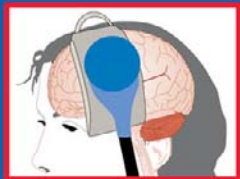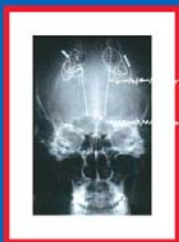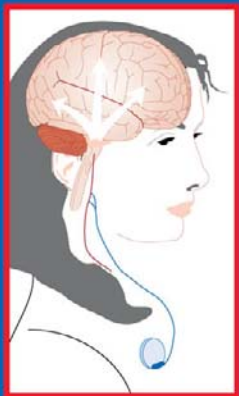# BRAIN STIMULATION THERAPIES
for Clinicians

Edmund S. Higgins, M.D.

Mark S. George, M.D.

with foreword by
Michael Trimble, M.D., F.R.C.P., F.R.C.Psych.

Brain Stimulation Therapies for Clinicians

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Brain Stimulation Therapies for Clinicians

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Illustrations by Edmund S. Higgins, M.D.

Note: The authors have worked to ensure that all information in this book is accurate at the time of publication and consistent with general psychiatric and medical standards. As medical research and practice continue to advance, however, therapeutic standards may change. Moreover, specific situations may require a specific therapeutic response not included in this book. For these reasons and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of physicians directly involved in their care or the care of a member of their family.

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About the Authors

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Mark S. George, M.D., is a Distinguished Professor of Psychiatry, Radiology, and Neuroscience, as well as Director of the Center for Advanced Imaging Research and the Brain Stimulation Laboratory at the Medical University of South Carolina, Charleston. He received his medical degree and completed dual residencies at MUSC in both neurology and psychiatry and is board certified in both areas. After a fellowship in London in 1989, where he first encountered transcranial magnetic stimulation, and four years at the National Institute of Mental Health in Bethesda, Maryland, he returned to Charleston, where he has conducted pioneering work with functional imaging of the brain and several of the brain stimulation techniques, particularly TMS and vagus nerve stimulation. He is on several editorial review boards, has published over 300 scientific articles or book chapters, holds eight patents, and has written or edited four books, including a previous book in collaboration with Dr. Higgins. Dr. George is the editor-in-chief of a new journal entitled *Brain Stimulation: Basic, Translational and Clinical Research in Neuromodulation.* He too resides on Sullivan's Island, South Carolina.

Foreword

Michael Trimble, M.D., F.R.C.P., F.R.C.Psych.

One of the most important neuroscience discoveries of the twentieth century, or perhaps of all time, arguably was that of Olds and Milner in the early 1950s (Olds 1973). For centuries, the brain had been viewed as a passive recipient of sensory impressions, which led in a Pavlov-type sequence to motor action, with, in some (behavioralist) philosophies, the assumption that little of relevance occurred between stimulus and response. And yet a growing undercurrent of knowledge was emphasizing the prepared brain, the brain not as a receptacle and *tabula rasa* but as an active organ, a synthesizing and creating brain. Proceeding from the philosophies of Kant and Nietzsche and the psychologies of Freud and his successors, the very drivenness of human activity, by unconscious and in some theories unknowable forces, became common currency. But these hollow frames lacked a neurological framework, a neurobiology of the emotions and movement.

What Olds and Milner did was uncover cerebral circuits for pleasure and reward, endowing hedonic tone to percepts and behavior. This research was being conducted at the same time that others, notably Papez and MacLean, were unraveling additional neuroanatomical structures associated with the emotions. Papez (1937) proposed a circuit for emotion, giving an organism a "stream of feeling." MacLean (1990) defined for us the "visceral" brain. The latter was renamed *limbic* after the earlier anatomical designations of Broca, and the term *limbic system* is now familiar to all neuroscientists with an interest in brain-behavior relationships.

With the identification of such a neuroanatomy of the emotions, the possibility emerged of altering emotional expression and hence providing amelioration of neurobehavioral disturbances by influencing such circuitry. Stimulation of the brain, whether indirectly across the scalp or directly by application of electrodes to the brain itself, could be realized. In fact, such ideas had been around for a long time, but the neuroanatomical knowledge and the technology were not available until the mid-twentieth century. One well-acknowledged method, still widely used, was electroconvulsive therapy (ECT). Exactly how it worked to lyse a psychosis or cure a melancholia was and remains unclear.

As is reviewed in the introductory chapter of this book, the early pioneers of direct stimulation had the right ideas but lacked the sophistication that today's electronic world has provided. Robert Heath (1954) was one such investigator. While at Tulane, Heath began stimulation of what he referred to as the "septal area" (closely analogous to what is also referred to as the *fundus striati*, loosely, the accumbens region), in patients with schizophrenia. The choice of target was interesting, given that the subcortical controls over the cortex, and therefore behavior, were implicated in his theories (he also stimulated the caudate, thalamus, hypothalamus, and cerebellum). Since patients were usually conscious, their subjective responses could be recorded. These included sensations of pleasure, akin to the findings in animal models of Olds and Milner.

There was one important snag in the animal studies, which interfered with the investigations, namely that some of the animals developed epileptic seizures and died. This experimental artifact was seized upon by Graham Goddard (1967), who recognized it as a possible model for the "kindling" of long-lasting changes of excitability in cerebral circuits, and as a possible experimental model of epilepsy.

The clinical work on treating major psychiatric disorders and abnormal movements by lesioning subcortical structures was quite successful, but the amount of operative tissue destruction that occurred often led to unwanted neuropsychological deficits. In any case, a new era of treatment evolved with the discovery of the modes of action of monoamine transmitters, especially

dopamine, and the development of an array of neuropsychoactive drugs, the success of which soon diminished enthusiasm for the neurosurgery to treat neuropsychiatric disorders.

On account of the development of new methods of brain stimulation, there is now a renaissance of interest in reevaluating the data from the early studies, in part to assess the most relevant neuronal structures for targets. Such information is guiding neurosurgical methods for deep brain stimulation (DBS) and is helping to reformulate hypotheses about the mechanisms of action of ECT and other stimulation techniques that have become available or that will be available in the near future. It is to these theories and to these techniques that this book is directed. If progress in this area is as rapid as it has been in the past few years, some form of brain stimulation will be a treatment modality—some may predict *the* treatment modality—for a wide variety of neurological and psychiatric disorders. Acquaintance with basic principles of electricity will be essential for all who work in this field, as is an understanding of, say, serotonin or dopamine today. Discussing treatment options with patients will necessitate an understanding of neuroanatomy, an explanation of the methods of action of various stimulation techniques, and the benefits and hazards of the options.

To these ends, this book is timely and important. Starting at the beginning (with history), the current *olla podrida* of brain stimulation techniques along with their supposed mechanisms of action are reviewed in a language that is clear and jargon-free. There is clearly much to learn, but progress is fast. Soon, implanted devices will be able to predict the onset of seizures and target pulses to stop them from evolving, treat a wide spectrum of movement disorders, and alter the progression of major psychopathologies, with little apparent problem with either compliance or significant side effects. I predict that a succession of revised versions will follow from this first edition of the book, and that even the authors will look back with surprise that they had not more accurately predicted the future.

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University College, London</div>

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Preface

The field of brain stimulation is exploding with research activity across basic and clinical domains. Currently, at least 13 forms of brain stimulation are undergoing development and evaluation as interventions for neurological and psychiatric disorders. Stimulation techniques are a unique form of treatment distinctly different from pharmacology, psychotherapy, or physical therapy. Although the developments in this burgeoning field are exciting, the amount of information can be overwhelming for practicing clinicians as well as patients. This book should serve as an overview of the brain stimulation therapies for anyone seeking a broad grasp of the field.

The brain stimulation therapies range from noninvasive techniques such as transcranial magnetic stimulation (TMS), which applies single or repetitive stimuli at the scalp surface, to deep brain stimulation (DBS), which involves neurosurgical implantation of electrodes in specific brain regions. These interventions differ in many fundamental characteristics, such as whether stimulation results in seizures or is nonconvulsive, is continuous or intermittent, or uses brain activity to determine the timing or site of stimulation.

The brain stimulation techniques thus represent a new class of therapeutics that has already displayed remarkable potential for producing novel therapeutic effects. For example, DBS for Parkinson's disease produces symptom remission almost instantly in patients whose symptoms are largely refractory to all medications. These therapeutic effects continue in many patients for up to 5 years without symptom progression. These remarkable therapeutic effects may arise because the focal brain stimulation

methods trigger therapeutic mechanisms different from those that follow from medications.

Related to this difference in approach, the side effects of the brain stimulation techniques also differ radically from conventional treatments such as medications or medical interventions. All the forms of focal brain stimulation reviewed in this book involve the passage of an electrical current through neural tissue, either peripherally or centrally. However, in general, electricity has no metabolite or other residue. Thus, the therapeutic and adverse effects of these interventions are largely determined by the endogenous or adaptive response of the brain to the electrical stimulation. In this sense, these methods are perhaps more "natural" than some other forms of therapy, although external electricity is not exactly natural. The brain stimulation therapies are thus creating another therapeutic option or class, complementing talking therapies, medications, and rehabilitation, and in some cases replacing ablative surgery.

Anyone who is not working daily in this field can be stymied by all the new information when confronted with a patient who might benefit from one of the brain stimulation techniques. As with genetics or brain imaging, there is an initially daunting "acronym soup" that can hinder access and cause confusion. This book tries to provide a clear and straightforward analysis of the prevailing techniques, and in some sense is an elaborate dictionary for these acronyms and the new methods. The book starts with a quick overview of electricity and physics—elements that are common to all the methods but not taught in medical school. We review the relevant neuroanatomy, physics, and methods for each technique. We then critically and efficiently review the clinical literature for each method. This book is thus intended to be a quick first start, helping clinicians, patients, and researchers efficiently understand the current knowledge about the techniques. As is often found in any new area of technology or medicine, there are some who falsely advocate certain techniques and claim therapeutic effects for which there is little or no supporting evidence. We have tried to impartially separate the wheat from the chaff so that everyone can quickly have the latest data at their fingertips and then decide for themselves.

Readers of this book should gain a good understanding of the current state of brain stimulation therapies. This base can then be used to help patients and provide the background for keeping up with this rapidly evolving and most exciting field.

We hope that you enjoy reading this book and find the contents "stimulating" and helpful. It was a labor of love for us, and we hope a similar response will be induced in the readers.

Edmund S. Higgins, M.D.
Mark S. George, M.D.

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Acknowledgments

There have been many people, both skeptics and advocates, who have helped me with my ideas and interests in brain imaging and brain stimulation. Thanks to friends and colleagues in both groups, and especially those who started in one group and then moved to the other on the basis of scientific data. James Ballenger, Robert Post, Tom Uhde, Harold Sackeim, Thomas Schlaepfer, Saxby Pridmore, Mark Hallett, and Eric Wassermann have all gone far out of their way to teach, to encourage, or to facilitate my understanding of these techniques. I would especially like to thank my friend and colleague of the last decade, Ziad Nahas, who has a wealth of ideas and energy concerning this field.

I would like to thank my family for their help and support over the years, and especially for not discouraging me when I was pursuing some "outside the box" brain stimulation research: my sisters Bebe and Jane and their families, for not freaking out the Christmas evening when I showed up with a scalp abrasion from some TMS studies; my wife Eloise; and my two children, Laura and Daniel, who grew up in and around MRI scanners and stimulation laboratories.

However, I am especially grateful to one group in particular. Those are the patients who have participated in clinical trials and have helped me and the field learn what works and what does not. Without their "leap of faith" participation in double-blind studies, we would get nowhere. Thanks. We dedicate this book to all of you.

Introduction

The human brain is perhaps the most complex organ known to exist in the universe. Approximately 100 billion neurons with 100 trillion connections sense, analyze, and respond to the environment in ways that are beyond our current comprehension. Ostensibly, it all boils down to electrical and chemical communication. Figure 1–1 shows the stereotypical synapse that highlights the electrical and chemical nature of one neuron communicating with another.

Historically, neurologists have been more aware of the electrical nature of the brain, whereas psychiatrists, until just recently, have concentrated almost exclusively on neurotransmitters and psychopharmacology. Psychiatry has become so enamored of neurotransmitters that "chemical imbalance" has become part of

Electro

1. The action potential arrives at the presynaptic terminal.

2. Depolarization causes voltage-gated calcium channels to open and results in a large influx of Ca^{2+}.

3. Exocytosis: Ca^{2+} causes the vesicles to fuse with the membrane and release the neurotransmitter.

4. Excitatory postsynaptic potentials (EPSP) spread out over the dendrite.

Chemical

A. Precursor molecules and enzymes are transported down the axon from the cell body along the microtubules.

B. Enzymes in the synaptic terminal convert the precursor molecules into active neurotransmitter.

C. The neurotransmitter is stored in the vesicles until released by the influx of Ca^{2+}.

D. The released neurotransmitter binds with the receptors on the post-synaptic terminal and generates an EPSP.

E. Reuptake of the neurotransmitter limits the duration of the signal and allows the cell to recycle the neuro-transmitter.

Enzymes convert tyrosine to dopamine

Ca^{2+}

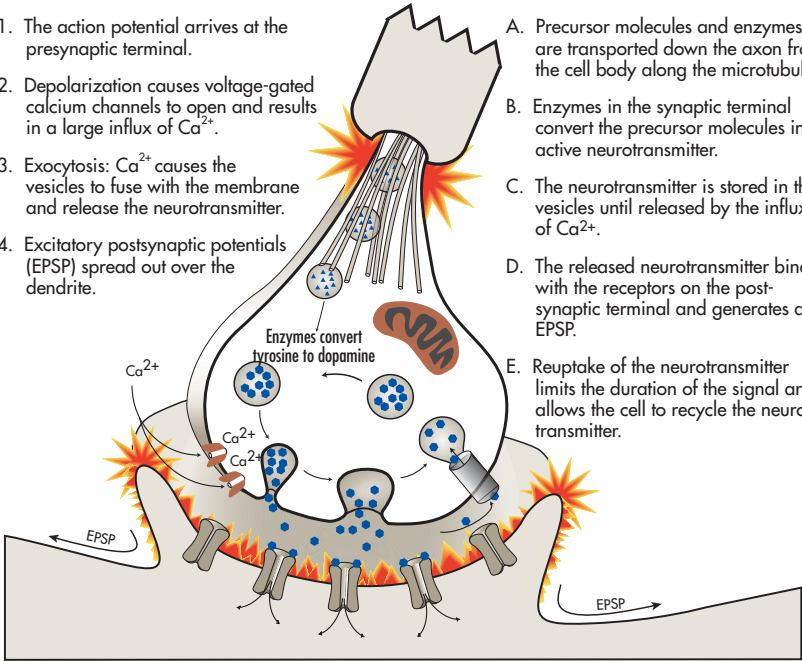Ca^{2+}

Ca^{2+}

EPSP

EPSP

FIGURE 1–1.   Electro-chemical communication.

Communication between two neurons in the brain includes both electrical and chemical mechanisms, which are linked. The electrical impulse becomes a chemical messenger, which then converts the information back into an electrical signal.

Source.   Adapted from Higgins and George 2007.

our common language. Some patients think it is an actual diagnosis. It is hoped that clinicians in the future will be more adept at recognizing the importance of both the electrical and the chemical features of each patient's problems.

Brain stimulation, unlike pharmacology, focuses on the electrical mechanisms of the brain, which then cause localized changes in pharmacology. Applications of electrical stimulation through a variety of new and old techniques can correct underlying disorders. Traditionally, brain stimulation therapies have been highly invasive and reserved for those with treatment-resistant disorders. However, there are also a variety of new brain stimulation treatments that are not invasive or solely for the severely impaired.

We conceptualize brain stimulation therapies as treatment options that will continue to grow in both number and scope in the coming years. New delivery mechanisms and wider applications of existing technologies are clearly in the future of central nervous system treatments. The goal of this book is to bring a greater understanding of the field to practicing clinicians (neurologists, psychiatrists, psychologists, nurses, and other health professionals). But before we get into the details of brain stimulation therapies, let us review some of the pioneers who brought us to this point.

History of Electrical Stimulation

The earliest brain stimulation devices were live fish. The ancient Greeks and Romans knew of the shocking powers of the Nile catfish and electric ray (Finger 2000). Galen and Scribonius Largus in Rome used electric rays to treat headaches and various other disorders (Figure 1–2). They placed the fish across the brow of a suffering patient or had the patient stand on several live rays. The fish were allowed to discharge their special powers, which, of course, were not recognized as electricity until many centuries later. Unfortunately, electric rays were not readily available, and it was not until the eighteenth century that machines were created that could produce electricity on demand.
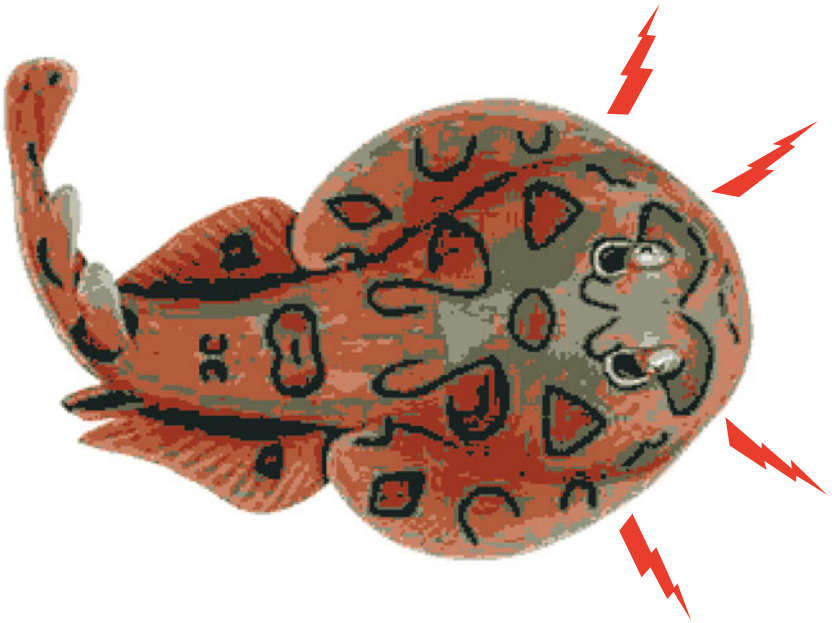
FIGURE 1–2.   Early brain stimulation device.

Electric rays are possibly the first brain stimulation devices. Used by the ancient Greeks and Romans to treat various disorders.

By the early eighteenth century the leading scientists still did not know what substance was flowing through nerves (Finger 2000). Serious thinkers speculated about spirits, special fluids, and even vibrations. It was Luigi Galvani who, in a series of experiments published in 1791, established that electricity flows through nerves. Using rudimentary batteries, he showed that an exposed nerve could be activated with electricity and produce a seemingly natural muscle contraction. Furthermore, he established that nature's own electricity (e.g., lightning) produced a similar response to electrical machines.

Macabre Research

Aldini, Galvani's devoted nephew, conducted some of the most unusual research and showed that human muscles also moved when electrically stimulated. He applied electricity to decapitated heads at the base of a guillotine and was able to induce jaw movements, grimaces, and eye openings.

MOTOR CORTEX

The discovery of the motor cortex was the next great example of the importance of electricity to central nervous system activity (Finger 2000). Gustav Fritsch noticed during the Danish-Prussian War of 1864 that accidentally irritating exposed brains of head-injured soldiers often resulted in a twitch to the opposite side of the body. In the late 1860s, Fritsch teamed up with Eduard Hitzig, a German physician. Together they systematically explored the cortex of dogs. Their success in identifying the motor cortex lay in gentle electrical stimulation of the cortex. Apparently, they would touch the electrode to their tongues to determine the appropriate current before stimulating the dog's cortex.

In the early 1900s, Charles Sherrington continued mapping out the details of the motor cortex. Using lightly anesthetized apes and monkeys, he recognized the contiguous nature of the motor control along the cortex. It was the great Canadian neuro-

Central sulcus

Elbow
Wrist
Hand
Digit V
Digit IV
Digit III
Digit II
Thumb
Neck
Brow
Eyelids
Eyeballs
Face
Lips
Jaw
Tongue
Throat

Shoulder
Trunk
Hip
Leg
Knee
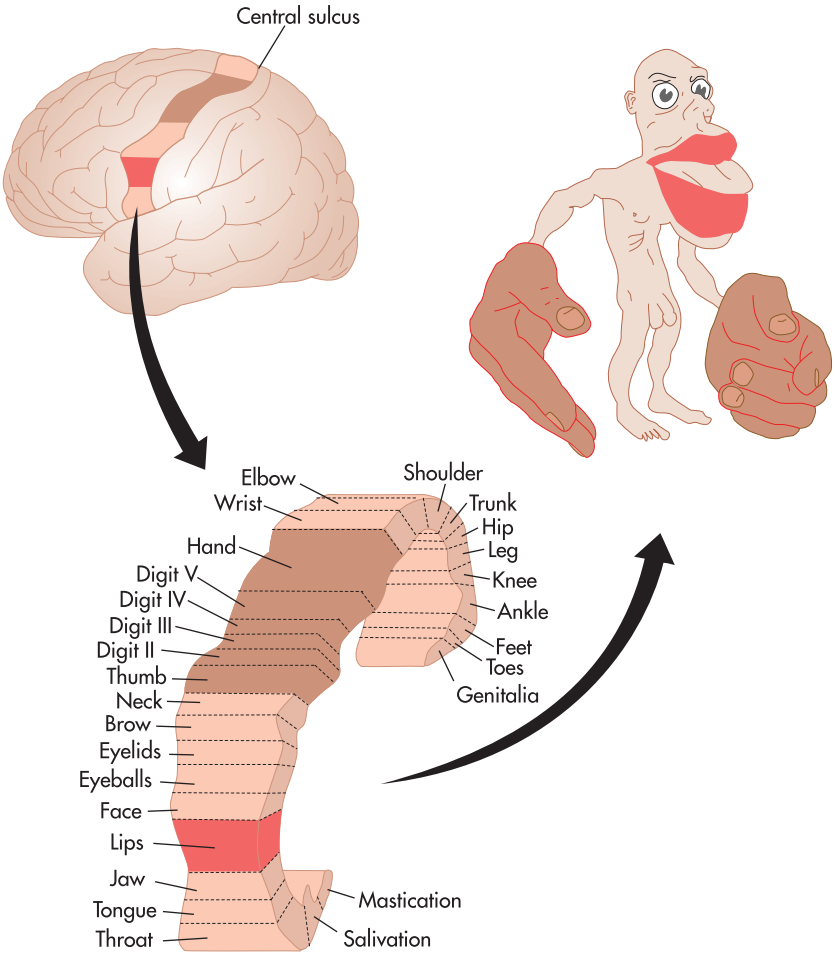Ankle
Feet
Toes
Genitalia

Mastication
Salivation

FIGURE 1–3.   The motor cortex and motor homunculus.

Source.   Adapted from Rosenzweig et al. 2005.

surgeon Wilder Penfield who, along with others, extended the work of Sherrington and delineated the odd-shaped little man hidden inside the cortex: the motor homunculus (Figure 1–3).

EPILEPSY SURGERY

In the 1930s Penfield explored the human brain in live epilepsy patients as part of the surgical excision of the epileptic focus of the seizures (Lewis 1983). Penfield was more successful than others before him in using surgical treatment for intractable seizures. His success was partly the result of extensive exploration of the cortex in the patients who remained awake with their brain exposed under local anesthesia. Penfield's goal was to locate the focus of the seizure activity, which was generally identified by the symptoms shown at the start of the seizure. Once the focus was located, Penfield worked to remove as much of the damaged tissue as possible while preserving as much normal brain function as possible.

Penfield would use a probe with weak electrical activity to stimulate the cortex in his patients. Since the patients remained awake, they could describe what they experienced. This enhanced the identification of diseased and normal brain tissue. One of the most interesting findings from this work was the reaction to temporal lobe stimulation. Although stimulating many regions of the brain (e.g., occipital cortex, motor cortex, Broca's area, etc.) generated predictable responses, the findings resulting from stimulation of the temporal lobes were unexpected.

