere. Later, bifrontal placement and more recent electrode configurations, such as focal electrically administered seizure therapy (FEAST), target the prefrontal cortex (reviewed in Chapters 5 and 6). There have also been developments in setting ECT electrical parameters, including pulse width and amplitude that are aimed at more focal stimulation such as lowering and individually titrating pulse amplitude (see Chapters 7 and 8).

Developed by Holly Lisanby and Harold Sackeim in the past 15 years, magnetic seizure therapy (MST) is a more focal form of convulsive therapy that utilizes transcranial magnetic induction of electrical currents. See Chapter 8 for a very thorough review of the technique and outcomes. The magnetic field passes through the scalp and skull unimpeded and induces current that is confined to the superficial cortex but that is of sufficient strength to trigger a seizure. The superior spatial targeting of MST compared with conventional ECT spares deeper structures triggering a seizure with the minimum current possible. Studies show that while MST preserves the efficacy of ECT, it results in fewer cognitive side effects even when compared with ultrabrief pulse ECT (McClintock et al. 2013), perhaps because MST has reduced impact on hippocampal plasticity.

**Nonconvulsive Stimulation**

**Transcranial Magnetic Stimulation**

TMS relies on Michael Faraday’s principle of electromagnetic induction. Electric pulses in a figure-of-8 coil induce a changing magnetic field at right angles to the coil that permeates through the scalp and skull and induces an electric field in the brain, focally and noninvasively depolarizing neurons. Secondary neurons are stimulated affecting more distant sites. Barker et al. (1985) built the first magnetic stimulator at the University of Sheffield, which they used to stimulate the motor cortex causing a muscle action potential. Initially, TMS was used for painless, noninvasive mapping of brain function. Repetitive pulses or trains of pulses (“rTMS”) were found to provoke long-lasting up- or downregulation of activity at synapses, including in brain regions that regulate movement and emotion (Huang et al. 2005). See Chapters 4, 9, and 10 for more on the mechanism of action of TMS.

rTMS can be used as a tool to probe brain function. For example, dopamine release, which is implicated in depression, addiction, and movement disorders, has been studied in humans using rTMS. Strafella et al. (2001) and Cho and Strafella (2009) have observed that dopamine release in the striatum and anterior cingulate cortex, respectively, is modulated by rTMS over the DLPFC. Similarly, rTMS over the motor cortex also modulates dopamine release in the striatum (Strafella 2003). Also, as outlined briefly below and extensively in other chapters, TMS can also be used to probe functional connectivity between brain regions.

The long-lasting changes triggered by rTMS, that outlast the stimulation itself, are also critical to the therapeutic effects of rTMS in treating depression and other neuropsychiatric conditions, which are reviewed extensively in Chapter 12. The observation of hypoactivity in the prefrontal cortex of depressed patients led Mark George and colleagues to evaluate the effectiveness of focal stimulation by rTMS for enhancing activity in this region and combating depression. rTMS has turned out to be devoid of the cognitive side effects associated with ECT. However, although it is more effective than antidepressant medication, it does not seem to be as effective as ECT (Reti 2013). Moreover, it is time-consuming and costly. Therefore, the challenge is learning more about clinical predictors or biomarkers of response and improving its efficacy. Along those lines, increased pulse number, placement over the F3 site of the 10–20 EEG system, concurrent use with antidepressants, and the addition of right sided DLPFC pulses probably account for improved efficacy reported in recent observational studies (Carpenter et al. 2012; Connolly et al. 2012) compared with
randomized trials conducted several years ago. A new development is recent FDA approval of the H-coil for treating depression, which can stimulate more deeply but also less focally (Levkovitz et al. 2014). It is not known how the H-coil compares with the conventional figure-of-8 coil as a treatment for depression.

In Chapter 10, Angel Peterchev and colleagues provide an overview of the state of the art of TMS devices, including pulse sources with flexible control of the output waveform parameters and a wide variety of coil designs. Flexible pulse waveform is an area of active investigation as the pulse shape affects the selectivity of the neural subpopulation activated. The coil geometry and position determine primarily the spatial distribution of the electric field induced in the head. Peterchev and colleagues illustrate the spatial stimulation characteristics of a large number of commercial and experimental coils with electric field simulations, demonstrating a tradeoff between depth and focality. None of the coil designs can achieve both depth and focality simultaneously. Nonetheless, advances are being made in TMS delivery and include the potential for integrating neural responses in real time, akin to work in DBS, described below. One interesting technology on the horizon that has the potential to overcome the difficulty of stimulating both focally and deeply is transcranial pulsed ultrasound that has been demonstrated in the intact mouse brain (Tufail et al. 2010; see also Chapter 9).

Transcranial Direct Current Stimulation (tDCS)

Treating medical ailments electrically dates back to antiquity and included harnessing electrical energy from fish (Stillings 1975). The first use of low intensity direct currents for treating neuropsychiatric conditions dates back to 1804 when Aldini reported its effectiveness for melancholia (Zaghi et al. 2010). In the 1960s and 1970s, it was demonstrated that direct currents applied intracerebrally (Bindman et al. 1964) or transcranially (Dymond et al. 1975) could alter cerebral blood flow, as well as EEG patterns and evoked potentials (Pfurtscheller 1970). tDCS was then largely forgotten until Michael Nitsche and Walter Paulus demonstrated, in their studies in the past 15 years, that weak direct current applied to the scalp could modulate cortical excitability, which lasted for minutes to hours after the termination of the stimulation. Whereas TMS triggers an action potential, tDCS instead modulates membrane potential making it more or less likely for another input to cause neuronal firing. (See Chapters 4 and 13 for more on the mechanism of action of tDCS.) Therefore, concurrent stimulation is probably more important for the efficacy of tDCS than it is for TMS, whether that be for psychiatric or neurological applications. For example, recent trials have demonstrated that concurrent cognitive training can augment the antidepressant effect of tDCS (Brunoni et al. 2014; Segrave et al. 2014).

tDCS is a simple and inexpensive form of brain stimulation. There are no cognitive side effects. Efforts are also being made to increase focality using alternate electrode configurations and smaller electrodes, so-called high definition tDCS. There is much interest in tDCS ranging from teenagers wanting to improve performance on video games to evaluating tDCS as a treatment for depression. In fact, there is evidence that tDCS can improve the cognitive performance on a task when it is administered concurrently (Martin et al. 2013), and according to the website clinicaltrials.gov there are presently at least a dozen ongoing trials of tDCS for treating depression or bipolar depression.

Connectivity

Appreciating neural circuits and their connections is critical for understanding neuropsychiatric disease and for developing effective treatments, especially brain stimulation treatments, many of which target specific pathways and networks. The term “functional connectivity” refers to how brain regions in a circuit or
network interact. It is defined as the correlation between remote neurophysiological events in the temporal domain (Friston et al. 1993; Horwitz 2003; Fox et al. 2012a). Functional connectivity can be both monitored and affected by brain stimulation modalities.

Assessing Functional Connectivity Using Brain Stimulation Modalities

One can assess functional connectivity noninvasively in normal and disease states using a wide variety of evolving techniques. These techniques include both brain stimulating modalities and functional imaging, sometimes in combination. In Chapter 11, Cantarero and Celnik present a very thorough review of the use of twin TMS for assessing functional connectivity. They describe a paired pulse protocol where one coil is stimulating over the primary motor cortex (M1) and the other coil over a brain region that connects to M1. The readout is the motor evoked potential. Such investigations can reveal markers of disease states that reflect altered connectivity between the two stimulation sites. For example, depression is associated with reduced peripheral cortical paired associative stimulation induced plasticity, a test that is independent of subject motivation and effort (Player et al. 2013). Although bifocal TMS gives precise temporal information about the connectivity of cortical regions connected to the motor cortex, it is limited to the motor system as one needs an observable output in the form of a motor evoked potential. To assess connectivity in other parts of the brain requires other modalities that can sample activity in other areas such as EEG or functional neuroimaging utilizing PET or functional MRI (fMRI).