Stimulation of the temporal lobes sometimes generated memories of distant events from the patients' lives. Some remembered experiences from childhood. Others heard songs they had not heard in many years. The memories would stop when the stimulation stopped and were often replicated when touched again. Although the importance of these findings has been exaggerated, the results introduced a new understanding of who we are; that is, our memories, the essence of our sense of self, are little more than electrical activity in the brain.

Memories and TMS

Transcranial magnetic stimulation (TMS) (see Chapter 6) can induce sensations from the occipital cortex, motor cortex, and Broca's area similar to the effects of direct electrical stimulation. However, unlike Penfield's findings, TMS over the temporal lobes does not seem to reproduce memories. This may be because Penfield was searching for the focal lesion generating the seizure. Thus, most of the reported memories, smells, and emotions were the patients' auras, elicited just prior to seizing.

SELF-STIMULATION

Brain stimulation allows exploration of the function of parts of the brain. Exciting the cortex in this way is the opposite of lesioning a site. Self-stimulation enables researchers to explore reward and punishment circuits in animals who are otherwise unable to describe the effects of the electrical stimulation. Work by James Olds and Peter Milner at McGill University in Montreal transformed the field with their accidental discovery in 1954.

Olds and Milner were studying brain stimulation of the reticular formation and the effects this would have on alertness and learning (Olds 1956). One of the electrodes was accidentally bent during placement in the brain of a rat. As part of their study, Olds and Milner wanted to be sure that stimulation of the electrode was not an adverse experience for the rat. Much to their amazement, the rat seemed to seek out more stimulation.

When the rat was allowed to self-stimulate with a Skinner box arrangement (Figure 1–4), the results were even more striking. Some rats would self-stimulate 2,000 times an hour for 24 hours. Hungry rats would self-stimulate before eating available food. Olds and Milner had discovered that the brain contains circuits for reward, or what some call *pleasure centers*. This discovery has led to recognition of reward centers in the brain, which are present to enhance species survival (eating, sex, power), but which also can be usurped by drugs of abuse.
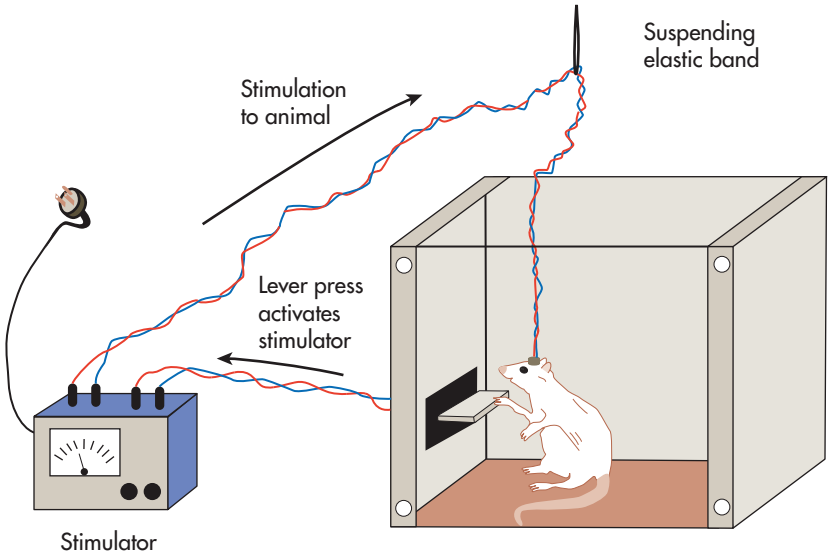
FIGURE 1–4.   In pursuit of stimulation.

Olds and Milner utilized a Skinner box to study the propensity of rats to seek electrical self-stimulation.

EMOTIONAL PACEMAKER

In the early 1950s Robert Heath, Chairman of Psychiatry at Tulane University in New Orleans, worked with neurosurgeons to implant electrodes in psychiatric patients with severe, unremitting disorders. The research was not fruitful. However, the discoveries by Olds and Milner stirred Heath to pursue stimulation of deep cortical structures associated with pleasure as a potential treatment for depression, intractable pain, schizophrenia, or homosexuality.

Heath believed that anhedonia is the basic underlying problem for many psychiatric conditions (Valenstein 1973). That is, the inability to experience pleasure is an integral part of many psychiatric disorders. He hoped that stimulation of the pleasure circuits would reawaken dormant neural pathways and result in improved mood, interest, and energy. Heath and others believed that a regimen of brain stimulation could be conceptualized as an "emotional pacemaker" for patients with serious mental disorders.

Although he was ahead of his time, Heath ultimately abandoned this line of research. He was disappointed with the lack of long-term benefits. Typically, the positive results quickly diminished after the stimulation was turned off. Moreover, he was working at a time when the equipment available was cumbersome and not portable or implantable.

BRAIN CHIPS

Jose Delgado, a professor of physiology at Yale, was one of the other great pioneers of brain stimulation (Horgan 2005). He too had participated in implanting electrodes during the 1950s, but he took the field one step further. He developed and implanted radio-equipped electrodes, which he called "stimoreceivers." Using cats, monkeys, apes, and even humans, he was able to remotely stimulate a device as small as a half-dollar completely implanted in the brain.

Delgado's most impressive experiments involved brain stimulation to inhibit aggressive behavior. In one particularly dramatic demonstration, Delgado stood in the ring with a charging bull. With the press of one button, Delgado brought the bull to a dead stop just a few feet in front of him.

Sexual Orientation

Heath was a creative man who liked to think "outside the box." He speculated that pleasurable stimulation could be used to reverse maladaptive responses to phobic situations. He even wondered whether brain stimulation could be used to alter sexual orientation.

In an infamous experiment, Heath implanted an electrode in a young man with a long history of psychiatric problems, including depression and substance dependence, who was also homosexual (Moan and Heath 1972). Heath then recruited a New Orleans prostitute to engage the patient in heterosexual intercourse while the patient simultaneously received pleasurable brain stimulation. Although the patient was able to enjoy heterosexual activity during the experimental session and afterwards, it is unclear whether or not the intervention changed his sexual orientation or diminished his psychiatric problems.

The experiment caused much controversy and was not well regarded in the medical community.

Delgado's work was troubling to many people. The idea of controlling behavior with technology seemed like mind control administered by a totalitarian dictator. Fortunately, brain stimulation techniques, and the therapies employing them that are the focus of this book, have been used to reduce suffering rather than to control behavior.

Conclusions

It is clear from this brief review of the history of brain stimulation that there really are no new ideas under the sun. Several pioneering scientists foreshadowed the current use of brain stimulation at a time when psychiatry was dominated by psychoanalytic thinking. This was a time even before the pharmacological revolution.

There were several disadvantages working against these early pioneers. They had more primitive and bulky technology with which to work. Additionally, they had limited understanding of the important brain structures. More than 20 years on, brain imaging has now yielded a much better understanding of regional functional neuroanatomy.

After beginning with these meager seeds, the field of brain stimulation is now a very fertile young tree with several branches. Our goal is to acquaint you with an overview of the current status of the field.

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CHAPTER 2

Basic Electricity

Overview

Electricity is one of the fundamental forces of nature. Brain stimulation involves applying focal harnessed electrical power back into the central nervous system (CNS). In this chapter, we review the basic principles of electricity to gain a better understanding of what is being applied in brain stimulation. Chapter 3 will describe what actually happens in the brain when we apply external electricity.

ELECTRONS

Electrical current is the flow of electrons. Atoms are made up of protons, neutrons, and electrons (Figure 2–1). The protons and

neutrons in the nucleus are held together with nuclear forces. The protons are positively charged; the neutrons are neutral. The electrons spinning around the outside of the atom are negatively charged. The positive charge on the protons attracts the negatively charged electrons and keeps the atom electrically neutral. Atoms can lose or gain electrons. It is the movement of negatively charged electrons that constitutes an electrical current.

Electrons need a force to coax them to move. Electrical "pressure" is needed to make electrons flow in a wire. The electrical pressure is a force called *electromotive force*, or **voltage**. An easy way to understand this is to compare electricity to plumbing. The current of electrons moving through a wire is like the water moving through a pipe. The electromotive force needed to move the electrons is like the drop in elevation (gravity) that makes the water flow down the pipe.

DIRECT CURRENT

A review of how a battery can generate a direct current can refresh our understanding of electricity. When electrons move in one direction, it is called a *direct current*. A battery, or dry cell, provides one source by which electrons move through a wire in the same direction.

A battery is basically two different metals in an electrolyte solution. Most metals have a propensity to give away electrons and become more positively charged. Some metals have a greater propensity to give up electrons than others. Two metals, one more willing to give up electrons and the other more willing to accept electrons, can create an electromotive force. The key is placing them in an electrolyte mixture where the electrons can be moved from one metal to the other so that they can flow.

Figure 2–2 shows an example of this process. Electrons tend to leave copper and move toward zinc. These electrons flow through the electrolyte solution ammonium chloride in a process that is beyond the scope of this text. The buildup of electrons on the zinc terminal creates electrical pressure. The potential electrical pressure is measured in **volts**—in this case, about 1.1 volts.

The wire connecting the copper terminal to the zinc terminal allows electrons to move back in the direction of the gradient—
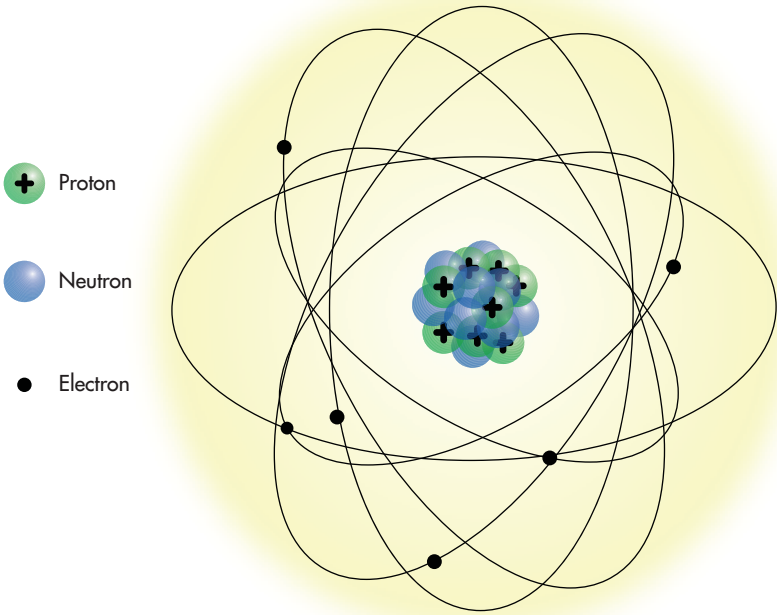
FIGURE 2–1. A simple atom.

An atom is composed of protons, neutrons, and electrons. The flow of electrons from one atom to another is the essential component of electricity.
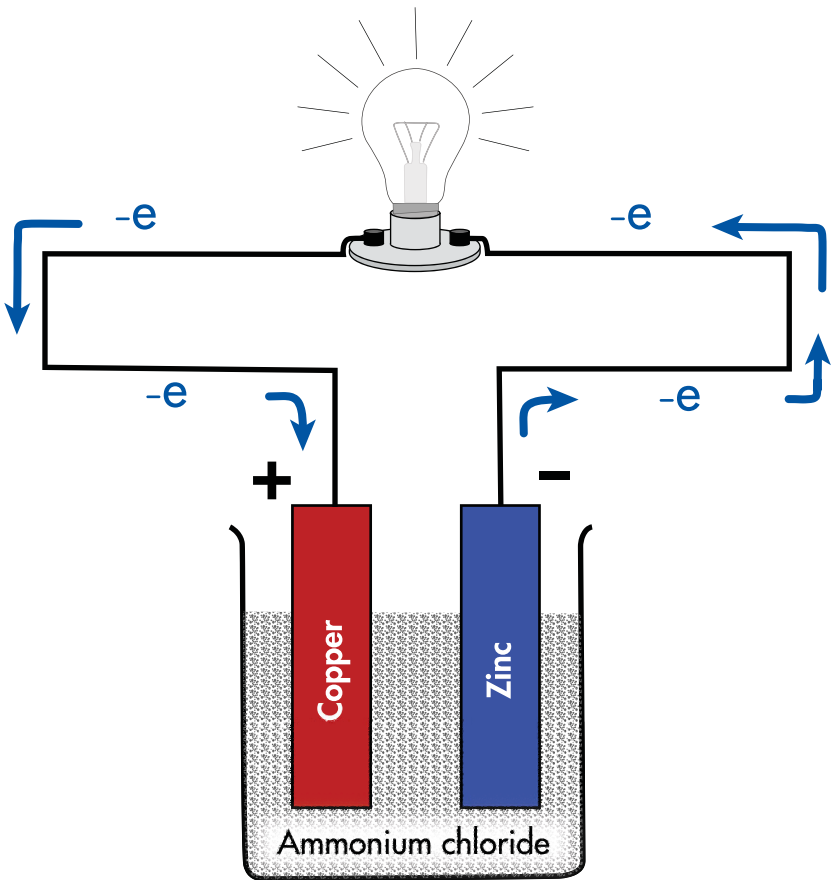
FIGURE 2–2.   A simple battery.

In a chemical process, electrons move from the copper to the zinc in the ammonium chloride. This creates an electrical potential. The wire enables the electrons to move back to the copper, creating an electrical circuit and powering the light.

like water flowing downhill. The movement of the electrons is the **current,** which heats up the filament in the light bulb and generates light. This process will continue until the copper has been eaten away or the electrolyte evaporates; therefore, **the pressure is voltage, and the flow is current.** These are related but different phenomena. Current, measured in *amperes*, is the amount of charge (measured in *coulombs*) flowing through something over time. In the diagram in Figure 2–2, the light bulb is the resistance in the system. This brings us to a concept important to the understanding of electricity—**Ohm's Law.**

The current (flow) is the same as the pressure (voltage) divided by the resistance: **I = (V/R).** You can thus increase current by increasing the voltage (pressure) or dropping the resistance. Another important term is **current density**, which is the amount of current in a specific area. High current densities can be toxic to nerve cells, and are thus a limiting aspect of most brain stimulation methods.

In the diagram, knowing Ohm's Law, we can set up the system so that the pressure stays the same regardless of what happens in the light bulb (constant voltage), or we can have it adapt to the full system and always provide the same flow (constant current). Interestingly, the different brain stimulation techniques have used each of these approaches, and they produce markedly different effects on the brain.

The amount of power flowing through a system is calculated as volts times amperes and is called a **watt (V *A).**

Resistance

Resistance is a measure of how difficult it is to move charges along a conductor. It is measured in **ohms**. Using the plumbing analogy again, electrical resistance is similar to friction when water flows through a pipe. Longer pipes and pipes with smaller diameter have greater friction, making it harder to move the water through. A similar situation exists for copper wires and electrical current. Long, thin wires have greater resistance. Resistance also applies to devices such as toaster ovens and televisions—which use electricity and slow down the movement of electrons.
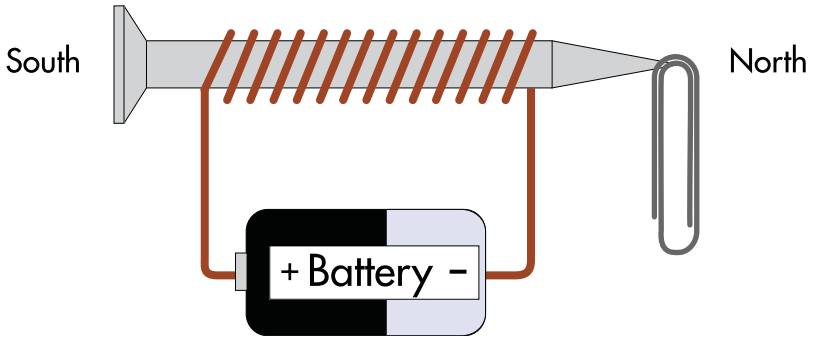
FIGURE 2–3.   A simple magnet.

When an electrical current flows through a wire, it creates a magnetic field. When the wire is wrapped around a steel nail, the nail becomes magnetized.

Resistance and conductivity are inversely related. Poor conductors have high resistance, whereas good conductors have low resistance. Various materials have different capacities to conduct and resist. Typically, we say that copper is a good conductor with low resistance, but rubber is a poor conductor with high resistance. In brain stimulation, the skull is a terrible conductor with high resistance. Different brain tissues such as neurons and spinal fluid are generally excellent conductors with low resistance.

Electroconvulsive therapy (ECT) provides a good example of the relevance of resistance in brain stimulation. The human skull is relatively resistant to the passage of an electrical current. In order to deliver a charge to the brain sufficiently intense to induce a seizure, a large-voltage electrical stimulation is applied to the scalp. Much of the current is lost to the skull before it reaches the brain.

CONDUCTANCE

The *conductance* of a system is the reciprocal (or opposite) of the resistance; that is, a system with high resistance has low conductance, and vice versa. Conductance is measured in **siemens.**

Now that we have refreshed the basic concepts and vocabulary of electricity, let's make it even more interesting.

ELECTROMAGNETISM

Electricity and magnetism are almost interchangeable. When an electric current is passed through a wire, it creates a magnetic field. This is a standard grade-school science project, which entails using a battery, some wire, and a nail to make a magnet (Figure 2–3).

Alternatively, when an object that conducts electricity (i.e., an object that is willing to give up electrons), such as a copper wire, is passed through a magnetic field, an electrical current is created in the wire (Figure 2–4). The essential point is that the wire must be cutting through the lines of magnetic force. A stationary wire inside a constant nonmoving magnet does not produce an electrical circuit.
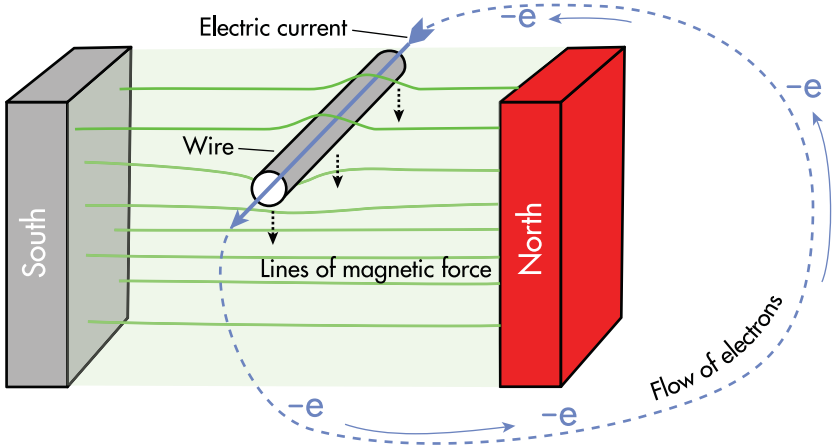
FIGURE 2–4.   Inducing an electrical current.

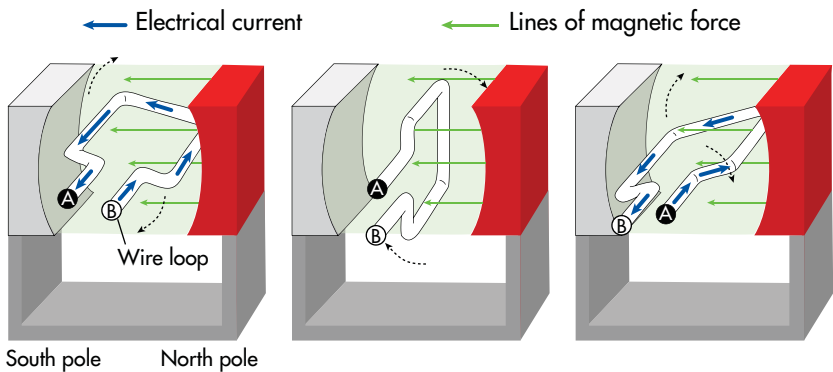A conductor (in this case, a wire) passing through a magnetic field will induce an electrical current and voltage.

FIGURE 2–5.   A simple generator.

A spinning wire loop inside a magnetic field induces alternating current.

ALTERNATING CURRENT

It is the movement of electrons that generates the electromotive force (remember, this pressure or force is called voltage). With direct current, the electrons all move in the same direction. Electrons can also move back and forth. This movement is called *alternating current* and is the kind of electricity we get from a household socket. A look at the mechanics of the electric generators that provide the electricity to our wall sockets provides a good way to understand alternating current.

War of Currents

The race to corner the market on the distribution of electricity in the 1880s produced a battle between industrial giants. Edison advocated direct current; Westinghouse and Tesla backed alternating current. Edison, in spite of all his genius, made the wrong choice. Direct current is less efficient over long distances and would have required power plants to be placed within a mile of every house or factory. Alternating current can be sent from a few large power plants over long distances at high voltage and then transformed down to a convenient low voltage.

Huge electric generators produce almost all the electrical power people use. A generator does not create energy, but instead changes mechanical energy into electrical energy. Some form of mechanical energy such as dammed water, wind, coal, or diesel fuel must be employed to provide the mechanical energy that is used to spin wire inside a magnetic field, which then induces an electrical current.

In Figure 2–5 a wire loop is spun clockwise by a mechanical force such as water rushing out of a dam. In the first frame, the wire "cuts" across the magnetic lines and an electrical current is induced by the movement of electrons from B to A. When the wire is parallel to the magnetic lines of force (middle frame), no lines of force are cut and no electric current is generated. A quarter-turn later, the wire is again cutting through magnetic force,

but this time it is moving in the opposite direction from the first frame. An electrical current is induced, but the electrons are now moving from A to B. Consequently, as the wire is rapidly turned inside the magnetic field, a current is induced that alternates direction inside the wire.

Figure 2–6 shows the same simple generator but includes a measurement of the voltage (electrical current) induced through one complete turn of the wire loop. When the loop is straight up and down (a, c, and e), no electrons are moving and zero voltage is generated. When the loop is cutting across the magnetic force (b and d), maximum voltage is generated. However, the direction, or polarity, of the voltage changes, depending on which direction the electrons are flowing. One complete revolution of the loop is called a *cycle.*

The voltage that a generator produces can be increased in several ways:

1. Increase the strength of the magnetic field.
2. Increase the speed at which the wire loop rotates.
3. Increase the number of loops of wire.

Parameters for Brain Stimulation

The focal application of electricity to the brain is the subject of this book. As with any treatment, the goal of brain stimulation is to give enough, but no more than is needed. We strive to produce benefits with minimal side effects. In this section, we will review the different parameters that can be modified to adjust the dose of electricity given to the brain.

DIRECTIONALITY

Is the electrical signal unidirectional, like direct current, or is it bidirectional, like alternating current? This fundamental difference produces important biological differences.
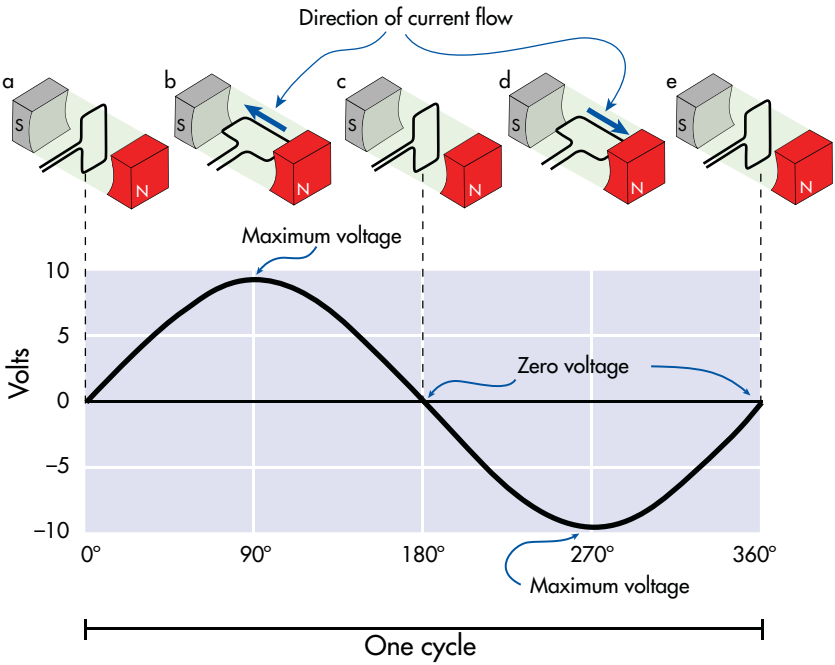
FIGURE 2–6. Alternating current.