fMRI is an MRI procedure used to assess brain activity by identifying associated changes in blood flow. This procedure can map out neural activity by correlating spontaneous fluctuations in blood-oxygen-level dependent (BOLD) signals in different regions of the brain (Deco et al. 2011). It can assist in determining connectivity in different parts of the brain, in both resting and functional states. When interactions between brain regions are being probed by fMRI when the person is at rest, it is known as “resting state connectivity.” Identified deficits can reveal potential markers of pathological disease states. For example, “hyperconnectivity” within and between the default mode and cognitive control networks has been observed in depression (see Chapter 7). Researchers can also probe connectivity in real time when the brain is reacting to an event, a task the subject is asked to perform, or concurrent TMS over a particular region of the cortex. Brain activity triggered by TMS can be monitored by fMRI or EEG, which is also reviewed in Chapter 11. Concurrent TMS–fMRI is particularly technically challenging because of the magnetic resonance generated by the TMS coil and because of the strong magnetic force of the fMRI scanner on the TMS coil. The design of such devices is thoroughly reviewed in Chapter 10. This is an exciting field as it allows one to detect real-time changes in brain responses in both the stimulated cortical targets and the remote connected regions, as demonstrated in recent motor (Yau et al. 2013) and prefrontal cortex (Chen et al. 2013) connectivity studies.

Effects of Brain Stimulation Modalities on Functional Connectivity

The common mechanism underlying convulsive and nonconvulsive therapies is an electric field that triggers either a seizure or nonconvulsive neuromodulation that results in a long-lasting alteration in connectivity. Such changes in connectivity can be assessed in a variety of ways, as described above, which can provide insight into how the brain stimulating technology works, who might respond to it, and how its therapeutic use can be optimized. For example, in the field of rTMS, work by Pascual-Leone and colleagues (Fox et al. 2012b) suggested that the antidepressant efficacy of focal brain stimulation might be optimized by targeting based on connectivity monitored by resting state fMRI, specifically, a negative correlation between the DLPFC stimulation site and the subgenual cingulate. Direct support for that hypothesis has recently been published (Liston et al. 2014). The effects of brain stimulating treatments on connectivity are thoroughly reviewed in this volume. For example, for effects on synaptic plasticity see Chapter 4, for effects of ECT see Chapter 7, for effects of TMS see Chapters 9 and 11, for effects of tDCS see Chapter 13.
Development of Invasive Brain Stimulation

Neurosurgery for neuropsychiatric conditions dates back to ancient times. Cave paintings from the Neolithic period demonstrate the practice of trephination or drilling burr holes into the skull to cure mental disorders and epilepsy (Brothwell 1963). More recently, frontal lobotomy, which consisted of destroying the prefrontal cortex or its connections, was practiced widely in the 1940s for the treatment of psychiatric illness, before the introduction of antipsychotic medication, and despite frequent and major adverse effects. It was an improved understanding of functional neuroanatomy and advances in modern neurosurgical techniques such as the development of stereotactic surgery in the 1940s that led to the development of more anatomically specific neurosurgical ablation for severe neuropsychiatric conditions that failed to respond to the increasing pharmacological armamentarium. In parallel with the development of the stereotactic apparatus for ablative surgery, sporadic reports appeared describing depth electrode stimulation of chronically ill psychiatric patients who received transient benefit from such interventions (Hariz et al. 2010). Further advances in our understanding of neural circuitry, experience with ablative surgery, and the development of miniature pacemakers heralded the modern age of invasive brain stimulation focused on movement, rather than psychiatric, disorders with the first trial of DBS for Parkinsonian tremor reported by Benabid in 1987. Movement disorders are now established indications for DBS, and a number of other neurological and psychiatric conditions are under active investigation.