Wire spinning inside a magnetic field induces electrical current (voltage) to move in one direction in the first half of the cycle and in the opposite direction in the second half of the cycle.
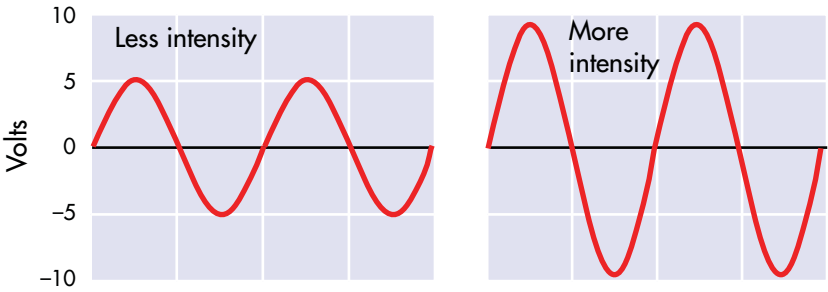
FIGURE 2–7.   Intensity.

An electrical stimulation with higher voltage delivers a more intense charge to the brain.

INTENSITY

Simply increasing the voltage (pressure) of an electrical stimulation increases the intensity of the charge delivered to the brain (see Figure 2–7).

Intensity is important for all the techniques, given that a minimum amount of electricity is necessary to interact with a neuron and affect its firing (stop or cause an action potential). This is most easily seen in transcranial magnetic stimulation (TMS) over the thumb area, where a low intensity does nothing until, at a higher intensity, there is enough stimulation to cause a thumb twitch (called the *motor threshold*).

FREQUENCY

The frequency of an alternating current is the number of cycles per second. For example, power provided by utility companies in the United States is 60 cycles per second, whereas in Europe it is 50 cycles per second. Cycles per second are called *hertz* (see Figure 2–8).
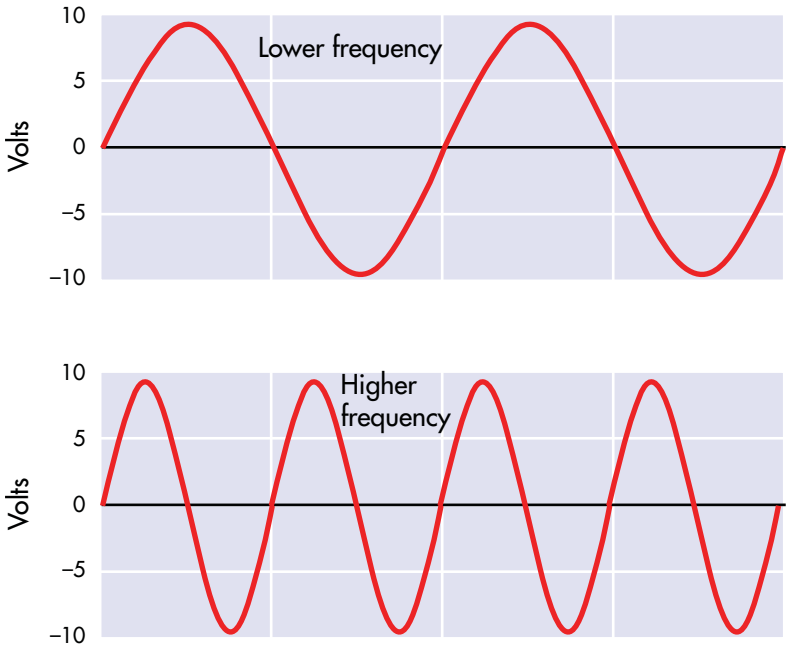
FIGURE 2–8. Frequency.

The number of cycles per second (hertz) is the frequency of an electrical pulse, shown here with a sine wave alternating current.

Frequency is a highly important concept for brain stimulation because different behavioral effects seem to follow frequency-dependent rules. For example, in Chapter 7 (Deep Brain Stimulation and Cortical Stimulation) we will review how a parkinsonian tremor only stops with application of frequencies greater than 100 Hz, for reasons that are not clear. Similarly, with TMS, low frequencies apparently are inhibitory, whereas high frequencies generally excite tissue.

PULSE WIDTH AND MORPHOLOGY

The pulse width, duration, and even morphology (shape) of the electrical pulse also carry a great deal of importance when applying electricity to the brain. For example, for many years ECT was done with very fat pulse widths. Recently, it was discovered that most of the electricity in the fat-pulse width in ECT was not needed, and in fact this contributed to toxicity (reviewed in Figure 4–4). Now we use ultra-brief pulse ECT, which is safer and probably just as effective. Fifty years of ECT research can be summarized as the discovery that one can simply change the pulse width to match what a neuron really needs to depolarize, and then deliver just that and no more.

DURATION

Duration describes the precise length of time of the stimulation. It would seem self-evident that a stimulation of longer duration, as shown in Figure 2–9, delivers more electricity to the brain. However, this is perhaps one of the harder concepts to understand in the field of brain stimulation: although it can seem counterintuitive, a longer duration is not always more effective. The brain is dynamic, and different cascading events occur over varying time domains, some of which inhibit the effects of the initial stimulation. The duration domain is also one of the most interesting aspects of brain stimulation because it is fundamentally linked to neuronal plasticity.
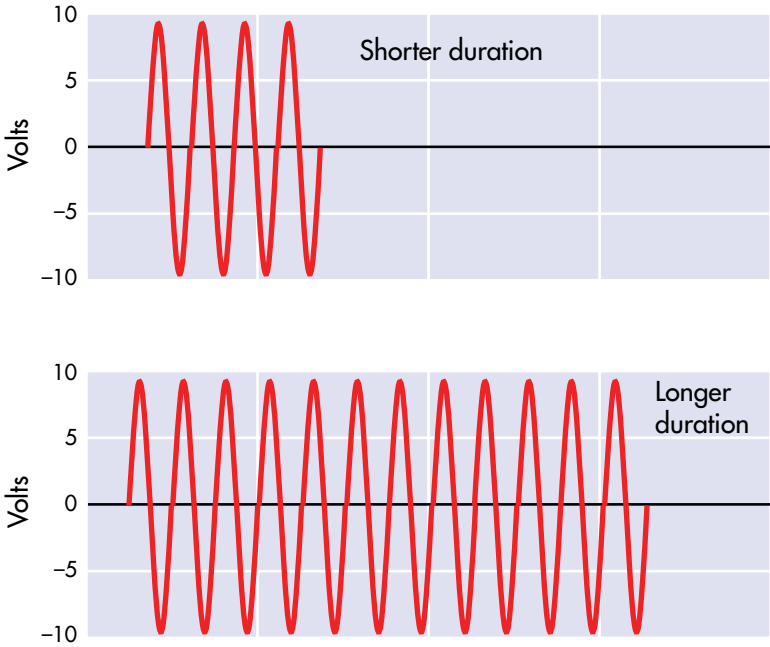
FIGURE 2–9. Duration.

A stimulation of longer duration delivers more electricity to the brain.

INTERTRAIN INTERVAL

The intertrain interval describes the length of time between pulses or trains of electrical pulses (Figure 2–10).

The intertrain interval is biologically important because the brain is often responding to the stimulation immediately after a pulse is delivered. A new pulse can have varying effects, depending on the time between pulses and the amount of time into a train. The brain is dynamically responding to the external stimulation and adapting over time. Thus, the length of the train duration is important to the overall effect that remains from the stimulation. This concept seems relevant to TMS and the notion of whether the brain can return to baseline between trains. With short intertrain intervals, the effects of one train carry into the next train and can build. Consequently, short intertrain intervals of TMS are more likely to cause seizures.

In vagus nerve stimulation the intertrain interval can also be manipulated, and short intertrain intervals can actually damage the nerve (and wear out the device's battery) without enhancing efficacy.

BIPOLAR VERSUS UNIPOLAR

We saw above that alternating current frequently is bipolar and occurs as a sine wave. As we begin to modify the pulse into rectangular shapes, we can either deliver the pulse in a bipolar or unipolar manner (Figure 2–11). These two approaches produce different effects. In general, bipolar stimulation is more efficient from the standpoint of delivering electricity. However, in general, unipolar pulses interact more efficiently with nerve cells, because the actual change in electrical current is what causes depolarization, and the rest of the pulse is not needed to cause neuronal discharge. Bipolar pulses resemble alternating currents.
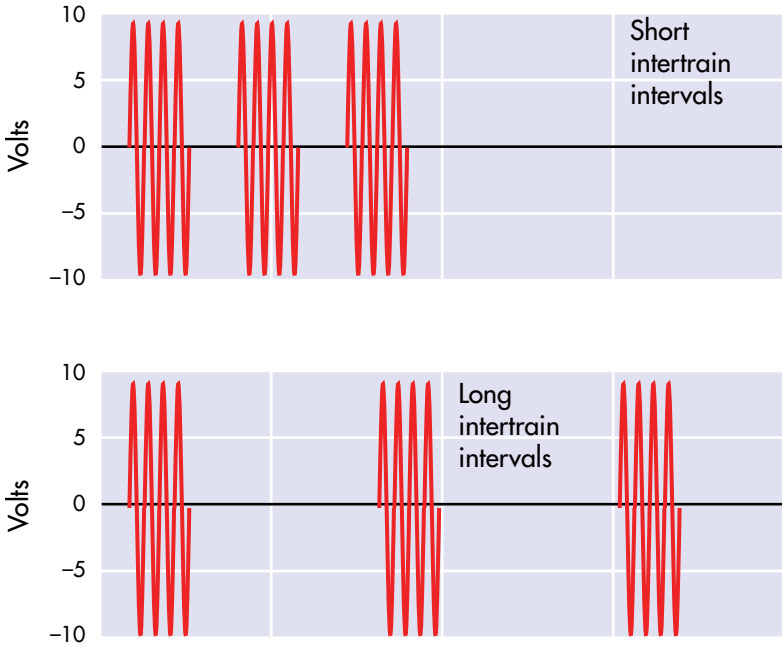
FIGURE 2–10.   Intertrain interval.

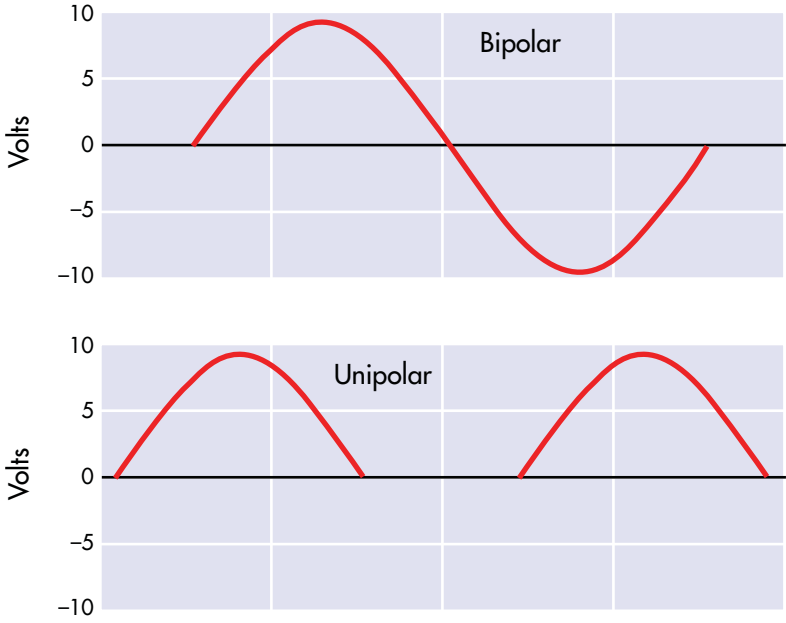Intertrain interval is the time between trains of stimulation.

FIGURE 2–11.　Bipolar versus unipolar.

Bipolar and unipolar electrical pulses.

What Is the Right Dose?

Having pulled all these concepts and terms together, we now have the vocabulary necessary for discussing electrical stimulation. We can now begin to get a feel for the amount of electricity that the different techniques deliver. To better understand this, it is important to examine how much resting electricity the brain itself creates.

Remember that the human brain is an electrical organ, and a highly inefficient one at that. In fact, so much of a person's daily caloric intake goes into just keeping the brain going that the question of why this inefficiency was selected for presents an evolutionary puzzle. All day long, even during sleep, the brain is constantly maintaining and discharging action potentials. The brain represents only 2% of body weight; yet it receives 15% of the cardiac output, 20% of total body oxygen consumption, and 25% of total body glucose utilization. The energy consumption required for the brain to simply survive is 0.1 calories per minute. This value can reach as high as 1.5 calories per minute during complex tasks such as puzzle solving.

So, if this is the background electrical activity in the brain, or energy being used, how much activity are we adding by applying the various brain stimulation techniques? In general, the answer is, very little. Although the popular idea exists that ECT is pumping massive amounts of electricity into the brain, the amount is actually very small compared with the background resting electrical activity. How small?

As we examine the specific techniques, you will discover that each method differs slightly. For example, those techniques that are intermittent (such as ECT or TMS) use less electricity than those that are constantly on (such as deep brain stimulation). We need a few more terms to best discuss this. Remember that current is the flow of electrons. If we describe the flow of electrons in a specific space or bit of tissue, that is called the **current density,** measured in *joules.* In the next chapter, we will see that when we pass electricity through a nerve cell the current density turns into a **charge density,** which builds up on a neuronal membrane. We can then calculate the specific absorption of energy per pulse, or

considered over time, the **specific absorption rate** (SAR). The SAR is an important concept for many medical devices such as ultrasounds and MRI scans, which deposit energy into the body or brain. There are strict guidelines for SAR limits on modern MRI scanners, for instance.

But how much energy do the devices deposit, compared to what is normal brain activity? The SAR of a typical TMS pulse at 1 Hz is about 2 mW/kg, whereas the resting brain metabolic rate is 13 W/kg. If the average adult brain weighs 1,300 g, or 1.3 kg, then TMS at 1 Hz is adding 0.002/17 W/kg, or 0.012% more energy. The other techniques are also in this ballpark, in terms of the amount of energy they deposit. Even in ECT, although we perceive we are delivering large amounts of energy, the actual amount is small compared to the background electrical energy of the brain. In ECT the typical current is 800 milliamps, delivered for 1–6 seconds. If most people respond in 10 treatments, the total time of exposure is 10–60 seconds, and around 8,000 milliamps delivered over a full treatment course. This is a small amount of energy indeed.

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CHAPTER 3

Electrical Brain

Getting Started

The first two chapters focused on the general principles of electricity in wires and circuits. But the really important issue for the study of brain stimulation is how electricity works within biological systems—nerves and cells. Here, we show how the principles from Chapters 1 and 2 are modified to actually work within neurons.

INTRACELLULAR CHARGE

All living cells possess an electrical charge, with the inside of the cell more negatively charged than the outside (Rosenzweig et al. 2005). The resting membrane potential in a nerve cell is approximately 50 to 80 millivolts. Nerve cells use this property to communicate with one another.

This negative charge inside a cell is maintained through three general mechanisms:

1. Electrostatic pressure
2. Concentration gradient
3. The sodium-potassium pump

Cells contain large, negatively charged molecules (such as proteins and DNA) that are trapped inside and cannot cross the cell membrane. These large molecules attract positively charged ions such as sodium and potassium. However, the cell membrane is selectively permeable to these ions. Potassium can easily pass through ion channels, but other ions such as sodium and chloride cannot.

Electrostatic pressure on the potassium is relatively strong and draws a disproportionate amount of the potassium ions into the cell. As the ions accumulate inside the cell, there is increasing concentration pressure pulling the potassium back out of the cell. These competing and opposing forces reach an equilibrium in which potassium is predominantly intracellular (Figure 3–1). The mnemonic that many people use is KIN, for potassium (K) inside the cell. This results in a resting membrane potential of about –65 mV.

SODIUM-POTASSIUM PUMP

Sodium ions are not entirely cooperative. They keep sneaking into the cell. Left unchecked, the sodium would eventually neutralize the negative electrostatic charge inside the cell. Consequently, cells have developed a mechanism to continually return sodium ions to the extracellular space. The sodium-potassium pump illustrated schematically in Figure 3–2 swaps intracellular sodium ions for extracellular potassium ions. The end result is high concentration gradients for potassium and sodium across the cell wall. This becomes important for the rapid propagation of the action potential.
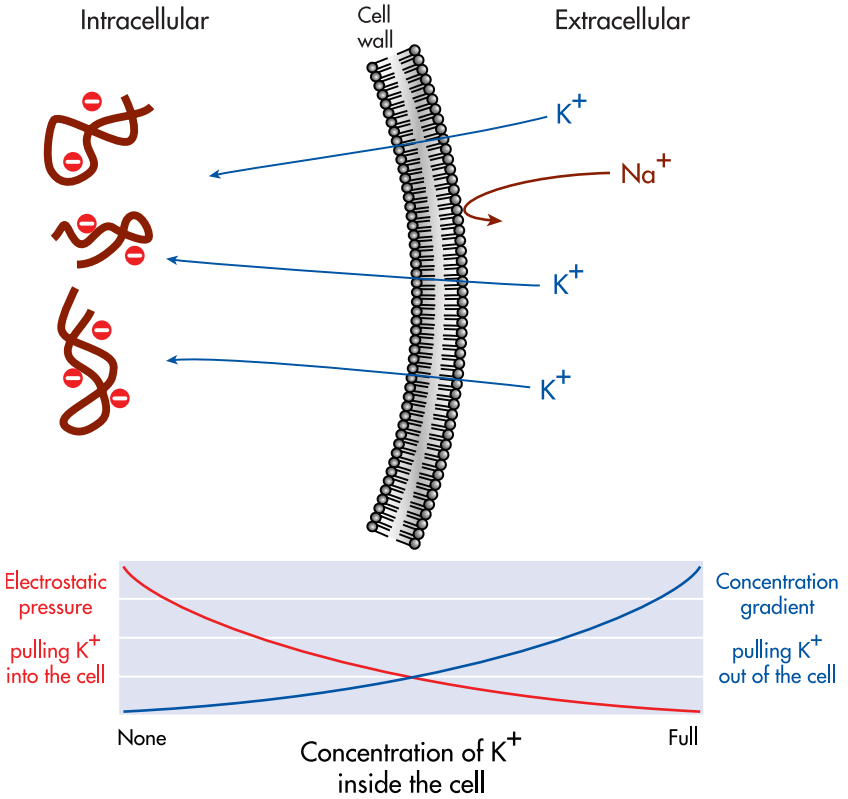
FIGURE 3–1. The electrostatic/concentration tug-of-war.

The large, negatively charged molecules inside the cell pull on the positively charged potassium ions. As the concentration of potassium increases inside the cell, the concentration gradient pulls the ions out.
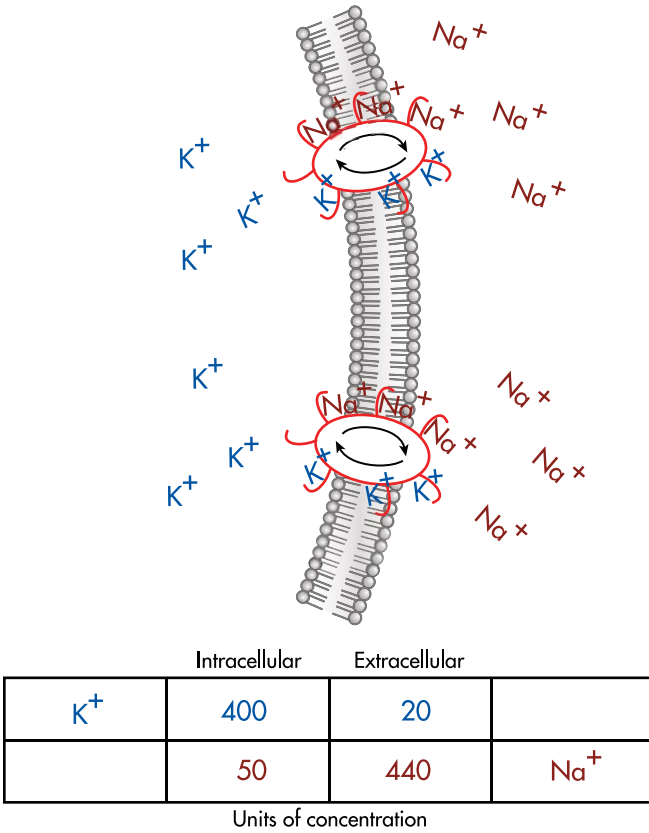
	Intracellular	Extracellular	
K^+	400	20	
	50	440	Na^+

Units of concentration

FIGURE 3–2. The sodium-potassium pump.

The sodium-potassium pump swaps sodium and potassium ions to maintain a high concentration gradient across the cell wall.

NERVE CELL STRUCTURES

Nerve cells can be divided into three zones: input, conduction, and output (Figure 3–3). The dendrites are the input zone of the cell, or what some call the "ears" of the neuron. They are covered with synaptic terminals that can receive signals from other neurons. If the electrical charge reaches the threshold at the axon hillock, an impulse, or action potential, is then sent down the axon. That signal is passed on to other neurons or end organs through the synaptic terminals at the distal end of the nerve.

Generating an Action Potential

Dendrites receive as many as 100,000 inputs from other nerve cells. How does the nerve cell decide if it should respond and fire its own impulse? The decision to fire an impulse is determined by the membrane potential at the axon hillock. The membrane potential is altered by input to the dendrites from other neurons. Some inputs depolarize the neuron and make it more likely to fire an action potential, whereas other inputs hyperpolarize the neuron and make it less likely to fire.

EXCITATORY AND INHIBITORY NEURONS

Excitatory neurons (predominantly glutamate neurons) are depolarizing. An influx of positively charged sodium ions from these neurons results in a more positive membrane potential that is more likely to fire an action potential. Inhibitory neurons (predominantly γ-aminobutyric acid neurons) are hyperpolarizing. An influx of negatively charged chloride ions from these neurons results in a more negative membrane potential that is less likely to fire. In other words, the movement of charged ions into the nerve cell at the synapses alters the electrical potential of the cell. This process is illustrated in Figure 3–4.
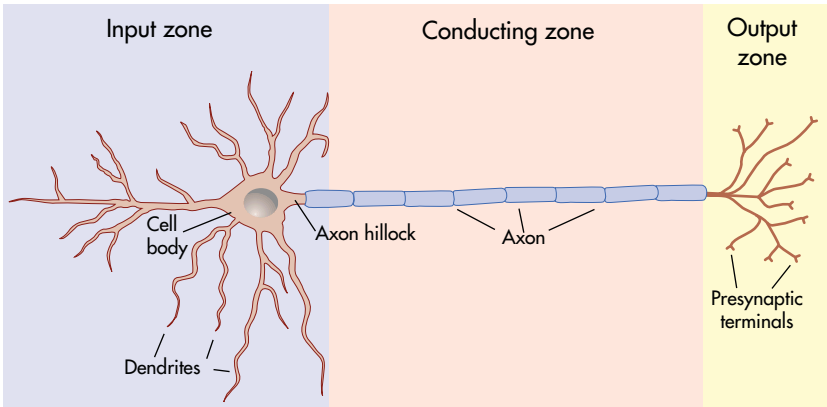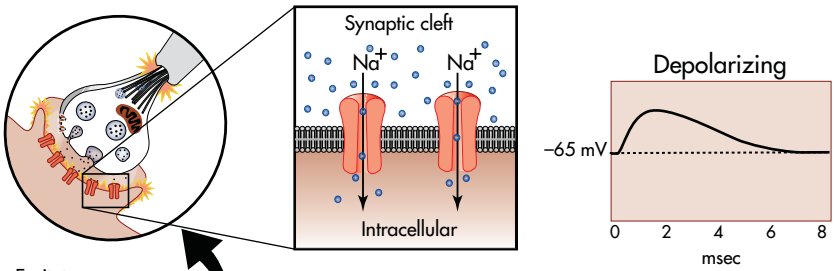
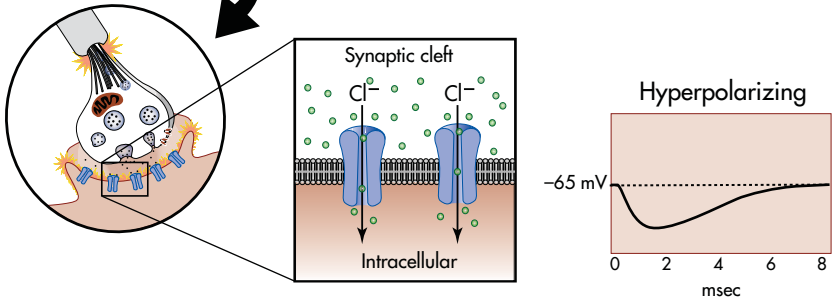**FIGURE 3–3.**   Nerve cell structures.