In comparison with noninvasive stimulation, invasive brain stimulation offers improved spatial accuracy and does not cause cognitive side-effects nor requires repeated anesthesia as for convulsive therapies. Stimulation can either be chronic, intermittent, or, as described below, precisely synchronized with electrophysiological or behavioral feedback signals. Interestingly, the therapeutic mechanism of DBS appears to vary by the neuropsychiatric condition it is being used to treat and the site it is targeting. Generally speaking, stimulation activates axons, soma, and dendrites. We are starting to learn more about which of these neural elements are responsible for the therapeutic actions of DBS, be they target afferents, target efferents, or fibers of passage. For example, when DBS at the subthalamic nucleus is used to treat Parkinson’s disease, its therapeutic target may be fibers of passage from the motor cortex (Gradinaru et al. 2009). The variable rate of onset when DBS is administered for different conditions also suggests different mechanisms are at work. Contrast the rapid therapeutic effect of DBS for Parkinsonian tremor with the much slower onset observed for other conditions such as DBS for depression. DBS for both neurological and psychiatric indications, including discussions on the mechanisms of action, are thoroughly reviewed in Chapters 15 and 16.

Other Invasive Brain Stimulation

While DBS offers the key advantage of focality, the major concern of the treatment is its invasive nature. DBS electrodes must be surgically implanted, causing microlesions along its path from the surface of the brain to the target site. When target sites are superficial, less invasive brain stimulation modalities can be considered. Both epidural cortical stimulation and VNS avoid direct contact of microelectrodes in brain tissue. In the former case, multicontact stimulating paddles are placed in the extradural space over specific cortical regions and connected to a pacemaker-like generator. Epidural cortical stimulation has been investigated for a variety of neurological and psychiatric indications. See Chapter 14 for a comprehensive review of this stimulation modality. In the case of VNS, electrodes are wrapped around the vagus nerve in the carotid sheath. VNS is effective both as an adjunctive agent for patients with partial onset seizures and for treatment resistant depression. See Chapter 17 for a very thorough review of this treatment. Interestingly,
like DBS, there is variability in how rapidly patients respond suggesting different mechanisms of action are at play. Whereas VNS appears to work on demand for epilepsy as well as have a prophylactic effect, the response for depression appears to emerge slowly over months. There are no satisfactory theories or evidence-supported explanations yet to account for this difference.

**Bumps Along the Road**
The promise of invasive brain stimulation is long-term relief for conditions that are unresponsive in a sustained manner to medications and noninvasive stimulation. However, there have been some setbacks. Northstar Neuroscience Inc, which went bankrupt in 2009, sponsored clinical trials of epidural cortical stimulation for depression and stroke, both of which failed. In the field of DBS for depression, earlier studies were positive for targeted stimulation at both the ventral capsule/ventral striatum (VC/VS) and Brodmann area 25. However, two recent commercially funded DBS trials for depression have failed, namely, a study sponsored by Medtronic Inc targeting the VC/VS (Williams and Okun, 2013) and a study by St Jude Medical Inc targeting Brodmann area 25, which recently failed a futility analysis (Cavuto 2014). Their failure might be related to the industry pushing too fast and too hard to commercialize the technology. Rather, better studies are needed to define the precise tracts that should be targeted, and more attention should be paid to optimizing the treatment parameters. However, DBS research is proceeding apace. Novel areas are being targeted for depression. Pilot studies indicate the medial forebrain bundle (Schlaepfer et al. 2013) and lateral habenula (Sartorius et al. 2010) are promising new targets. Larger clinical trials are underway. In the field of Alzheimer’s disease, both fornix (Lyketsos et al. 2012) and nucleus basalis (Kuhn 2014) are active DBS targets.

**Real-Time Feedback**
For treatments such as DBS and epidural cortical stimulation, chronic stimulation may be unnecessarily excessive. Stimulation parameters are typically optimized by multiple empirical titrations of the stimulation parameters or electrode couplings (Kupsch et al. 2011). This process is time-consuming, requiring close follow-up to monitor both the acute and delayed effects of stimulation (Kupsch et al. 2011). This is particularly problematic for physicians facing the decision of whether to select more vigorous stimulation parameters or wait longer to check if the existing paradigm generates a delayed effect. Moreover, chronic brain stimulation may result in accelerated habituation and rebound symptoms. For example, with thalamic DBS for essential tremor, 13–40% of patients develop tolerance despite accurate electrode placement as quickly as three months after implantation surgery (Pilitsis et al. 2008; Shih et al. 2013). While these effects may be attributed to the natural progression of neurodegeneration, they emphasize the need to improve DBS technologies by dynamically adapting stimulation parameters to patient status. As a proof of concept for the value of this approach, patients who were instructed to turn on DBS only with the onset of essential tremor showed continuous sensitivity to treatment during the 30 months of follow-up (Kronenbuerger et al. 2006). The Defense Advanced Research Projects Agency, an agency of the US Department of Defense, recently announced a funding priority for advancing DBS technologies that not only treat, but also monitor and alter stimulation in real time to maximize efficacy. In response, there has been a boom in sophisticated techniques that integrate DBS with sensors to detect the onset of behavioral symptoms and electrophysiological signals that correlate with them (Rosin et al. 2011; Santos et al. 2011; Carron et al. 2013). Currently focused on Parkinson’s disease, these so-called closed-loop DBS technologies have shown greater efficacy compared with conventional chronic stimulation, improving motor scores by 29% and decreasing stimulation times by 56% (Little et al. 2013).
INTRODUCTION TO BRAIN STIMULATION

Ethical Issues

Although ECT has been around for more than 70 years, the field of brain stimulation is rapidly evolving with interest from researchers, clinicians and patients. When brain stimulation is applied as a treatment, it is often time-consuming and expensive, and in many instances it is still experimental. Because the neuropsychiatric disorder for which the brain stimulation technique is being used is likely severe and could impair a patient’s judgment, patients are particularly vulnerable. This is especially the case with invasive brain stimulation where the patients are quite ill, desperate, and the treatment can have major adverse effects. Accordingly, it is wise to be cautious as well as mindful of psychiatry’s history of periodic misadventures, a prominent example being frontal lobotomy (McHugh 1992).

As described in the chapters of this book focused on convulsive and invasive brain stimulation, there are potentially significant neuropsychiatric complications associated with these treatment modalities. For example, DBS in Parkinson’s disease has been reported to result in adverse effects including anxiety, mood fluctuations, and even gambling (Bejjani et al. 1999; Saint-Cyr et al. 2000; Krack et al. 2001; Kulisevsky et al. 2002; Berney et al. 2002). Close psychiatric follow-up is, therefore, critical in these patients. Moreover, the implanted devices can interfere with daily activities in other ways, for example, taking an MRI scan or passing through magnetized areas that interfere with the neurostimulation pacemaker. A DBS implant might also interfere with the patient’s ability to receive ECT.

The capacity to give informed consent may be compromised by the neuropsychiatric condition for which the brain stimulation is indicated. Because clinicians and researchers may have substantial financial and even academic gain from treating or enrolling patients in a brain stimulation device trial, conflict of interest or the perception of such may arise. Accordingly, particular care needs to be taken in deciding if a patient is appropriate for treatment or enrollment in a clinical trial. Patients should consult with specialists who have no potential interest in the patient receiving the treatment. A review committee comprising experts in the field may also assist for this purpose. This is especially the case for invasive brain stimulation that requires multidisciplinary collaboration in the fields of neurosurgery, neurology, psychiatry, and psychology.

The informed consent procedure needs to be thorough and should preferably involve the family. This is particularly relevant when the patient is a child as brain stimulating treatments have rarely been systemically assessed in children, and the effects on brain development are unknown. For example, many institutions require the review of a pediatric ECT referral by two uninvolved child psychiatrists. For clinical trials, supervision by the local Ethics Committee is essential.

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