Nerve cells can be conceptualized as having an input zone (dendrites), a conducting zone (axon), and an output zone (synapses formed with neurons or glands).

FIGURE 3–4. Excitatory and inhibitory inputs.

Input from an excitatory neuron (A) depolarizes the receiving neuron. Input from an inhibitory neuron (B) hyperpolarizes the receiving neuron.

Axon Hillock

The response of the neuron depends on the electrical charge at the axon hillock (Purves et al. 2004). The neuron will fire and send an action potential down the axon if the membrane potential reaches the threshold at the axon hillock. The membrane potential at the axon hillock is a summation of the depolarizing and hyperpolarizing signals received by the dendrites. Figure 3–5 shows how varying input from other neurons alters the membrane potential at the axon hillock, which in turn determines whether an action potential fires.

Action Potential

The "all-or-none" aspect of the action potential is one of the important features of the signal. Once the threshold is reached at the axon hillock, the neuron sends a large, uniform, electric signal down its own axon. The electric charge results from the large and rapid influx of positively charged sodium ions into the negatively charged intracellular space. The ability to pass the signal down the axon with no diminution in its strength allows the signal to travel great distances—for example, the length of the spinal cord of a whale.

Chemical Signal

Ultimately, the action potential arrives at the terminal end of the neuron (see Figure 1–1 in Chapter 1, Introduction). Here, the electrical signal induces an influx of calcium, which in turn results in a fusing of the neurotransmitter-filled vesicles with the synaptic cell wall. The neurotransmitters are dumped into the synaptic cleft and, if sufficient, stimulate the next neuron or end organ.

If you can imagine this basic sequence repeating 100 billion times (the number of neurons in the brain), with some of these firing many times per minute, you have envisioned the summated electrical activity of the brain. Remember from Chapter 2 (Basic Electricity) that this consumes a little less than 0.1 cal/minute (40–50 cal/hour, 900–1200 cal/day) just to keep all those action potentials charged and to recharge them after information has
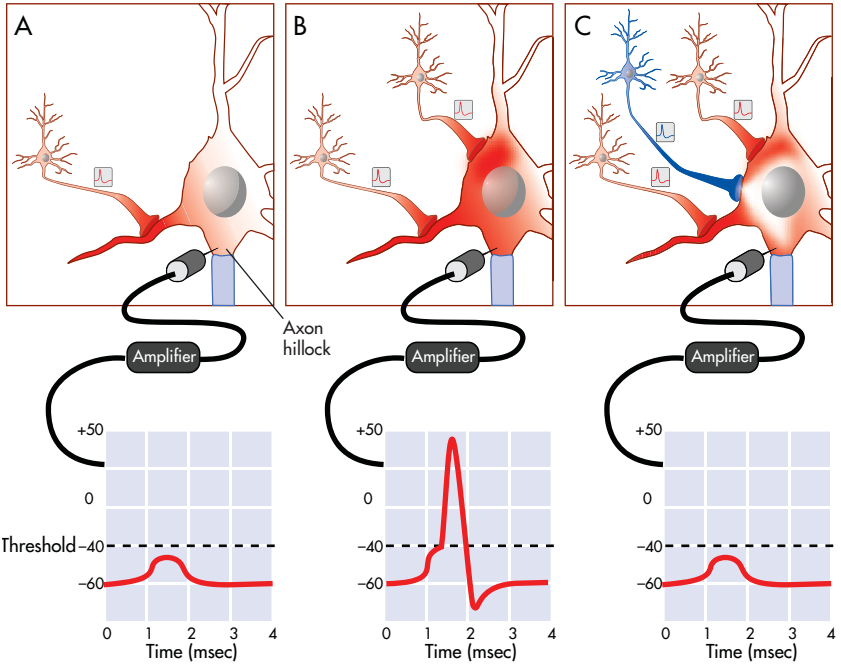
FIGURE 3–5. Reaching the threshold.

Input from one excitatory neuron (A) does not increase the membrane potential enough to reach the threshold. Input from two excitatory neurons (B) pushes the membrane potential at the axon hillock over the threshold, and an action potential is fired. The additional input of an inhibitory neuron (C) hyperpolarizes the neuron, and the membrane potential again does not reach the threshold.

flown by in the form of an action potential. This symphony of discharges becomes unbelievably complex, but it all starts from these basic building blocks. The brain stimulation techniques by and large modify this basic mechanism in selected brain regions or circuits by introducing focal electrical stimulation.

Clinical Relevance

EEG

As early as 1875, electrical activity had been recorded from the exposed cerebral cortex of a monkey (Bear et al. 2006). However, it was Hans Berger, an Austrian psychiatrist, who, in 1929, first recorded electroencephalogram (EEG) scalp tracings from awake humans. Berger went on to show that different states of mind produced many different EEG rhythms. The EEG remains a useful tool for understanding epilepsy and sleep.

EEG recordings are generally made through two dozen electrodes fixed to the scalp in predetermined locations. The electrodes are connected to amplifiers and recording devices. Small voltage changes are measured between pairs of electrodes. Usually, the voltage fluctuations are only a few tens of microvolts in amplitude.

The EEG measures a summation of electrical activity from a large number of neurons beneath the electrode. Research with animals has determined that most of the electrical activity being recorded is coming from synaptic activity on the dendrites of the large pyramidal neurons. Figure 3–6 illustrates the activity summated during an EEG recording. Signals from afferent neurons release the neurotransmitter at the synapse. The movement of positive ions into the pyramidal neuron leaves a slightly negative charge in the extracellular fluid. As the current spreads and escapes out of the deeper parts of the neuron, those extracellular sites become slightly positive.

EEG recordings are measuring the summation of activity from thousands of neurons. If the activity is out of synch or irregular, the EEG summation will have a high frequency and small amplitude. On the other hand, if the activity is synchronized, the EEG summation will record low frequency, high amplitude waves.
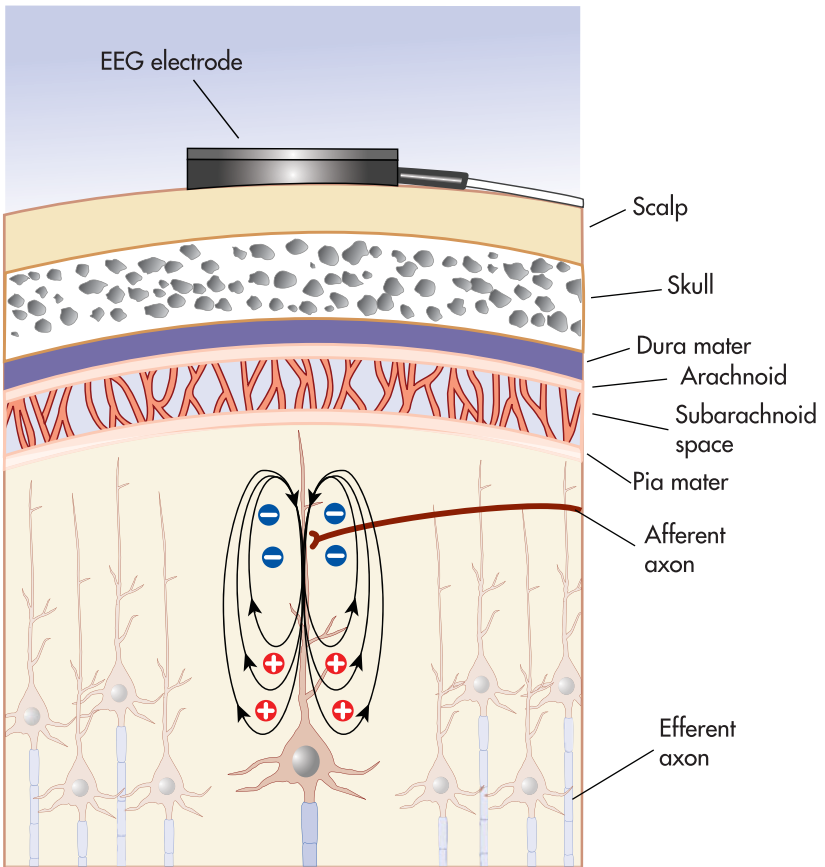
FIGURE 3–6. Synaptic activity produces slight electrical charge.
When thousands of other cells contribute their small voltage, a signal
becomes strong enough to be detected by the EEG electrode at the scalp.

Source.   Adapted from Bear MF, Connors BW, Paradiso MA: *Neuro-
science: Exploring the Brain*, 3rd Edition. Baltimore, MD, Lippincott Wil-
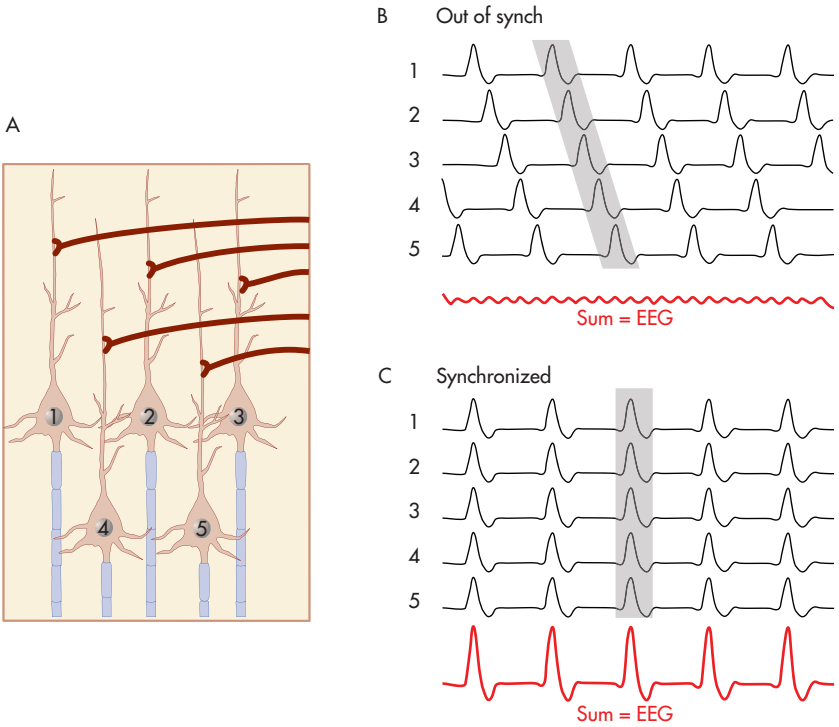liams & Wilkins, 2006, p. 587.

FIGURE 3–7.   How synchrony determines electroencephalographic frequency.

Activity from 5 neurons is being recorded (A). When the signals are out of synch and irregular, the summation (shown in red) is high frequency, low amplitude EEG (B). Synchronized signals produce low frequency, high amplitude EEG recordings (C).

Figure 3–7 gives an example of this summation. In other words, the characteristics of EEG waves reflect the synchrony of the neurons, not some measure of their activity.

Remember also from Chapter 2 (Basic Electricity) that electricity and magnetic fields are interchangeable, and that whenever electrical current flows there is a magnetic field induced around the wire (or axon). Magnetoencephalography is the magnetic equivalent of the EEG, the technique used to record the tiny magnet field changes caused by synchronous neuronal firing.

One of the more interesting ideas being investigated within the field of brain stimulation involves modifying the stimulation based on the EEG data or some other physiological reading. In deep brain stimulation, this treatment is called *responsive stimulation therapy (RST);* it has been pioneered largely by one company, NeuroPace. Similar ideas of tailoring the stimulation based on EEG or some other biomarker are being investigated with the other brain stimulation techniques in use.

Attention-Deficit/Hyperactivity Disorder (ADHD)

EEG biofeedback offers a way for patients to exercise their brains and improve attention and concentration. When the brain is in beta rhythm, although there is less synchrony, it is actually more focused and attentive. Special computer devices can measure a patient's EEG rhythms and provide feedback. Patients can learn to keep their brain in beta rhythm. The result seems to be the equivalent of exercising the brain and has been used to potentially improve ADHD symptoms. However, well-designed randomized clinical trials have not been conducted.

SLEEP

The frequency and amplitude of the EEG best reflects the state of alertness of the individual (Higgins and George 2007). EEG recordings from awake and asleep individuals show the changes in EEG rhythms. Figure 3–8 shows examples of different rhythms and the usual mental state associated with each. Higher frequency rhythms such as beta rhythms are found when individuals are alert and focused. Slower waveforms such as theta and delta are manifested during sleep. Signals from the thalamus seem to be driving the synchronization of the cortical neurons during sleep. However, it remains unclear why this synchronization is an important aspect of the sleeping brain.

SEIZURES

A seizure is the rhythmic firing of large groups of neurons. It is the most extreme form of synchronous brain activity. Inducing a seizure for therapeutic benefits becomes the focus of treatment discussed in Chapter 4 (Electroconvulsive Therapy). However, spontaneous seizures are a sign of a disorder. Much of the focus when examining a patient with new-onset seizures is directed toward finding what is causing the problem.

Summary to This Point

We have now reviewed the basics of electricity and circuits, introduced many basic concepts and terms, and examined how neurons use chemical gradients to propagate electrical information. With this information in hand, we can now begin discussing the brain stimulation technologies, in which we use some form of focal electrical or magnetic energy to modify brain activity.
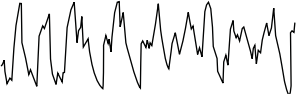
Rhythm	Mental state	Example	Frequency
Beta	active attention		14–16 Hz
Alpha	quiet awake		8–13 Hz
Theta	drowsy / light sleep		4–7 Hz
Delta	deep sleep		<4 Hz

FIGURE 3–8.   Electroencephalographic rhythms.

The four basic EEG rhythms of the brain during sleep and awake states.

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CHAPTER 4

Electroconvulsive Therapy

Introduction and History

The Italian physician Ugo Cerletti was the first clinician to utilize electroconvulsive therapy (ECT) as a treatment for a psychiatric patient (Shorter 2004). The year was 1938. The idea to induce a seizure with an electrical shock as a therapeutic intervention for a psychiatric disorder was not entirely out of the blue. "Physical therapies," such as malarial-fever treatment for neurosyphilis, were emerging as effective treatments for psychiatric illnesses. Medically induced convulsive therapies were introduced in 1934.

Medically induced seizures involved the intramuscular administration of camphor and, later, pentylenetetrazol to elicit a therapeutic seizure (Prudic 2005). The procedure had some success, which was remarkable during that time when few treatment options were available. In one report, approximately 50% of the patients had some degree of remission of their psychotic symptoms after an intervention. Unfortunately, chemically induced seizures were painful and could be difficult to control. Seizures could last longer than desired.

The introduction of ECT by Cerletti and his assistant Bini provided a much improved mechanism to induce a therapeutic seizure. Cerletti speculated that electricity might provide a safer method of inducing convulsions. Working first with dogs and then with pigs, Cerletti established a safe mechanism to evoke a seizure without harming the animal.

The story of the first person to receive ECT is one of the landmark interventions of psychiatry (Cerletti 1950). The patient was a 39-year-old former engineer who was found wandering the Italian streets in a delusional state. He was unable to speak coherently and appeared to have no family. He was diagnosed with schizophrenia. His condition remained unchanged and his prognosis was poor. By modern standards, such a patient would not be able to consent to an untested intervention, but at that time he was considered an ideal candidate.

The first electrical stimulation administered, unfortunately, did not induce a seizure. At the prospect of receiving a second stimulation, the otherwise uncommunicative patient exclaimed, "Not a second. Deadly!" Cerletti was not to be deterred. The voltage and duration was increased and a second dose was given. This time, the patient had a true seizure and actually stopped breathing for almost a minute. Cerletti later wrote what happened next:

> The patient sat up of his own accord, looked about him calmly with a vague smile, as though asking what was expected of him. I asked him: 'What has been happening to you?' He answered, with no more gibberish: I don't know; perhaps I have been asleep (Cerletti 1950).

The patient received 10 more ECT sessions in the following weeks and had a remarkable recovery. Within 2 months, he was reunited with his wife and eventually resumed his job. A year later, he was still working and living at home. With this case and others to follow, Cerletti established that ECT was effective and reasonably safe.

The psychiatric community quickly embraced ECT. In 1940, ECT was demonstrated at the annual meeting of the American Psychiatric Association (Shorter 2004). The following year, a group in Boston (where else?) published a handbook on ECT. Refinements in the technique further enhanced the acceptance of ECT. The addition of succinylcholine and anesthesia reduced problems associated with the procedure. ECT was quickly accepted into mainstream psychiatry. By 1959, which may have been the high-water mark for the utilization of the procedure, ECT was the "treatment of choice" for major depression and bipolar disorder (Shorter 1997). However, the glory days of ECT were soon to end.

Chlorpromazine (Thorazine), introduced in 1954, and imipramine (Tofranil), in 1958, were the first effective antipsychotic and antidepressant medications (Shorter 1997). At that point, there were three options for patients: psychotherapy, medications, and brain stimulation. The interest in ECT dropped dramatically (Shorter 2004). But it was not just due to the availability of pharmacological interventions. It was also a cultural rejection of the overutilization of ECT in the 1950s. The novel (1962), and later the movie (1975), *One Flew Over the Cuckoo's Nest* had a devastating effect on the public perception of ECT. In 1974, California passed a law severely restricting the use of ECT.

Fortunately, since the mid-1980s the tide has begun to turn (Dukakis and Tye 2006), and there has been a resurgence of interest in ECT. Training programs have resumed teaching the procedure, and increasing numbers of patients are benefiting from the treatment. In truth, it is hard to eliminate such an effective treatment. Although indicated for a range of disorders, ECT is typically reserved for acutely depressed, manic, or catatonic patients whose conditions do not respond to other treatments, or for those with life-threatening conditions in need of emergent resolution.

How Is It Done?

The essential ingredient of ECT is the induction of a seizure, which is necessary but not sufficient for therapeutic effects. In 1960, Cronholm and Ottosson established in their classic investigation that it was the seizure activity that produced the therapeutic response with ECT, and not just the electrical activity. They confirmed this by randomly administering an anticonvulsant (lidocaine) to some patients in the study. Those that received the lidocaine displayed less seizure activity, required more electrical stimulation, and did not respond as well. Clearly, with regard to ECT, the seizure produces the therapeutic effect.

Modern ECT, at least in the United States and other industrialized nations, is administered with brief anesthesia, muscle relaxants, and supplemental oxygen. In some Third World countries, such amenities are not provided. Figure 4–1 shows the general components of ECT. The ECT device takes power from an external source and delivers a brief impulse through the paddles or electrodes to the patient's scalp. The electrical stimulation must be sufficient to induce a seizure.

The general principles of brain stimulation parameters (frequency, intensity, and duration) apply to ECT. That is, sufficient stimulation is needed to produce an effect, but too much results in adverse events. One variable that presents a notable problem with ECT is resistance. The scalp and especially the skull impede the flow of electricity to the brain.

DOSING

Patients have varying amounts of skull resistance to the electrical charge—as much as 50-fold (Prudic 2005). A particular dose for one patient may be too much or insufficient for another. This is a significant issue because a higher stimulation dose results in greater efficacy but also greater cognitive side effects.

Many ECT practitioners use published scales or algorithms based on age and sex in order to estimate the appropriate dose. Others use a method called dose titration. In this situation, electricity is delivered in ever-increasing amounts until a seizure
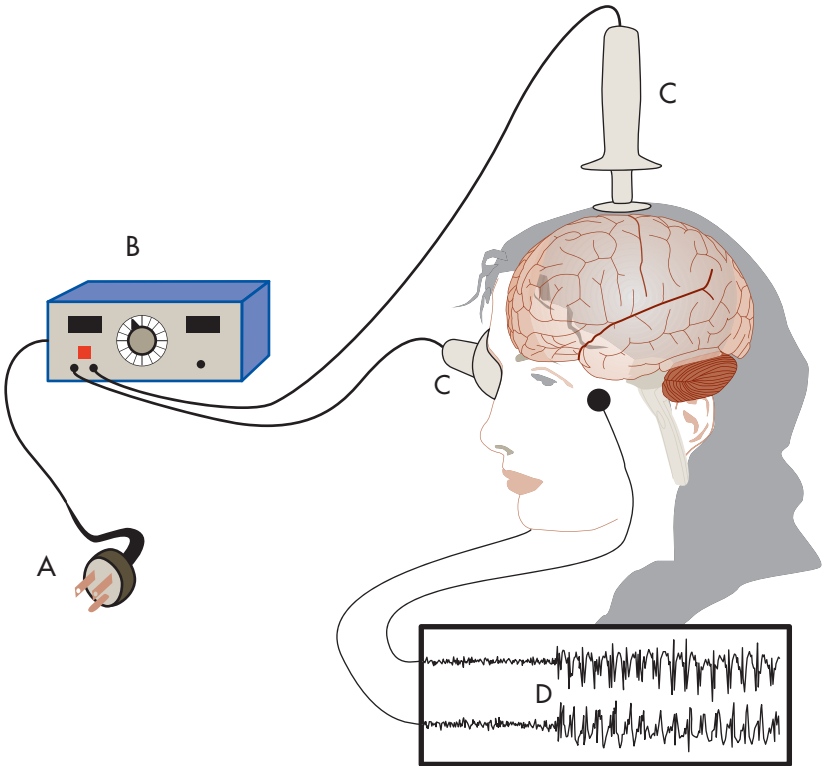
FIGURE 4–1. The ECT apparatus.

With modern ECT, electricity (alternating current) from the wall (A) is then stored and released through the ECT device (B). The electrical pulse from the device is commonly a brief pulse (milliseconds). More recent work with ultrabrief pulse has reduced the width of this signal even further, so that it now approaches chronaxie, that is, the minimum needed to cause an action potential in a nerve. The current is passed through electrodes on the scalp (C), inducing a seizure. Commonly, EEG and EMG (from a nonparalyzed part of the body, typically the foot) are recorded to document the seizure (D).

Unilateral   Bilateral
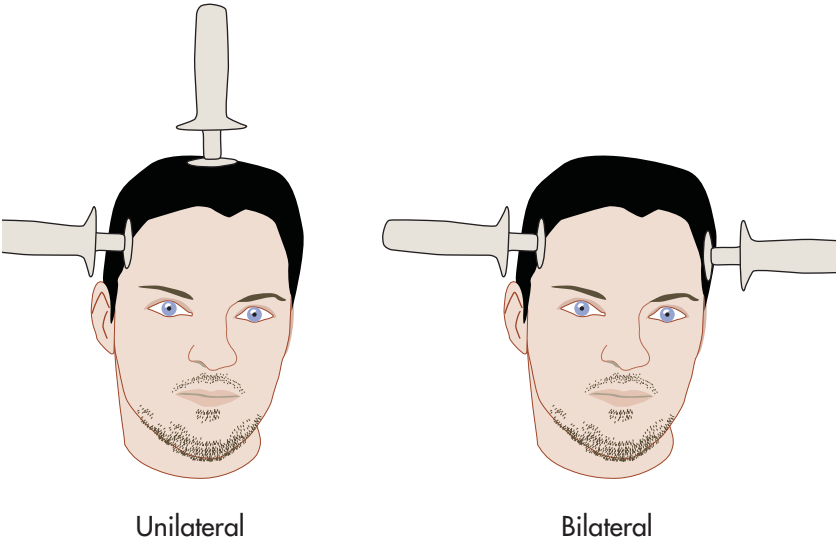
FIGURE 4–2.   Unilateral and bilateral electrode placement for ECT.

occurs; the point at which a seizure occurs is called the *seizure threshold*. Later sessions then deliver the dose based on this initial number—for example, 150% of the seizure threshold. Typically, the seizure threshold also increases over the several weeks of the ECT course as the brain responds to the seizure and attempts to prevent future ones. Some speculate that the antidepressant effects of ECT may be linked to this progressive increase in seizure threshold, although this is controversial.

ELECTRODE PLACEMENT

The placement of the electrodes on the head has a significant effect on outcome. The two most commonly used positions are bilateral and unilateral, as shown in Figure 4–2. Bilateral is more widely used, presumably due to its increased efficacy. However, bilateral ECT is also associated with greater cognitive side effects. Sackeim et al. (2000) showed that unilateral ECT requires greater electrical stimulation to have similar efficacy, but can still have fewer side effects.

Figure 4–3 and Table 4–1 show the results of the Sackeim et al. study. In all, 80 depressed patients were randomly assigned to receive unilateral ECT with electrical stimulation at 50%, 150%, or 500% above the seizure threshold, or bilateral ECT at 150% of the seizure threshold. Figure 4–3 shows the reductions on the Hamilton Rating Scale for Depression: high-dose unilateral ECT and bilateral ECT were equally effective. However, Table 4–1 shows that patients receiving bilateral ECT took longer to regain their orientation and had greater retrograde amnesia for famous events after the procedure.

WAVEFORM

The ECT machine determines the shape of the electrical signal—called the *waveform*. Figure 4–4 displays two commonly used waveforms. The sine wave is the older waveform although still in use in some hospitals. This alternating current waveform is essentially unchanged from what emerges from the socket. The brief-pulse waveform has the advantage of inducing a seizure with less electrical stimulation. Note the area under the curves and the milliseconds of phase duration are smaller for the brief pulse.
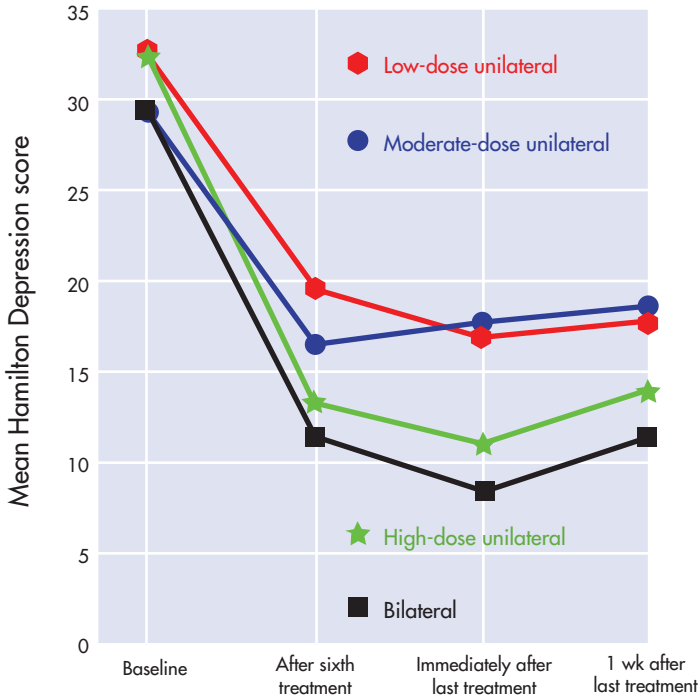
FIGURE 4–3.   Electrode placement and depression response.

Mean reduction in Hamilton Rating Scale for Depression score for different doses of unilateral ECT compared with bilateral ECT.

Source.   Adapted from Sackeim et al. 2000.

TABLE 4–1. Cognitive side effects with different forms of electroconvulsive therapy

Time to recover orientation in minutes			
Low-dose unilateral	Moderate-dose unilateral	High-dose unilateral	Bilateral
19	17	31	46
Retrograde amnesia for famous events			
Low-dose unilateral	Moderate-dose unilateral	High-dose unilateral	Bilateral
4	0	−2	−17
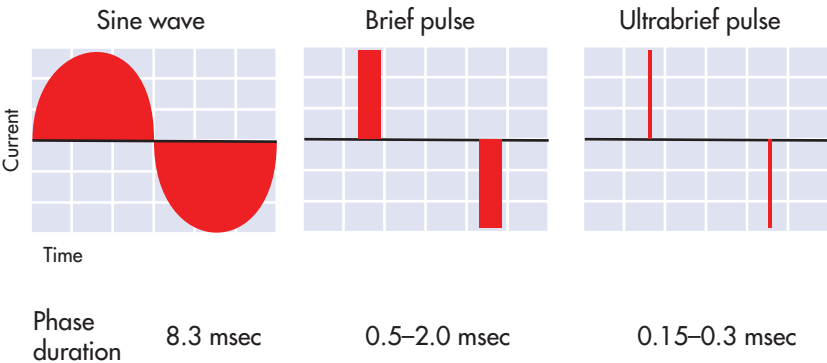
FIGURE 4–4. ECT waveforms.

Example of one cycle for three different waveforms from different ECT machines. Note that historically the sine wave was used in the mid-twentieth century, followed by the brief pulse in the 1980s, and, within the past few years, the ultrabrief pulse.

The sine waveform produces extra electrical stimulation without added benefits. Once the nerve cell has fired, it enters a refractory period during which additional electrical energy is unwarranted and probably increases side effects (more on this below). Most recently, scientists have begun using what are called *ultrabrief pulses*. Here, the pulses are even briefer and are much more *physiological* in that they deliver only what is minimally needed to cause depolarization.

Because the skull acts as a resistor, it is hard to focus exactly where an ECT seizure will be induced. One of the key questions then is, does it matter where the electrodes are placed? In a pioneering series of studies, Sackeim and colleagues (1993) showed that one can place the ECT electrodes over the back of the brain and induce a full tonic-clonic seizure, but that this has absolutely no antidepressant effect. So, induction of a seizure is necessary, but not sufficient. To produce the antidepressant effects of ECT, the seizure must originate in specific regions.

If a seizure in specific areas is needed to produce the therapeutic effects of ECT, how did generalized chemical convulsions get people "undepressed"? The regions of the brain with the lowest seizure threshold (and thus most likely to start seizing first) are the hippocampus and other medial temporal lobe structures. Thus, it is likely that the medications used to generate convulsions actually caused focal seizures in the needed limbic areas. This is perhaps another example of the just-darned-good-luck found in the history of the development of brain stimulation techniques.

ANESTHESIA

One of the greatest advances in ECT has been the development and use of anesthesia during the ECT session. Typically patients are given a muscle relaxer and a general anesthetic. The muscle relaxer, usually succinylcholine, paralyzes the body and stops the actual motor convulsions, preventing bruising and fractures. A blood-pressure cuff is inflated around the ankle, which prevents the succinylcholine from entering the foot. The nerve impulses, however, are not blocked and the psychiatrist is able to observe the convulsions from the seizure in the nonparalyzed foot.

Most hospitals in the United States now use propofol as a general anesthetic. Paradoxically, propofol raises the seizure threshold, making it harder to induce a seizure. An interesting new trend is to use ketamine. Ketamine, without ECT, has been reported to have antidepressant effects, so the combination of ECT and ketamine would seem to be a reasonable choice. Many clinicians complain, however, that the recovery time is slower from ketamine than from propofol. The ideal anesthetic for ECT has yet to be discovered.

Because the anesthesia is so brief, typically only 10–15 minutes total, most patients are not intubated. Respiration is maintained with a breathing mask administered by an anesthetist or anesthesiologist.

FOCAL SEIZURES

There is much interest in developing a method to produce a more focal seizure. Such a method could theoretically reduce side effects, such as poor cognition, caused by unintended passage of electricity through nearby brain regions where seizure induction is not needed for efficacy. One method used in attempting to minimize side effects is called *magnetic seizure therapy* (MST). Here, a powerful transcranial magnetic stimulation device (see Chapter 6, Transcranial Magnetic Stimulation) is employed to create a focal seizure. MST has been applied in humans; a small clinical trial on its effect on acute depression is underway. The data so far show that subjects wake up more quickly after a seizure induced by MST, compared with ECT. Unfortunately, it has been difficult to produce an MST seizure in the frontal cortex. Likewise, there are no data on its effectiveness for depression.

Another way of theoretically producing a more focal seizure is to make the electricity unidirectional—that is, more like direct current. Charges would then build up in the brain tissue under the different electrodes. By delivering this unidirectional current in a pulsatile way, one might induce enough charge to cause a focal seizure. This technique has been performed in primates and in three human subjects (undergoing ECT). The method is called *focal electrical alternating current seizure therapy* (FEAST).

Using the terminology of this book, this form of stimulation might also be called *pulsatile transcranial direct current stimulation*, or *powerful pulsatile tDCS,* intended to produce a seizure. (One of the problems with the new field of brain stimulation is getting everyone to agree on a common naming convention.)

Third World Experience

ECT use is not limited to industrialized nations and remains remarkably popular in many developing countries. However, even though an alternating current to produce the stimulus is readily accessible, amenities such as anesthesia are not. The conditions present in these countries are much like those that existed for Cerletti and his patients in 1938.

What Does ECT Do to the Brain?

Patients conceptualize ECT as resetting or rebooting the brain (Dukakis and Tye 2006). It is as though the procedure erases the problems and lets the brain restart afresh. Experts offer different explanations, but the actual curative effect of ECT remains unknown. The patients' explanations may be equally plausible.

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In treating depression one would intuitively assume that there is some aspect of the ECT-induced seizure that "awakens" the brain and restores it to its premorbid well condition. In actuality, what occurs is just the opposite. Figure 4–5 shows a composite positron emission tomography (PET) scan constructed from the scans of 10 patients before and after a course of ECT for depression (Nobler et al. 2001). The most remarkable finding is the decreased metabolism in the prefrontal and parietal regions. In general, the reductions in prefrontal activity correlate with treatment outcome. That
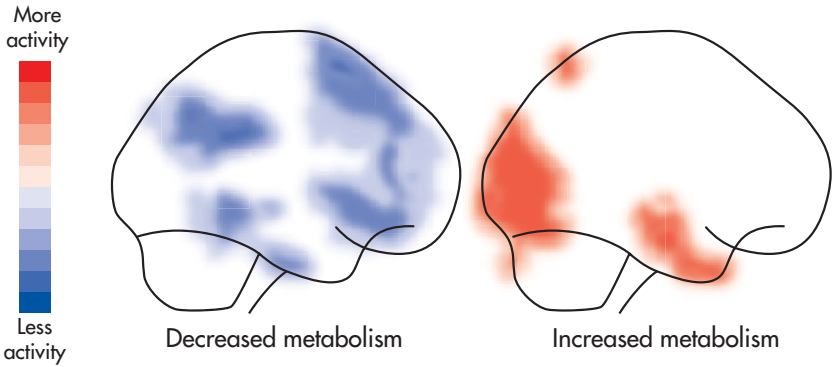
FIGURE 4–5. Brain activity following a course of ECT.

Prefrontal and parietal regions show decreased cerebral glucose metabolism after a course of ECT. Relative increases in glucose metabolism were primarily limited to the occipital lobes.

Source. Adapted from Nobler et al. 2001.

is, rather than restoring function and returning the brain to its pre-morbid state, ECT appears to be pushing the brain into a different homeostasis, with many areas of the brain paradoxically showing decreased function while the patient is free of depression.

Surprisingly, ECT, which produces a seizure, actually serves as an anticonvulsant in the long term (Sackeim 1999). By induc-ing a seizure, ECT in fact *decreases* electrical activity of the brain. If depression is the result of aberrant electrical activity, as some believe, then the antidepressant effect of ECT may be due to its capacity to quiet the brain. By inhibiting electrical activity, or pro-ducing a cascade of pharmacological events that the brain natu-rally uses to stop seizures from spreading, ECT may enable the brain to function more efficiently.

NERVE GROWTH FACTORS

Animal and human research results over the past decade suggest that depression may result from a decrease in nerve growth fac-tors such as brain-derived neurotrophic factor (BDNF; Higgins and George 2007). The theory proposes that the loss of nerve growth factors such as BDNF results in a decrease in activity in the neural networks involved in mood. Disparate treatments such as antidepressants, lithium, and exercise all increase BDNF. Furthermore, the stimulation therapies—transcranial magnetic stimulation and vagus nerve stimulation, as well as ECT—also increase BDNF.

Therefore, one possible explanation for the effectiveness of ECT could be that it restores growth-factor proteins to normal levels (Bocchio-Chiavetto et al. 2006); the growth-factor proteins in turn stimulate neural growth, which reinstates normal mood.

NEUROENDOCRINE

Subtle neuroendocrine abnormalities are common among the se-riously mentally ill (Wolkowitz and Rothschild 2003). The hypo-thalamic-pituitary-adrenal axis and the thyroid gland are frequently described as having links to mood disorders. Max Fink and others postulated that ECT works by changing the hor-monal balance of the brain (Fink 2001). In theory, the ECT-

induced seizure causes the release of deficient hormones from endocrine glands. Release of the hormones stimulates further production of some as-yet-to-be-identified molecule, which in turn improves the patient's condition.

Although the theory has a certain appeal, there is little evidence to support it. No hormone has been identified that would fit this model.

Safety/Adverse Events

MORTALITY

ECT is relatively safe. However, it is a medical procedure involving repeated sessions of general anesthesia, and there is known morbidity and, though rarely, mortality. The mortality rate is estimated to be similar to that reported for minor surgery or childbirth. The American Psychiatric Association Task Force on ECT estimated that a current rate for mortality from ECT is approximately 1 per 10,000 patients or 1 per 80,000 treatments (American Psychiatric Association 2001).

COGNITIVE IMPAIRMENT

Reports of adverse effects of ECT on cognition are the most troubling aspect of the procedure. The seizure induces an obtunded state from which the patient slowly emerges over minutes to several hours. Some patients, particularly the elderly, fail to clear quickly and can remain in a lingering delirium. Although this effect is not common, such patients must delay additional treatment until the delirium clears.

For all patients, memories of the events immediately around the procedure are never recovered. In fact, the long-term memories of the ECT procedure are not even stored due to the disruption caused by the seizure. Memories of events prior to the ECT are impaired at first (retrograde amnesia), but return rapidly, within a matter of weeks. The extent to which the long-term memories return remains a point of controversy between ECT advocates and the antipsychiatry movement.

The ECT advocates, typically clinicians who practice the procedure and study the research, propose that retrograde amnesia is a short-term problem. They believe that ECT does not affect the neural structure of long-term memories. The antipsychiatry enthusiasts, on the other hand, present cases of individuals who suffer from the troubling inability to recall events from their past—even years after the procedure (Breggin 1994).

Unfortunately, hard-science reports on the accuracy of recall of long-term memories after ECT have been limited. The problem has always been how to measure memory for distant events—which tend to fade with time under the best of circumstances. The development of autobiographical memory interviews that can be individualized to each patient and administered before and after the procedure has provided a solution.

Sackeim and colleagues (2007) measured cognitive effects of ECT in 347 patients treated in seven New York City hospitals. As would be expected, most patients displayed significant cognitive impairments immediately after the ECT course was completed. Almost all of the problems resolved within 6 months. However, some patients continued to have deficits in autobiographical memory at the 6-month follow-up. Further analysis indicated that the extent of the remote-memory impairment was related to the type of ECT used. The results are shown in Figure 4–6.

This study demonstrated that remote memories, even autobiographical ones, remained impaired up to 6 months after acute ECT treatment. The authors noted in their discussion that patients receiving bilateral ECT displayed almost three times the amount of forgetting compared with an age-, gender-, and education-matched comparison group who did not have a history of psychiatric illness.

CARDIAC ARRHYTHMIAS

There is a high rate of cardiac arrhythmias in the immediate postictal period. Most of these events are benign and resolve quickly. Patients with preexisting cardiac disease are at greatest risk for developing irregular rhythms.
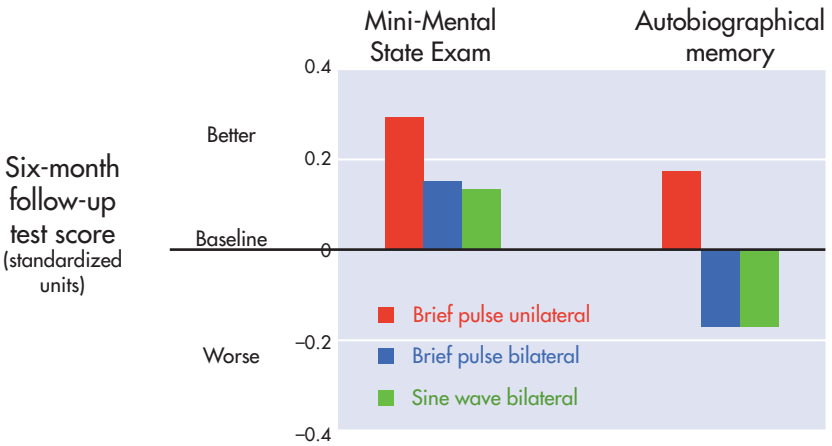
FIGURE 4–6. Long-term memories after ECT.

For these patients with major depression who were treated with ECT, Mini-Mental State Examination scores improved from baseline at 6 months. Autobiographical memory scores were worse at 6 months for patients who received bilateral ECT.

Source. Adapted from Sackeim et al. 2007.

PROLONGED SEIZURES

Rarely, a patient will have a prolonged seizure or even status ep-ilepticus. Failure to terminate a persistent seizure not only pro-longs the patient's mental confusion after the procedure, but risks complications from inadequate oxygenation and secondary ischemia.

HEADACHES

The most common physical symptom reported following ECT is headache. As many as 45% complain of a headache. In some, the pain is severe enough to induce nausea and vomiting.

TREATMENT-EMERGENT MANIA

As with any antidepressant treatment, a small minority of pa-tients will become activated by ECT. It is important to distinguish mania from delirium. If the effect is determined to be mania, some practitioners will continue the treatment, given that ECT can treat the mania as well. Others will stop the ECT and manage the mania pharmacologically.

Out-of-Date Equipment

> Perhaps the greatest safety concern regarding ECT is that some practitioners in the community continue to use outdated equipment and nonstandard treatment protocols (Fink 2007). This results in excessive electrical stimulation that offers no greater benefits but does increase the preventable side effects.

Critical Review of ECT in Neuropsychiatric Applications

Because ECT has been around the longest of the brain stimula-tion techniques, more literature regarding its use has been gener-ated. It is beyond the scope of this book to review all these studies. Fortunately, the American Psychiatric Association con-

vened a task force that conducted a thorough review of the literature on the efficacy of ECT. A report on their findings was published in 2001 (American Psychiatric Association 2001). Their conclusions on the indications for the use of ECT are summarized in the sections that follow.

MAJOR DEPRESSION

Although ECT was initially introduced as a treatment for schizophrenia, the focus of interest quickly moved to patients with mood disorders. Numerous randomized controlled trials have been conducted of ECT for depressed patients. The most remarkable were the trials comparing ECT with sham-ECT—a study design that is no longer considered ethical. In the 1940s and 1950s, when ECT was the primary treatment for depression, response rates of 80% to 90% were typically reported.

The development of the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) provided alternative treatments for depression and a comparator for ECT. Numerous trials have been conducted comparing ECT with medications and placebo. In a meta-analysis of studies comparing ECT with antidepressants, ECT was found to have a 20% greater response rate compared with TCAs, and 45% greater response compared with MAOIs (Janicak et al. 1985). It is worth mentioning that some of the pharmacologic treatments given in these studies would not be considered adequate medication trials by modern standards.

The task force reviewed other aspects of ECT and concluded that it is effective for

- Bipolar depression
- Catatonia
- Psychotic depression

On the other hand, ECT may be less effective for patients with

- A long duration of current symptoms
- Depression secondary to medical conditions
- Patients with personality disorders

The current use of ECT in depression is typically reserved for patients for whom several adequate trials of medication have not alleviated symptoms. In these patients with treatment-resistant depression, ECT remains the most effective option, but the results are not as robust as those found with treatment-naïve patients. Response rates in treatment-resistant patients are in the range of 50% to 60%.

In summary, the findings for depression are as follows:

• ECT is an efficacious treatment for unipolar and bipolar depression.
• No trial has ever found an alternative treatment superior to ECT.
• ECT is particularly useful in patients with an emergent need for symptom resolution—for example, catatonic and suicidal patients.
• Continuation of some somatic treatment after the course of ECT is indicated.

Mania

Prior to the proliferation of antimanic medications, ECT was known to be a fast treatment for mania. Mukherjee et al. (1994) reviewed the literature on ECT in mania and concluded that ECT results in remission or marked clinical improvement in 80% of the cases. However, with the availability of effective antimanic medications, ECT is usually reserved for patients with treatment-resistant mania or those in emergent need of stabilization.

Schizophrenia

Before it became evident that patients with mood disorders were better suited for ECT, many patients with schizophrenia—particularly in public institutions—were given the treatment. The development of antipsychotic medications rapidly altered this practice. However, ECT remains an option for patients whose symptoms are not responsive to medications.

Current psychiatric practice entails initiating treatment for schizophrenia by prescribing antipsychotic medications. In general, the literature shows that the combination of ECT and antipsychotic medication is superior in outcome to either of these alone (American Psychiatric Association 2001). Unfortunately, the definitive randomized trial comparing ECT with and without antipsychotic medications for schizophrenics who do not respond to medications has yet to be conducted. The question remains: who will benefit from the addition of ECT to their treatment?

Clearly, some patients with schizophrenia improve with the addition of ECT to their treatment. The literature suggests that patients with a more acute onset of symptoms and symptoms of shorter duration are more responsive to ECT. Some clinicians believe that every patient with treatment-resistant schizophrenia deserves at least one full course of ECT, given that there will be some who respond to the treatment. They argue that few other options exist for those with chronic, unremitting schizophrenia.

PARKINSON'S DISEASE

ECT can improve general motor function for patients with Parkinson's disease, independent of psychiatric symptoms (American Psychiatric Association 2001). Patients struggling with the "on-off" phenomenon may find particular benefit. Fregni et al. (2005) conducted a review of noninvasive brain stimulation for Parkinson's disease and could only find five studies comprising 49 patients that met their inclusion criteria. They concluded that ECT appears to have a significant positive effect on motor function in Parkinson's disease patients, but the results should be interpreted cautiously because only limited studies are available for review.

EPILEPSY

Paradoxically, ECT can stop a seizure. Since the 1940s, ECT has been known to have anticonvulsant properties (American Psychiatric Association 2001). During a course of ECT treatment, seizure threshold increases (Sackeim et al. 1983). ECT provides an option for patients with intractable seizures who do not respond to medications.

CONTINUATION TREATMENT

Despite the remarkable, acute efficacy of ECT, the long-term benefits are difficult to sustain. The relapse rate is particularly high after sessions are discontinued. ECT treatment of major depression is the most widely studied application and provides a good example of the dilemma faced in the decision about whether or not to continue treatment. The solid lines in Figure 4–7 show the results of a follow-up study of continuation therapy following successful ECT treatment (Sackeim et al. 2001). The authors concluded that without medication, virtually all the patients relapsed within 6 months. Monotherapy was marginally effective, but the combination of an antidepressant and lithium provided the best prevention of relapse.

Kellner et al. (2006) conducted a similar continuation study but compared maintenance ECT to nortriptyline plus lithium. Maintenance ECT entailed weekly treatments for 4 weeks, biweekly for 8 weeks, and monthly for 2 months. This totaled 10 additional ECT sessions during the 6-month follow-up period. The results are shown with a dashed line in Figure 4–7.

The authors concluded that maintenance ECT and the combination of nortriptyline plus lithium were equally effective *and* equally disappointing. They declared, "More effective strategies for relapse prevention in mood disorders are urgently needed."

Summary of Clinical Use

ECT is the father of the brain stimulation techniques. There has been a slow evolution of how ECT is performed, which has resulted in improvement in response rates and reductions in side effects. Modern ECT with general anesthesia and unilateral ultrabrief pulses is very different from the ECT Cerletti and others pioneered. However, ECT still carries risks and has cognitive side effects. It is our most effective acute treatment for depression, particularly in treating psychosis, but its benefits are hard to sustain. It is also a useful treatment for acute mania, Parkinson's disease, and status epilepticus.
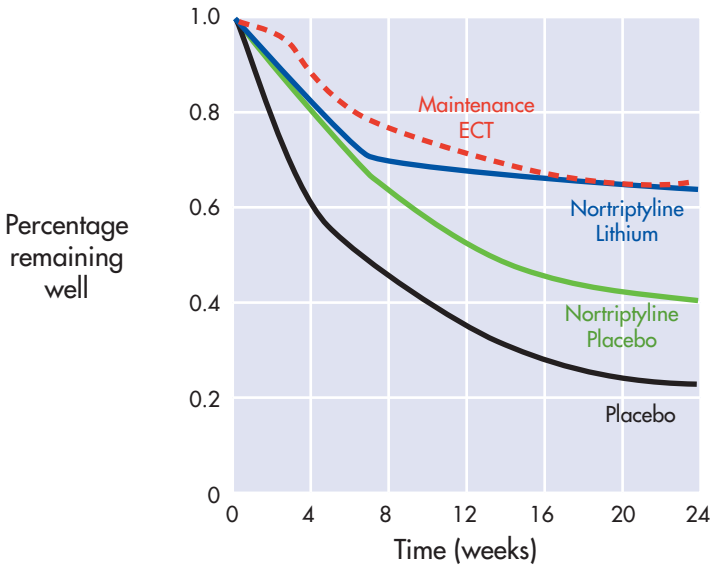
FIGURE 4–7. Six-month relapse rates.

Relapse prevention data after successful ECT for depression highlight the difficulty of keeping people well. Despite limiting enrollment to ECT remitters and using the best possible therapies for maintenance, almost half the patients relapsed within 6 months. In real-world settings where many patients are only partial responders, the relapse rates are likely to be even higher.

Source. Solid lines from Sackeim et al. 2001. Dashed line from Kellner et al. 2006.

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CHAPTER 5

Vagus Nerve Stimulation

Introduction and History

The focus of vagus nerve stimulation (VNS) is, of course, the vagus nerve. The vagus nerve, as shown in Figure 5–1, is the tenth cranial nerve and emerges from the brain at the medulla. It is the longest cranial nerve, extending into the chest and abdominal cavity. *Vagus* comes from the Latin word for wandering, and this nerve is remarkably complex, both in where it comes from and in the variety of information it passes to and from the brain to the viscera.
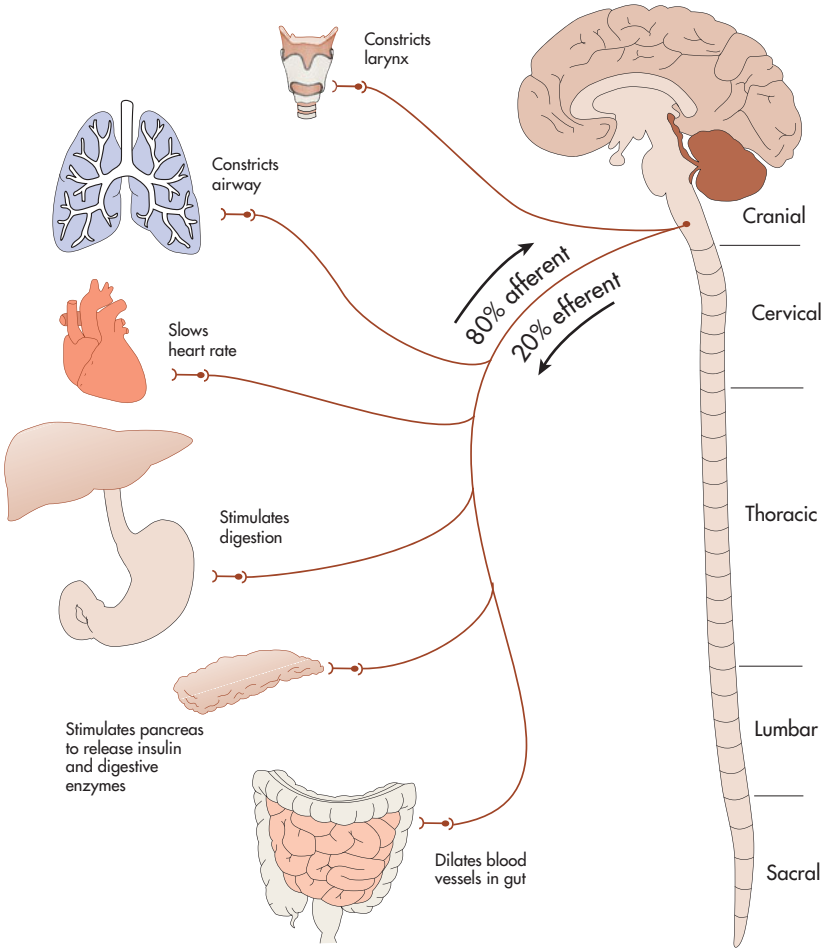
FIGURE 5–1. The vagus nerve.

The vagus nerve provides parasympathetic innervation from the brain to numerous internal organs (efferent activity). However, most of the electrical activity through the vagus nerve proceeds from the thorax back into the brain (afferent activity). Also, note how the branch to the larynx diverges close to the brain stem—typically, above the placement of the VNS electrode.

Traditionally, the vagus has been conceptualized as modulating the parasympathetic tone of the internal organs. For example, vagal signals from the brain (efferent) are highly active during that wonderful, peaceful time after a good meal. However, most of the signals traveling through the vagus nerve actually go from the organs back into the brain (afferent). Foley and DuBois established in 1937 that 80% of the signals traveling through the vagus nerve are afferent, but only 20% are efferent.

In 1938, Bailey and Bremer made an important discovery (Bailey 1938). They stimulated the vagus nerve of cats and reported that this synchronized the electrical activity in the orbital cortex. In 1949, MacLean and Pribram conducted similar studies with anesthetized monkeys (MacLean 1990). Using an electroencephalogram (EEG), they found VNS generated slow waves over the lateral frontal cortex. If you think about it, the vagus nerve is to the body what the optic nerve is to the external world. The optic nerve carries information about the external world, whereas the vagus nerve represents the "eyes" into our internal world—our body and basic life processes.

The afferent fibers traveling in the vagus eventually terminate in the orbitofrontal cortex and the insula, in somatotopically defined regions. They terminate in areas of the limbic brain, which regulates emotion. It is no surprise, then, that when we grieve we have a "broken heart." We actually sense the sensation in our heart, because the vagus cardiac fibers terminate in brain regions where the limbic system and gut sensations overlap (George et al. 2002).

Jake Zabara, in the mid-1980s, was the first to demonstrate convincingly the therapeutic benefits of VNS (Groves and Brown 2005). The story of how Zabara came to discover the therapeutic potential of VNS is another example of serendipity, science, and psychiatric treatment. As he once told the story to one of this book's authors, Zabara was studying the vagus nerve when his wife was pregnant. As a dutiful husband, he attended the Lamaze classes to help his wife master the proper breathing techniques that would assist her through the pain of childbirth. He wondered if the therapeutic benefits of deep and regulated breathing were mediated from the diaphragm through the vagus nerve into the brain.

Zabara began experimenting with dogs. He exposed and stimulated the vagus nerve. One dog developed a seizure and Zabara was able to stop the seizure by stimulating the vagus nerve. Eureka! Later, Zabara induced seizures in dogs with strychnine and showed that repetitive electrical stimulation of the vagus nerve interrupted the motor seizures. Of particular interest to Zabara was the lasting effect of vagus nerve stimulation. That is, the anticonvulsant benefits could outlast the period of stimulation by a factor of 4. Constant stimulation was not required for enduring effects.

The first self-contained devices were implanted in humans in 1988 in patients with intractable, medically unresponsive epilepsy. Results were positive and side effects minimal for these difficult-to-treat patients. VNS became available for use in Europe in 1994 and was given a U.S. Food and Drug Administration (FDA) indication for epilepsy in the United States in 1997.

In 1997, Cyberonics, Inc., the company holding the VNS patent, approached several psychiatric experts, including one of the authors (M.S.G.), and asked if VNS might be useful in mood disorders. Several lines of evidence suggested that VNS might be helpful in patients with depression. Although no objective studies had yet been done, there were numerous anecdotal reports of patients treated with VNS who said they had never felt better in their lives. Furthermore, and perhaps most impressive, functional imaging studies demonstrated that VNS increased activity in several regions of the brain thought to be involved with depression (Figure 5–2) (Henry et al. 1998).

Pilot studies were conducted using VNS with patients who had treatment-resistant depression. Later, randomized controlled trials were undertaken. These studies will be reviewed below. In Europe, VNS was approved for depression in 2001. The FDA approved VNS in 2005 for patients with depression for whom four adequate trials of medication had not been effective.
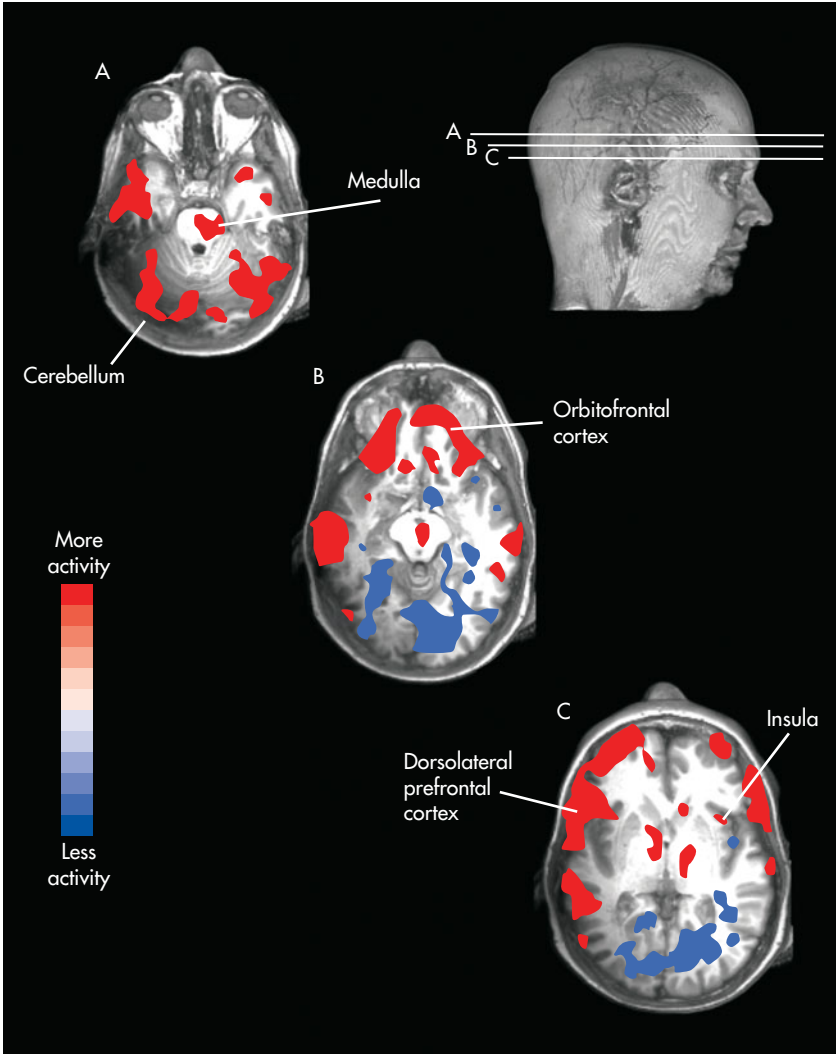
FIGURE 5–2.   Effects of vagus nerve stimulation on the brain.

Ten patients with VNS treatment for epilepsy underwent positron emission tomographic (PET) measurement before and during vagus stimulation. Vagus nerve stimulation, compared to rest, caused relative activation of areas associated with depression (e.g., dorsolateral prefrontal cortex, insula, orbitofrontal cortex, and cingulate gyrus).

Source.   Adapted from Henry et al. 1998.

How Is It Done?

There are a variety of ways to stimulate the vagus nerve, but in humans, VNS refers to stimulation of the left, cervical, vagus nerve using a commercial device. In many ways, the VNS device is similar to a cardiac pacemaker. A battery-operated generator is implanted subcutaneously in the left chest wall and is attached to an electrode tunneled under the skin, wrapping around the nerve and stimulating an important organ. With VNS, the electrode is wrapped around the left vagus nerve in the neck (Figure 5–3).

In the United States, VNS implantation is usually an outpatient procedure, typically performed by neurosurgeons. The battery in the device generates an intermittent electrical stimulation that is delivered to the vagus nerve. Clinicians following the patient control the frequency and intensity of the stimulation. Adjustments to the stimulation parameters are transmitted from a computer to the VNS device by a handheld infrared wand placed over the device.

The wire connecting around the nerve is directional, with clear instructions given as to which end should be proximal to the brain. Some speculate that this unidirectional feature helps minimize efferent side effects. However, it is likely that at least some patients have had the leads reversed without noticeable harm.

WRAPPING A WIRE AROUND A NERVE

The vagus nerve is actually a large nerve bundle, made up of different sizes of nerves going to and from the brain. Some nerves are myelinated and send information quickly; others are naked axons that pass the signals along at a slower pace (Figure 5–4). Some nerves sit close to the outside and are easily accessible to stimulation; others are hidden in the center and are more difficult to reach.

The key point is that the vagus nerve is a complex structure. The modern form of VNS can be compared to wrapping a rope around a tree and trying to influence the flow of phloem and xylem in order to change behavior in a particular branch. The relatively crude nature of the intervention does not allow for as precise a stimulation as we would like. Microsurgical techniques theoretically might allow for more focal VNS.
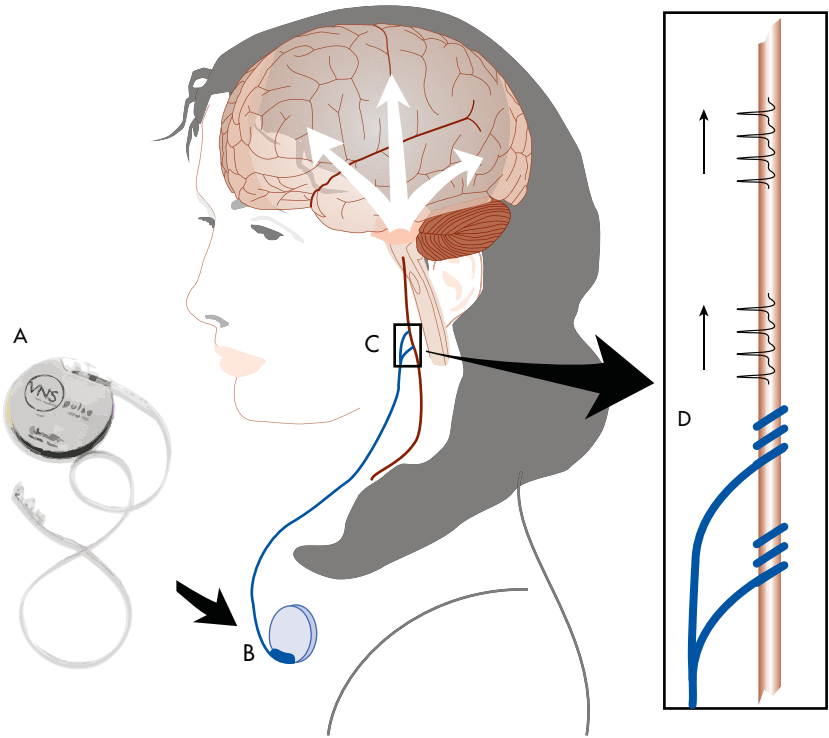
FIGURE 5–3.   The commercially available VNS apparatus.

The VNS generator (A) contains a small battery that generates electrical impulses. A surgeon implants the device under the skin over the chest (B) and attaches the electrodes to the left vagus nerve (C). Regular signals from the VNS device travel up the vagus nerve (D) and ultimately alter activity in the cerebral cortex.

Vagus nerve   Individual axons
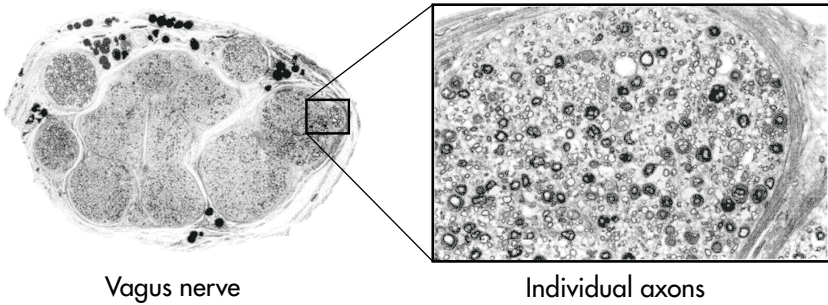
FIGURE 5–4. Cross-section of the vagus nerve.

The vagus nerve contains approximately 100,000 afferent and efferent axons. A closer view shows that most axons are unmyelinated (the dark circles are myelin).

TABLE 5–1. Stimulation parameters for high-dose and low-dose groups in the original epilepsy trials of VNS

	High stimulation	Low stimulation
Frequency	30 Hz	1 Hz
Pulse width	500 microseconds	130 microseconds
Length of stimulation	30 seconds "on"	30 seconds "on"
Length of time between stimulations	5 minutes "off"	90–180 minutes "off"
Total vagus electrical stimulation per day	129.6 seconds/day	0.047 seconds/day

Note. The high-stimulation group received more stimulation, more frequently (approximately 2,500 times as much!).

Where to Stimulate the Vagus?

There are numerous locations where the "wandering" vagus nerve can be stimulated. The left side was chosen because of concerns that the right vagus controls the pacemaker regions of the heart. However, some patients with left vagus trauma have received safe VNS of the right side.

There is a cutaneous branch of the vagus that innervates the ear. Some have speculated that one might stimulate the vagus through skin stimulation of the ear. It is interesting to speculate about whether ear acupuncture or cutaneous stimulation is in some way stimulating vagus fibers. Others have stimulated the vagus fibers closer to end organs, such as near the stomach, in order to modify food craving or satiety.

DOSING

How much stimulation is needed with VNS to produce an effect? Actually, this has never been completely explored. The original dosing parameters (intensity, frequency, duration, etc.) were established by Zabara when he experimented with dogs. He induced seizures in dogs and found dosing parameters that were effective at stopping most of the seizures. Primarily for safety reasons, those same parameters are largely still in use today. A thorough analysis of dosing and response for various disorders has yet to be conducted.

In the initial epilepsy studies, two dosing parameters were compared: high stimulation and low stimulation (see Table 5–1). The other variable, intensity, was similar in both groups. The low-stimulation group was believed to be receiving subtherapeutic stimulation and therefore functioned as a control group.

The current version of the generator can be programmed for the following domains: intensity, pulse width (130, 250, 500 microseconds), frequency (1, 20, 30 Hz), on-time, and off-time. Unfortunately, it must be programmed to follow these strict rules and cannot be programmed in the domain of "intermittent." That

is, one cannot have the device fire for only a few hours a day or set variations in the delivered dose. This is unfortunate because with intermittent dosing you could have the device fire only during sleep or at specific times of the day, timed perhaps with circadian changes. We know that the brain quickly adapts to consistent stimuli but has trouble adapting to variety. It will be interesting to watch, as knowledge of the field progresses, whether intermittent stimulation has profoundly different biological properties.

A series of studies on VNS inside the functional magnetic resonance imaging scanner have shown that varying these parameters makes a difference in terms of which brain regions are affected. Different pulse widths, frequencies, and intensities all result in varying maps of VNS effects in the brain. It is clear that by altering the electrical pulse in the neck you can change the major brain regions affected by VNS. This is likely to have important clinical ramifications in the future.

Compliance

> With VNS and DBS, patients receive 100% of the prescribed dose. People cannot leave town and forget their devices, as they do with pills.

EMERGENCY SHUTOFF

Each patient is given a magnet which, when held over the device, will shut off stimulation. Consequently, patients have the ability to turn off the device temporarily to eliminate troublesome side effects. For example, some patients experience a voice tremor when the VNS is delivering stimulation. Thus, some patients wish to stop the voice tremor during public speaking. When the magnet is removed, normal programmed stimulation quickly resumes. Patients who wish to shut off stimulation for extended periods of time must find ways to secure the magnet directly over the device until they are ready to resume treatment.

What Does VNS Do to the Brain?

VNS has antiseizure and neuropsychiatric effects. How VNS alters the brain and produces these effects is a matter of speculation. Some of the theories that have been proposed are reviewed below.

"Bottom-up" Stimulation

ECT and TMS are stimulation therapies that originate at the top of the brain (outer cortical mantle) and work their way down. VNS, on the other hand, is a "bottom-up" therapy with information flow beginning in the cranial nerve, then moving to the brain stem. The afferent signals coming up the vagus nerve relay information to the nucleus tractus solitarius in the medulla (Figure 5–5). The nucleus tractus solitarius relays the signal through several pathways, perhaps the most important of which goes through the locus coeruleus. These signals are in turn relayed to higher areas of the brain, as shown in the functional imaging studies displayed in Figure 5–2.

Changing Rhythms

Some authors have suggested that VNS controls seizures by changing the electrical rhythms of the brain. We mentioned that early researchers noted slowing of the EEG (not in humans) with vagus stimulation. This slowing may be accomplished through stimulation of the ascending reticular activating system, which projects to numerous forebrain structures. Interestingly, VNS does not readily change the EEG in humans, although it does in other animals. This has frustrated efforts to accurately understand how VNS operates and how to adjust the dose for patients. One of the more common theories about how VNS works is that it may affect the thalamus, altering the rhythmic firing of the thalamus and cortex (thalamocortical firings). This theory has not been proven.
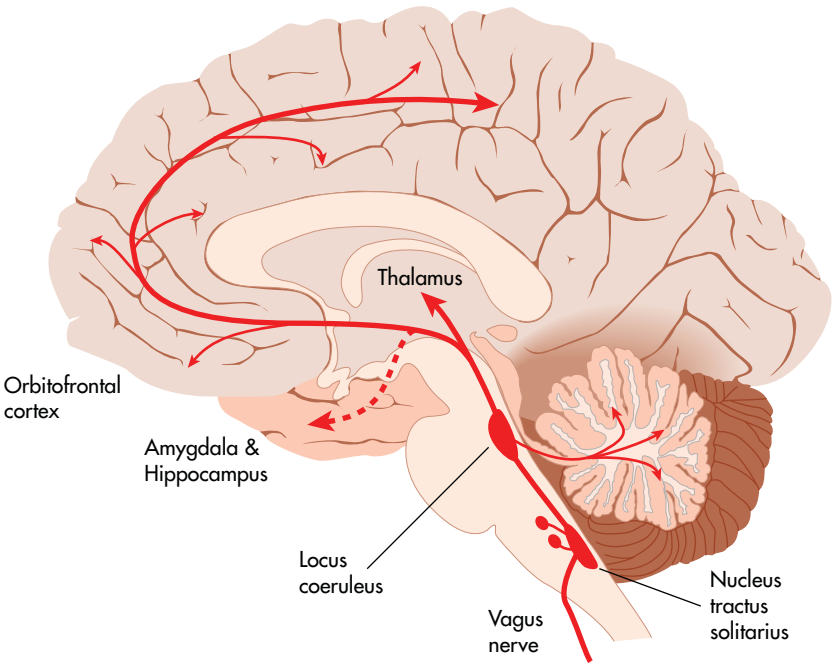
FIGURE 5–5.   Vagus nerve afferent connections.

The afferent fibers of the vagus nerve terminate in the nucleus tractus solitarius, which has connections with the locus coeruleus (and several other structures such as the raphe nuclei). Projectors from the locus coeruleus to other areas of the brain are believed to mediate some of the effects of VNS.

NOREPINEPHRINE

The locus coeruleus clearly plays a vital role in the effectiveness of VNS. Lesions of the locus coeruleus in rats eliminate the ability of VNS to suppress seizures. The locus coeruleus is also of particular interest because it is one of the primary locations for cell bodies of norepinephrine (NE) neurons. NE activity is altered by medications that improve depression, anxiety, and attention. The enhanced activity of the NE neurons may explain the neuropsychiatric benefits of VNS.

However, NE reuptake inhibitors such as desipramine and atomoxetine (psychiatric medications with known effects on depression, anxiety, and attention) also lower the seizure threshold. How can this be so? Why does increased NE activity through VNS increase the seizure threshold, whereas increased NE activity through medications lowers the seizure threshold? These paradoxical findings illustrate once again that we often cannot explain why our interventions work.

GAMMA-AMINOBUTYRIC ACID

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain. Anticonvulsants such as valproate, phenobarbital, and the benzodiazepines exert their antiseizure effects in part by enhancing GABA. It is also well known that many anticonvulsants have psychiatric benefits in addition to controlling seizures.

VNS appears to enhance GABA activity (Groves 2005). VNS has been shown to increase the free GABA in the cerebrospinal fluid. Additionally, responders to VNS have been shown to have increased GABA receptor density. We can conceptualize that VNS may reduce seizure activity by increasing GABA and the inhibition of the brain.

CONTINUED IMPROVEMENT WITH TIME

One of the most distinctive features of VNS (see Figure 5–6) is its enhanced efficacy with continued use over time. That is, more patients respond at 12 months than at 3 months. This suggests that

Alternative Medicine

Some speculate that the calming features of such activities as yoga and chanting are mediated through vagus stimulation. A study of experienced yoga practitioners showed that 1 hour of yoga increased brain GABA levels by 27% (Streeter et al. 2007). Only further research will reveal whether these changes are induced through the vagus nerve.

vagus stimulation gradually changes something in the brain. Just as with exercise and weight loss, the results are not immediate.

As we discussed in Chapter 4 (Electroconvulsive Therapy), VNS as well as ECT increases brain-derived neurotrophic factor (BDNF). VNS might help the brain through its gradual effects on growth factors such as BDNF, which in turn "repair" the damaged brain.

Safety/Adverse Events

The adverse events associated with VNS are best separated into those associated with the complications of the surgery and those resulting from the side effects of stimulation.

SURGICAL COMPLICATIONS

The risks associated with surgery are minimal (O'Reardon et al. 2006). As with most surgical procedures, those surgeons who are more skilled will have fewer complications. Wound infections are infrequent (less than 3%) and can be managed with antibiotics. Pain at the surgical site almost always resolves within two weeks. Rarely, left vocal cord paresis persists after surgery (<1 in 1,000), but this usually resolves slowly over the ensuing weeks.

Temporary asystole during the initial testing of the device is a rare but serious surgical complication. In approximately 1 out of 1,000 cases, asystole has been reported in the operating room during initial lead testing. It may be a result of aberrant electrical stimulation resulting from poor hemostatic control. That is, blood
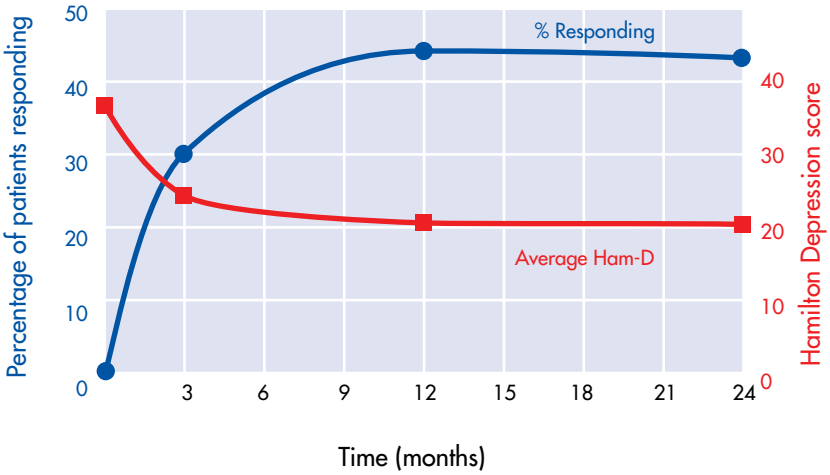
FIGURE 5–6. Long-term response to VNS.

Follow-up analysis of the original 59 VNS patients showed continued improvements up to 1 year and sustained benefits up to 2 years.

in the surgical field causes arcing of the current, and the cardiac branch becomes depolarized. Fortunately, no deaths have been reported, because normal cardiac rhythm has always been restored. Postoperatively, these patients have been able to safely receive VNS. More importantly, no cardiac events have been reported when the device is turned on for the first time after surgery.

PHYSICAL SIDE EFFECTS FROM STIMULATION

After the initial testing in the operating room, the patient is typically allowed to heal for two weeks before the stimulator is again turned on. The most common side effects are associated with stimulation, and thus will only be experienced when the device is on. Hoarseness, dyspnea, and cough are the most common side effects. They appear to correlate with stimulation intensity and can be minimized with reductions in the stimulation parameters.

Most side effects decrease with time. Hoarseness or voice alteration is the most persistent problem. Between 30% and 60% continue to experience this side effect during times of stimulation, although, for reasons that are unclear, this effect also diminishes over months to years.

Parasympathetic Response?

One would speculate that VNS might increase the impulses going down the vagus nerve to the internal organs and induce a parasympathetic response. However, this has not been an issue. Vital signs have remained stable. Cardiac slowing has not been a problem. This may be due to the placement of the leads above the branches from the vagus nerve going to the heart.

PSYCHIATRIC SIDE EFFECTS

As with any effective treatment for depression, unintended activation is a worrisome side effect. Hypomania and frank mania have been reported (1%–3%) (Rush et al. 2007). Usually, these symptoms developed in patients with a prior diagnosis of bipolar

disorder. Reducing the intensity of the stimulation or adding a mood-stabilizing agent is the best way to manage the symptoms.

Emergence of suicidal ideation is a concern with antidepressants but has not been a problem with VNS. Likewise, cognitive impairment has not been an issue, and, in fact, many patients report improved cognitive function. The lack of cognitive impairments is one advantage to using VNS in children with epilepsy. Most of the anticonvulsant medications have side effects of cognitive slowing or problems with alertness.

Critical Review of VNS in Neuropsychiatric Applications

FDA approval for stimulation therapies is obtained differently from approval for medications. With stimulation procedures, the FDA approves the specific device for use in patients with a specific disease. Thus, only one patented device has received FDA approval for vagus nerve stimulation, even though many devices could potentially deliver similar impulses. Additionally, the FDA in general does not require as many trials or as many patients studied for approval of a device as it requires for approvals of medications.

EPILEPSY

There have been two large, acute, double-blind, controlled studies of VNS in patients with treatment-resistant epilepsy (Ben-Menachem et al. 1994; Handforth et al. 1998). As described above, a low-stimulation group served as the control and was compared with a high-stimulation group. In this difficult-to-treat population, seizure frequency decreased 28%–31% in the high-stimulation group compared with baseline, whereas seizure frequency dropped only 11%–15% in the low-stimulation group.

Unfortunately, few patients were able to stop their anticonvulsant medications. However, many were able to reduce the number of medications they took per day. This indicates an advantage for VNS, because many children experience deleterious cognitive side effects from the anticonvulsants.

Long-term follow-up studies show the typical pattern for VNS. Findings reveal continued improvement for up to 1 year and then stabilization of effect. There appears to be no tolerance to VNS. The patient with the longest exposure to VNS has had the system operating for 17 years. Although initially slow to be accepted, VNS has assumed a small but significant role in epilepsy practice (George et al. 2002).

DEPRESSION

Findings on the effectiveness of VNS as a treatment for depression are less straightforward than reports with epilepsy. An initial pilot study involving 59 patients with treatment-resistant depression demonstrated good results—a 30% response rate at 10 weeks. Even more encouraging were the extended results of the pilot study. Patients continued to improve after the acute phase of the trial, and were actually doing better at 1 year than they were at 3 months (Figure 5–6). This is unusual in the treatment of depression.

The results of a pivotal multicentered, randomized, double-blind trial of VNS were not as encouraging, however. In this trial, active VNS failed to show a statistically significant difference from sham treatment. The response rates for the acute treatment of treatment-resistant depression were 15% for active treatment and 10% for sham treatment.

A parallel but nonrandomized group was also studied and compared to those patients who received VNS in the pivotal trial described above. Thus, one group received the addition of VNS and the other received "treatment as usual." They were followed for 12 months during which both groups received similar treatment (medications and ECT), except for the VNS difference. At the end point the response rates were significantly different: a 27% response rate for the VNS group and 13% for the treatment-as-usual group.

The FDA considered all these studies when evaluating VNS for depression. They were most impressed with the long-term, enduring benefits for this difficult-to-treat population. In 2005 the FDA approved VNS for patients with chronic or recurrent de-

pression, either unipolar or bipolar, who have a history of not responding in at least four antidepressant trials.

OBESITY

The vagus nerve transmits information about hunger and satiety from the gut to the brain. It is possible that stimulating the vagus nerve could fool the brain into thinking the body is full—raising the exciting prospect of a potential treatment for epidemic obesity. Early studies with dogs demonstrated significant changes in eating behavior, as well as weight loss, with vagus stimulation subdiaphragmatically (Roslin and Kurian 2001). A small trial in humans failed to find a large effect.

For humans, a device has been developed called *implantable gastric stimulation* (IGS), which delivers electrical impulses directly to the gastric mucosa near where the vagus fibers exit. Unlike VNS in the neck, this device delivers the impulse downstream, right at the organ. Presumably as a consequence, the signal traveling up the vagus nerve is more specific to the gut and food intake. A large randomized controlled trial was undertaken with 103 morbidly obese individuals (Shikora 2004). Every subject had a device implanted, but only half received active stimulation. Unfortunately, after 7 months there was no difference in weight loss between the groups.

ANXIETY

William James argued that all anxiety resides not in the brain, but rather in the periphery (James 1884). The James-Lang theory of emotion posited that we are anxious when we see a charging bull not because of our cognitions about a bull, but rather because our heart races and our lungs need air. Although this debate about the origins of anxiety and emotion is still not settled, most believe that anxiety results both from central sources *and* peripheral sensations, all of which are carried through the vagus nerve. Theoretically, VNS could be a powerful anxiolytic. However, there have not been any controlled trials and only one open clinical trial in which VNS has been investigated as a treatment for anxiety (George et al. 2008).

Pain

The vagus nerve carries pain fibers from the gut and then innervates regions involved in pain perception, such as the insula. It is thus natural to ask whether VNS can affect pain perception. Jeff Borckardt took VNS-implanted patients and hooked them up to devices that could measure their pain thresholds. Different VNS parameters cause an acute improvement in pain thresholds. There are also case series where VNS has helped with chronic pain. This is an interesting area for future work (Borckardt et al. 2005).

Summary of Clinical Use

VNS is a safe and effective treatment for epilepsy. It appears to work in all forms of epilepsy. It is especially useful in pediatric epilepsy because the device does not have cognitive side effects.

Two positive results have been reported in open studies on depression, although findings from the prospective double-blind acute-phase study were not statistically significant. Uncontrolled long-term studies suggest that the device may help patients with treatment-resistant depression. Reasoning from the known anatomy of the vagus, researchers are hopeful that VNS may ultimately have clinical utility for the treatment of other behaviors such as obesity, pain, and anxiety.

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CHAPTER 6

Transcranial Magnetic Stimulation

Introduction and History

Transcranial magnetic stimulation (TMS) involves inducing an electrical current within the brain using pulsating magnetic fields that are generated outside the brain near the scalp. It is important to understand that TMS is not simply applying a static or constant magnetic field to the brain. The man shown in Figure 6–1 is holding a magnet against his head. This may or may not have any effect on his brain, but it is certainly *not* TMS. To understand TMS we must review some basic electromagnetic principles.

In Chapter 2, Basic Electricity, we stated that by 1820 scientists had discovered that passing an electric current through a wire induces a magnetic field. This has become a common grade-school
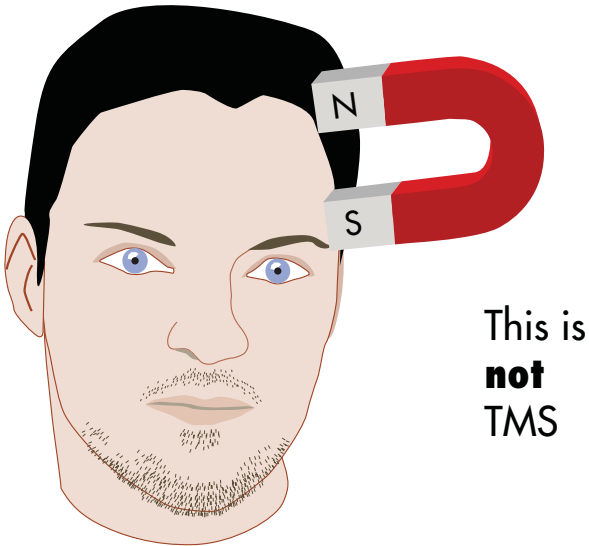
FIGURE 6–1.   Man holding a magnet to his head.

The constant magnetic force does not produce any electrical pulse. Our current knowledge suggests that the effects of a constant magnetic field on the brain are minimal, if there are any at all.

science experiment. Students will wrap a wire around a nail and attach each end to a battery, turning that nail into an electromagnet (see Figure 2–2). In 1832 Michael Faraday showed that the inverse is also true.

Faraday showed that passing a magnet through a coil generates an electrical current. Figure 6–2 shows an example of this process. It is important to understand that the current is only generated while the magnet is passing through the coil. It is the changing magnetic field that generates the electricity. A static magnet resting inside the coil will not generate a current.

The electromagnet offers an alternative way to create a changing magnetic field and thus induce an electrical pulse. In this situation the electricity is used to turn the magnet on and off (Figure 6–3). This produces a pulsating magnetic field. It is this changing field that can induce an electrical current. And, as we have discussed in previous chapters, focally applied electricity can have powerful effects on the brain. For most TMS applications, it is likely to be the electricity induced from the pulsating magnet, not the magnetic field itself, that produces the profound and sometimes therapeutic effects on the brain.

The first known examples of anything close to modern TMS occurred in the years 1910 and 1911 (George and Belmaker 2007). At that time, several researchers used large electromagnets the size of suitcases (or even trunks) to induce phosphenes: the sensation of seeing light without actual light passing into the eye. It is unclear from that work whether the magnets stimulated the retina or the occipital cortex. These early experiments were fascinating, but of little practical value. After that, interest in the field waned for many decades.

In 1959 Kolin and his colleagues demonstrated that a fluctuating magnetic field could stimulate a peripheral frog muscle (Kolin et al. 1959). However, it was not until 1985 that the modern era of TMS started. That year, Anthony Baker in Sheffield, England, described the use of a noninvasive magnetic device resembling modern TMS instruments (Barker et al. 1985). The device was slow to recharge and quick to overheat, but it was a start.
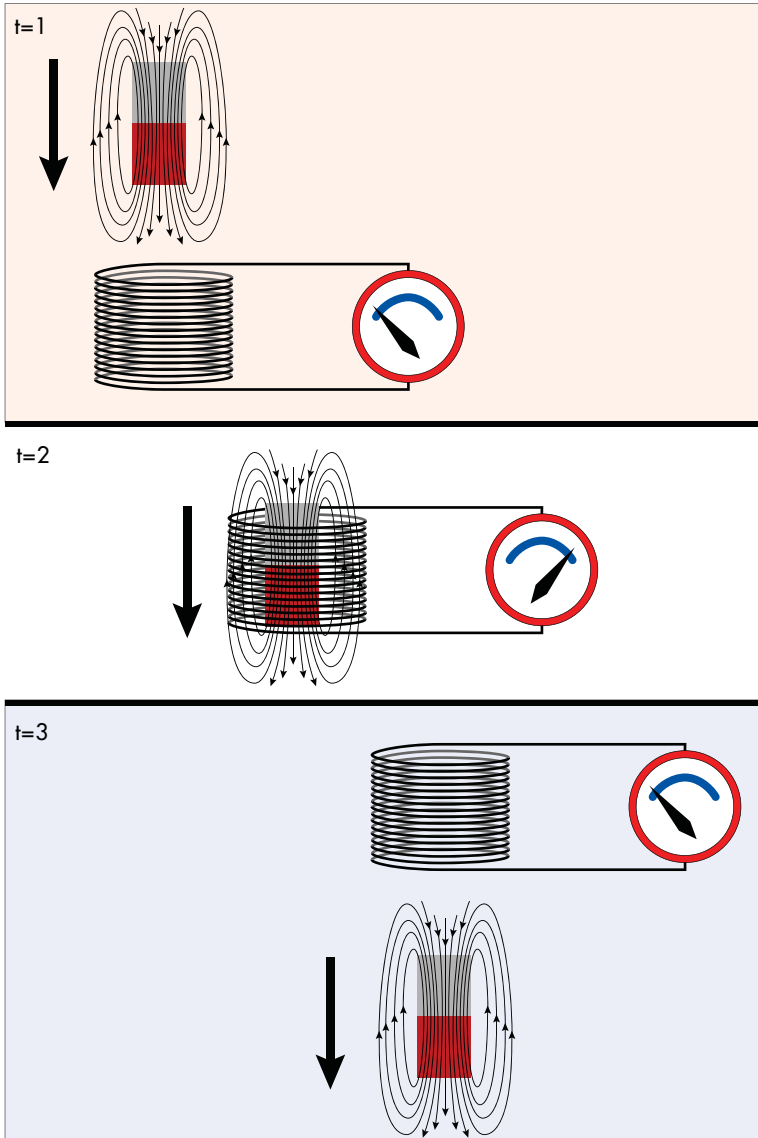
FIGURE 6–2.   Faraday's Law.

Passing a magnet through a coil generates an electrical current. This law of electromagnetism describes the basis on which all hydroelectric power plants are run (water turns a magnet in a coil, producing electricity). It is also the basis of TMS.

In the illustration, t=time.
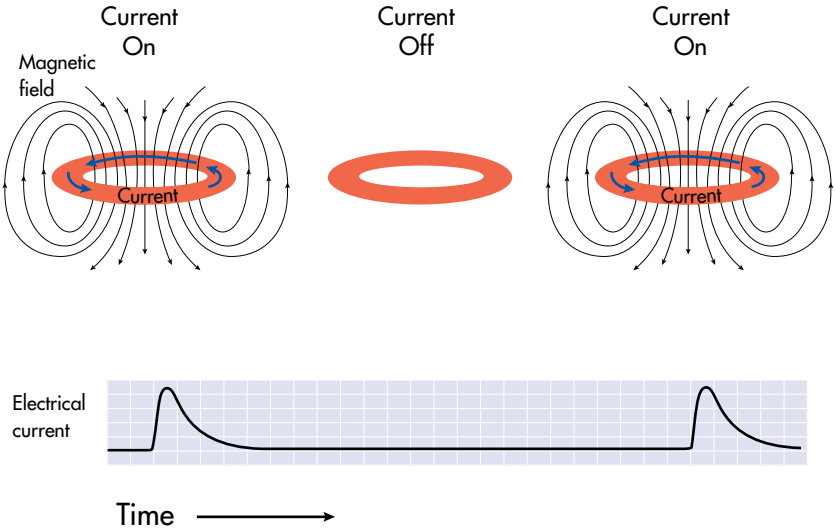
FIGURE 6–3. Electromagnetic induction.

An electrical current induces a magnetic field in the coil. Turning the magnetic field on and off induces an electrical change in the area around the coil.

Animal Magnetism

There is a long history of dubious claims about the healing power of magnets (Shermer 2002). One of the earliest and most famous claims came from the German physician Franz Anton Mesmer, who in 1775 introduced the term "animal magnetism." Mesmer believed that humans possess an invisible magnetic field whose properties were altered in the physically ill. For a time, he aroused considerable interest in his magnetic cures—passing magnets over the bodies of patients to alter their magnetic fields. The remarkable Benjamin Franklin, commissioned by the king of France, helped debunk Mesmer's claims.

More recently, there has been a resurgence of interest in magnets. An Internet search reveals numerous companies offering magnetic shoe insoles, belts, mattress pads, and the like that are purported to relieve pain and suffering. A review of the available scientific literature on studies of static magnets reveals little evidence to support the benefits of this treatment (Ratterman et al. 2002).

The first attempts to use repetitive TMS (rTMS) as treatment were with depressed patients. In the early 1990s, one of the authors (M.S.G.), working in Robert Post's lab at the National Institute of Mental Health, wrote the first paper on this topic and described in detail the outcome for one patient with treatment-resistant depression who received daily prefrontal rTMS. Figure 6–4 shows her Hamilton Rating Scale for Depression score over the course of three TMS treatment phases (George et al. 1995).

This case report is particularly interesting because the authors, with all due respect, did not necessarily know what they were doing. Like Cerletti with ECT, they were making educated guesses about the best way to administer a new treatment. Research suggested that left prefrontal cortex dysfunction plays a significant role in depression, so they placed the coil over the left prefrontal cortex.
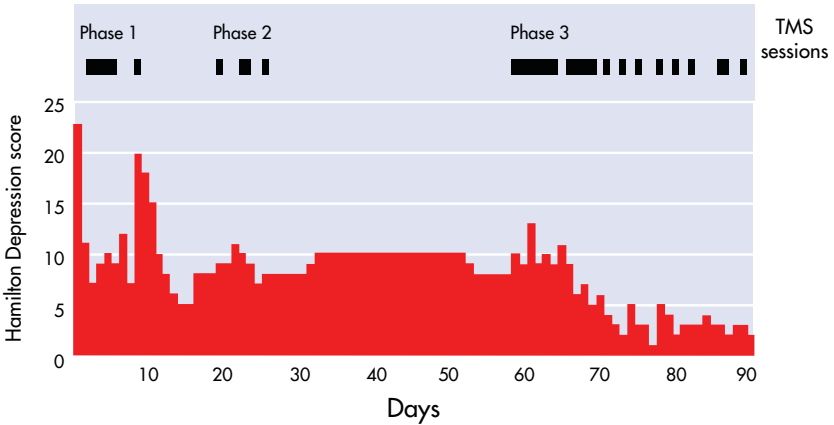
FIGURE 6–4. Early TMS experience.

Case study showing one woman's response to repeated daily prefrontal TMS in the early days of its use.

Source. Adapted from George et al. 1995.

How many sessions of TMS are needed to treat depression? Figure 6–4 shows that the researchers underestimated the number of sessions needed in the first two treatment phases for this patient. It was not until after the extended third treatment course that the patient achieved remission. The example offered in this study shows once again that the parameters of a new treatment are often only uncovered through trial and error, especially if there are no easy surrogate biomarkers to determine dose.

Does TMS Really Change Brain Activity?

One of the most troubling questions for many skeptical scientists and clinicians regarding TMS is, can an electromagnet really affect the brain? Four quick points establish that TMS clearly is having profound and easily observable effects on the brain.

1. Transcranial magnetic stimulation of the motor cortex will induce corresponding muscle contractions in the appropriate arm or leg.

2. Seizures are a real but rare side effect of TMS.

3. Placing an active coil over the occipital cortex will induce visual sensations.

4. Repetitive TMS over Broca's area will induce temporary aphasia.

How Is It Done?

TMS requires an elaborate machine to produce its effect. The devices are first regulated by the U.S. Food and Drug Administration (FDA) for general safety. Most machines have FDA approval for sale in the United States. They are then also regulated with respect to the right of the manufacturer to advertise the use of the device for a particular disorder. In the United States, a device manufactured by Neuronetics is being reviewed by the FDA for potential approval of this device to treat depression (O'Reardon et al. 2007).

The common unit of magnetic field is the tesla, denoted "T," equal to $N/(A \cdot m)$ (Force/Current-Distance); one T is about 20,000 times the earth's magnetic field. Technically, TMS devices produce a fairly powerful magnetic field, but only very briefly. Table 6–1 shows examples of common magnetic forces for comparison.

Early TMS devices emitted only a single, brief pulse. Modern devices can generate a rapid succession of pulses called repetitive TMS, or rTMS. These devices are used for behavioral treatments and can discharge on and off for several minutes. For example,

TABLE 6–1. Examples of common magnetic force in tesla

Example	Force in tesla
Earth's magnetic field	0.00005
Refrigerator magnet	0.1
12 V battery nail electromagnet	0.5
MRI	3.0
TMS	1.5–3.0
World's strongest magnet (Florida State University)	45.0

the typical treatment for depression is a 20–40 minute session, 5 days a week for 4–6 weeks. To keep the patient still and the device correctly placed, the patient reclines in a chair and the device is held securely against the head (Figure 6–5).

The TMS coil (encased in plastic housing in Figure 6–5, C) generates a magnetic-field impulse that can reach only the outer layers of the cortex. Some devices are single coils; others are two coils, side by side (also called a *figure eight*). The impulse may penetrate only 2–3 centimeters below the device. Deeper focused, noninvasive penetration is the Holy Grail of TMS research.

DEEP PENETRATION

A TMS device that could generate impulses that reach deeper regions of the brain might enable clinicians to treat conditions such as Parkinson's disease. Additionally, a deep impulse could reach the nucleus accumbens—the pleasure centers of the brain. Such a device would be popular at college parties. The FDA might then have to step in and regulate this as a "controlled device" analogous to a controlled substance! Thankfully, none of the stimulation devices produced to date generates pleasurable sensations, so none are subject to abuse.
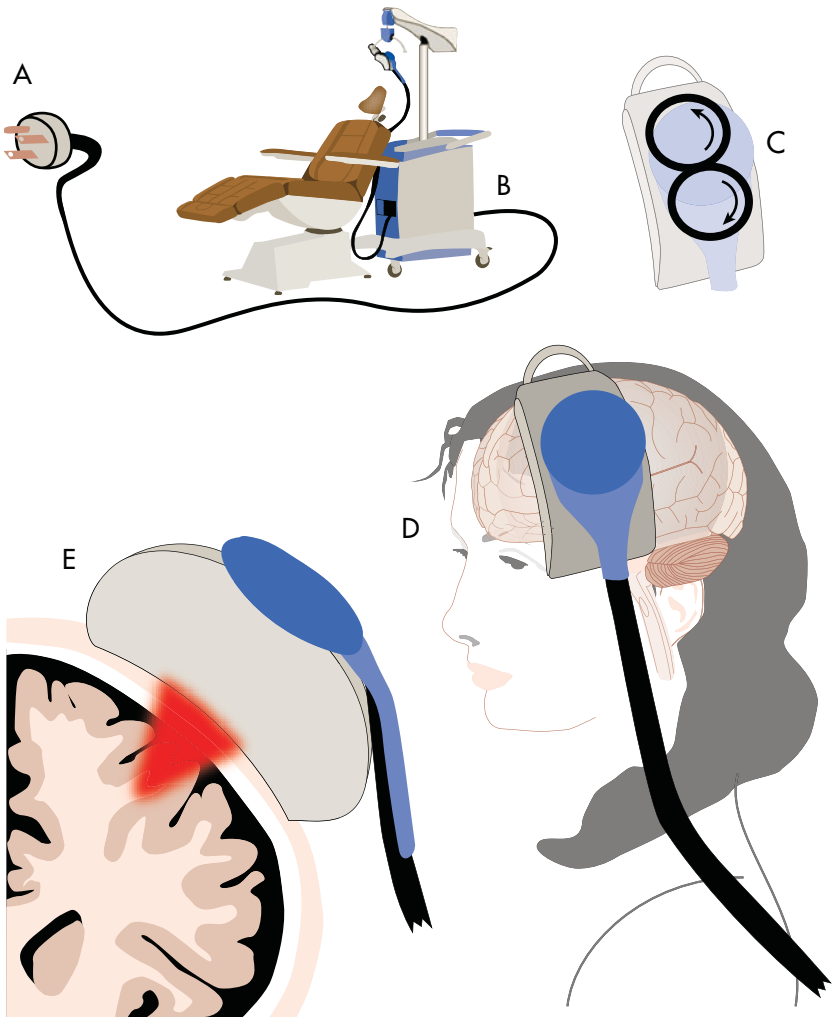
FIGURE 6–5.   The TMS apparatus and how it is commonly used to treat depression.

Alternating current from the wall (A) is used to charge a bank of large capacitors (B). A pulsating electrical current generated in coils inside the device produces a pulsating magnetic charge. The patient reclines in the chair and the TMS coil is placed over his or her left prefrontal cortex (D). The electrical charge is rapidly discharged through the magnetic coil and induces a magnetic field that travels through the skin and skull. This fluctuating magnetic field, in turn, induces an electrical current in brain areas just below the skull, depicted in (E).

MOTOR THRESHOLD

When the TMS device produces a pulse over the motor cortex, a volley of electrochemical activity descends through the brain. The stimulus travels through the brain, into the spinal cord, and out the peripheral nerve, where it can ultimately cause a muscle to twitch. The minimum amount of energy needed to produce contraction of the thumb (abductor pollicis brevis) is called the motor threshold (MT). This is used as a measure of general cortical excitability (see Physiology section later in this chapter).

A percentage of the MT serves as a safe and effective setting for dosing rapid TMS (e.g., 120% of MT). Although this convention has helped make TMS safer, it is severely insufficient in that the measurement is referenced only to each machine, and thus is not a universal number. Future work will focus on establishing more universal, constant measures of the magnetic field delivered.

FREQUENCY

Usually with TMS, a stronger, more intense pulse results in more activation of the central nervous system tissue and a wider area of activation. The circumstance with frequency is a bit different. In general, frequencies of less than 1 per second (<1 Hz) are actually inhibitory (Hoffman and Cavus 2002). This may be because low-frequency TMS more selectively stimulates the inhibitory γ-aminobutyric acid (GABA) neurons.

The ability to focally inhibit some regions of the brain could be of great therapeutic benefit. Some disorders such as epilepsy, panic disorder, and hallucinations are likely to result from uncontrolled neural hyperactivation. Having an instrument to "cool off" these neurons could be of potential value for patients with such conditions (see Schizophrenia section later in this chapter).

HOME TMS

A handheld device is being developed (by Neuralieve, Inc.) and studied as a treatment to interrupt migraine headaches. The device delivers a single large pulse. When the patient experiences

the aura phase of an impending headache, he or she holds the device to the back of the head and directs the pulse toward the occipital cortex. The pulse attempts to extinguish the migraine when it is still mild, before it gets out of control. The beauty of the device, if it works, is that a patient can carry it around and use it when he or she senses a headache brewing.

What Does TMS Do to the Brain?

The TMS device interacts with and generally activates the cortex immediately underneath the site of administration. This effect has been shown repeatedly in functional imaging studies. Although the direct stimulation of deep brain regions does not occur with TMS, secondary activation of deeper structures is a feature of the procedure. Figure 6–6 shows the cortical activation of the left prefrontal cortex, directly below the TMS coil, and the indirect subcortical activation of the thalamus (Li et al. 2004).

The effects of TMS pulses on the neuron are inadequately understood. It is believed that the electrical impulse generates an action potential in the neurons that it can reach. The action potential runs down the neuron and can excite other neurons. The net result is that numerous brain structures are affected. The problem is that within any section of cortex, there are local inhibitory neurons as well as excitatory neurons that send signals elsewhere. It is unclear exactly how best to deliver TMS to selectively activate different neuronal elements.

For example, when treating depression, TMS most likely activates the prefrontal cortex, which initiates a cascade of signals to other regions of the brain. These signals increase or decrease activity in regions of the brain that are connected to the networks of the prefrontal cortex. Just as a TMS pulse to the motor cortex will trigger a distant twitch in the corresponding muscle, so will a pulse to the prefrontal cortex induce downstream limbic effects. Some of these effects appear to modulate the neural systems that alleviate depression and pain.

Cortical: Left prefrontal cortex   Subcortical: Thalamus
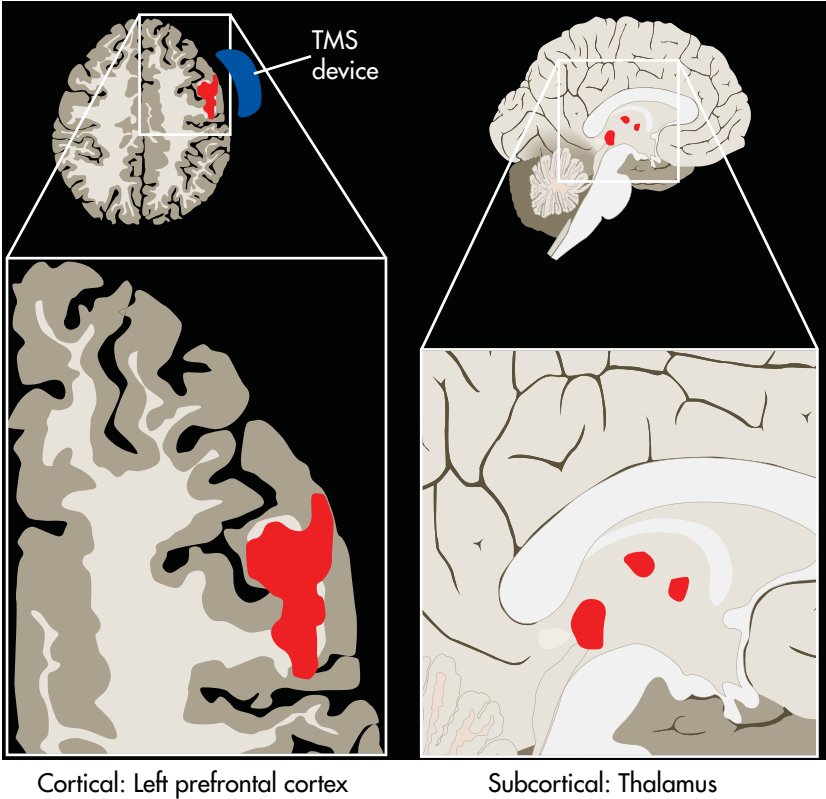
FIGURE 6–6. Effects of TMS on the brain.

TMS device placed over left prefrontal cortex activates gray matter directly underneath coil, as well as deeper subcortical structures that are beyond the direct reach of the TMS signal.

Source. Adapted from Li et al. 2004.

At a molecular level, TMS is known to have effects similar to those seen with ECT:

- Increased monoamine turnover
- Increased brain-derived neurotrophic factor
- Normalization of the hypothalamic-pituitary-adrenal axis

Presumably, TMS exerts its effects on the brain through the activation of networks, which, in turn, changes the molecular environment of the central nervous system.

Safety/Adverse Events

TMS is generally regarded as safe and without enduring side effects. There have been no reported lasting neurologic, cognitive, or cardiovascular sequelae as a result of its use. However, TMS can alter brain function (such as improving mood), so we must remain vigilant about the possible development of long-term problems.

SEIZURES

The inadvertent induction of a seizure is the primary safety concern regarding TMS treatment. George and Belmaker (2007) summarized eight cases of seizures induced with TMS. They estimate these eight cases occurred in a sample size of several thousand. This puts the risk at less than one-half of one percent. Most of these patients were healthy volunteers without a history of epilepsy. Fortunately, there are no reports that the individuals affected experienced recurrence. Also, all of the seizures occurred during TMS administration when the patient was sitting down and near an investigator. Finally, all of the seizures were self-limited, and the subjects did not require medications or other interventions.

In the reported cases, the majority of patients were receiving TMS to the motor cortex—the most epileptogenic region of the cortex. Additionally, most (but not all) were receiving trains of stimulation outside of suggested limits. These cases indicate that TMS-induced seizures will remain a small but significant adverse

event, even in patients without histories of seizures, and even when TMS is used within suggested guidelines.

HEARING LOSS

One patient reported a temporary hearing loss after TMS, and some animal studies have found hearing changes after TMS. In light of this, an extensive study of auditory threshold was conducted before and after 4 weeks of TMS in more than 300 patients who wore earplugs. No changes were found. However, patients should wear earplugs when receiving TMS.

HEADACHE

Headaches are the most common complaint cited by patients following treatment with TMS. George and Belmaker (2007) found that 19% of healthy subjects in one study reported headaches after receiving TMS. However, 17% of those receiving sham TMS also said they experienced headaches after the session. These are generally self-limiting and respond to simple analgesics like aspirin.

Cognitive Impairment

Repeated analysis of neurocognitive functioning of TMS patients has not revealed any enduring negative effects from the procedure. After a session, patients are able to drive home and return to work.

Critical Review of TMS in Neuropsychiatric Applications

TMS has been tested as a treatment in numerous conditions (Ridding and Rothwell 2007). Presumably, TMS has the potential to not only change the immediate electrical activity in the cortex nearest the device but also to induce alterations in brain neural structures that will endure beyond the sessions. This issue is addressed in the review of the conditions discussed below.

DEPRESSION

Depression has been the condition most widely studied in relation to TMS treatment. Figure 6–4 shows one of the early case studies. Not highlighted are the dramatic changes the procedure produced in the patient's positron emission tomography (PET) scan at the end of the study. Not only did the patient feel better, but there was convincing objective evidence to indicate that her brain was more active. This kind of result stimulated numerous controlled studies. In turn, the controlled studies have generated several iterations of meta-analysis of the procedure (Ridding and Rothwell 2007).

A meta-analysis of rTMS for depression examined 25 published sham-controlled studies (Mitchell and Loo 2006). The investigators concluded that left prefrontal TMS provided statistical superiority over sham treatment for patients with depression. However, they went on to say,

> The clinical benefits are marginal in the majority of reports. There is also still considerable uncertainty concerning the optimal stimulation parameters. Those clinical features which appear to be associated with greater response include younger age, lack of refractoriness to antidepressants, and no psychotic features.

The authors recognized that TMS provided benefits for depressed patients, but they were left wondering about the widespread clinical utility of the procedure.

FDA Application. The application from Neuronetics, Inc., to the FDA for approval to use their TMS device for depression gives an updated and more comprehensive perspective (O'Reardon et al. 2007).

Before conducting the experiment, the researchers at the company chose the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary outcome measure. The FDA requires a predetermined primary outcome measure to determine the effectiveness of a medication or device. Unfortunately, at 6 weeks the MADRS scores for the active treatment group were not quite statistically different from the control group: $P=0.058$. The Hamilton Rating Scale for Depression scores, considered secondary outcome measures, proved superior for those in the active treatment group.

These frustrating mixed results actually reflect an accurate picture of the current status of the suitability of utilizing TMS for depression. It is clearly effective to some degree. It appears to be safe and well tolerated. Undoubtedly, it will be an ideal treatment for some patients. Yet the efficacy data in trials to date are not as robust as we would like.

SCHIZOPHRENIA

Auditory hallucinations are one of the positive symptoms of schizophrenia. These types of hallucinations are believed to result from aberrant activation of the language perception area at the junction of the left-temporal and parietal cortices (Higgins and George 2007). Low-frequency TMS could potentially inhibit this area in patients with schizophrenia and provide relief from auditory hallucinations.

In a meta-analysis, investigators examined the efficacy of low-frequency TMS as a treatment for resistant auditory hallucinations in schizophrenia (Aleman et al. 2007). The authors found 10 sham-controlled studies incorporating 212 patients. Their review concluded that TMS was effective in reducing auditory hallucinations. Unfortunately, TMS had no effect on other positive symptoms or the cognitive deficits of schizophrenia. Larger studies are needed to definitely establish the efficacy, tolerability, and utility of TMS for schizophrenia.

There have been four randomized controlled trials that focused on the use of intermittent daily prefrontal TMS to treat negative symptoms (blunted affect, poor social interaction) in patients with schizophrenia. The results of only one of these studies showed positive findings.

TINNITUS

Tinnitus is a common, often disabling, and distressing disorder for which there is no adequate treatment. A proportion as high as 8% of adults over age 50 years experience tinnitus. Recent functional imaging studies have identified increased activity in the auditory cortex of patients with tinnitus.

Low-frequency TMS offers a possible mechanism that can help "cool off" the overactive auditory cortex that may be producing tinnitus. In several small controlled trials, one research group in Germany has produced impressive results. Larger, multicenter studies are needed to see if these positive effects can be replicated.

PAIN

Numerous small controlled studies have evaluated the utility of TMS in patients with pain (George and Belmaker 2007). Multiple brain sites have been tested, including the prefrontal cortex, motor cortex, and parietal cortex. In general, TMS provides effective pain relief in these different locations in diverse pain conditions. Unfortunately, the effect of TMS on pain lasts for only a short time. Consequently, the utility of TMS as a practical treatment for chronic pain conditions has yet to be established.

Reports from recent studies suggest TMS may be somewhat useful in managing acute pain. In a clever study of patients recovering from gastric bypass surgery, 20 minutes of real or sham TMS was administered to the prefrontal cortex of every patient (Borckardt et al. 2006). The use of self-administered morphine was then followed over the next 48 hours. Those receiving real TMS used 40% less of the medication (Figure 6–7).

Headache. The handheld device, mentioned previously in the Home TMS section, is being studied as a treatment for migraine headaches. Preliminary results have been encouraging. Larger studies are under way.

STROKE

Following an ischemic event to the motor cortex, the brain attempts to reorganize the damaged networks. Indeed, the extent of reorganization correlates with the clinical recovery of motor function. TMS may accelerate the reorganization process and therefore enhance recovery.
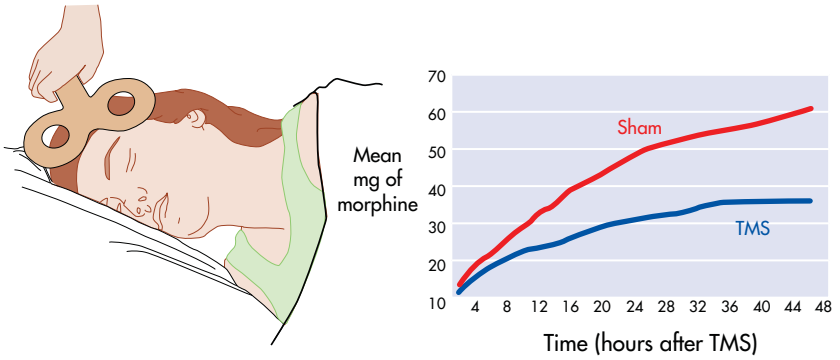
FIGURE 6–7.　TMS for pain relief.

TMS delivered immediately postoperatively for 20 minutes reduced the use of morphine by 40%.

Source.　Adapted from Higgins and George 2007.

Different types of TMS may be beneficial in stroke recovery. High-frequency TMS to the affected area may enhance reorganization. Alternatively, low-frequency TMS to the opposite, intact hemisphere is believed to reduce the interference from the non-stroke side. Some believe that too much input from the unaffected side of the brain impedes recovery. Reducing excitability with low-frequency TMS may enhance recovery.

Ridding and Rothwell (2007) have reviewed the studies of TMS in stroke recovery. Although the total number of patients in controlled trials was only 87, the results were encouraging. Clearly, larger studies are needed, but it appears that TMS might be able to improve the natural healing process after a stroke.

EPILEPSY

Theoretically, low-frequency TMS could be used to treat cortical epilepsy. Early studies showed that TMS could reduce EEG epileptiform abnormalities. Initial case studies yielded positive results. A controlled study of daily TMS by Theodore et al. (2002) over the cortical site of seizures for one week revealed a statistically significant reduction in seizures. However, the authors concluded that the data indicating TMS treatment benefits were not clinically significant.

More recently, in another controlled trial, Cantello et al. (2007) concluded that "active" rTMS was no better than placebo for seizure reduction. Thus, the idea of using inhibitory doses of TMS to calm cortical targets is intriguing, but the controlled trials to date have not been as successful.

RESEARCH USES

TMS has great potential for basic science research, not just in treatment applications. Because of its noninvasiveness and relatively favorable safety profile, TMS is used to help us understand the functional mechanisms of the brain. Because of their invasiveness and safety concerns, the other brain stimulation techniques would never be used as a primary research tool. Although a full review is beyond the scope of this book, we can outline these broad areas here.

Physiology. Delivered over the motor system, TMS can provide a range of relevant information about how excitable a section of brain is. So far, we can study this outcome only over the motor cortex, where we measure the peripheral effects of stimulation by examining the responses in muscles (local and distributed motor cortex physiology). Stimulation of the motor cortex can make the thumb move; the amount of muscle contraction is measured (as the "motor evoked potential") by connecting the thumb to an oscilloscope. Using the motor evoked potential, one can determine the motor threshold, cortical silent period, and cortical excitability by using paired-pulse TMS.

The cortical silent period is the amount of time it takes a muscle to return to its resting state after it has been made to discharge with TMS. In paired-pulse TMS, researchers apply two pulses through the same coil in quick succession. By varying the time between pulses, or the relative strength of the first pulse compared with the second, one can minimize or enhance the second motor evoked potential. These approaches can be used to understand the cortical effects of central nervous system–active medications (for review, see Ziemann 2003) and how different behaviors change cortical excitability. They can also be used to investigate different disease states.

Interruption–Speech Arrest. An entirely separate area of research involves using TMS to produce interruption of a behavior. This can be seen while using TMS over the motor cortex for the hand. While the TMS coil is discharging, it is difficult if not impossible to use the same hand for anything else. The intermittent TMS firing causes the hand to operate in a clumsy and uncoordinated way.

A similar phenomenon occurs when you place a TMS coil over Broca's area (involved in speech production). If subjects are asked to speak, the moment the active TMS coil is over the correct area they suffer an immediate (and, thankfully, temporary) speech aphasia. Although they can voice some syllables, they are not able to speak in proper words. In their internal voice, they are talking perfectly. This speech arrest is a dramatic demonstration of the power of TMS to influence circuits. It has been suggested that all clinicians treating stroke patients should participate in such an experiment so they can appreciate the frustration of being aphasic.

Influencing or Biasing. Cognitive neuroscientists are using TMS to tease out the mechanisms of some behaviors. For example, one group has shown that single pulses of TMS at the right time at specific locations can alter how a person responds to a choice between two objects. With a pulse, the subject chooses A; without a pulse, he or she chooses B. Some have gone so far as to call this "mind control." Nevertheless, such research helps cognitive neuroscientists understand the regional activity involved in specific behaviors.

Summary of Clinical Use

TMS offers a noninvasive, safe mechanism to influence brain activity. There are more than 30 randomized controlled trials of daily left-prefrontal rTMS to treat depression. Current controversy is focused on whether its antidepressant effect is clinically significant. Much work is needed to better understand and refine use parameters. The findings in some randomized controlled trials also suggest its potential use for hallucinations in schizophrenia, and as a treatment for epilepsy, pain, headache, and tinnitus. Future work will involve establishing better parameters (intensity, duration, and location) to enhance the effectiveness and utility of TMS.

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Deep Brain Stimulation and Cortical Stimulation

Introduction and History

Ablative neurosurgery for movement and psychiatric disorders was relatively common in the 1950s and 1960s (Wichmann and DeLong 2006). The development of stereotactic techniques provided greater accuracy and more consistent results in some disorders for which there was little other treatment available. Results were generally positive, although the overuse of frontal lobotomies and other neurosurgical approaches greatly inhibited growth and research in this field.

The goal of neurosurgery for movement disorders was to remove the overactive region of the brain. For example, removing part of the ventral intermediate nucleus of the thalamus (Vim) was found to improve Parkinson's disease (PD). For psychosurgery the objective was the disruption of the offending networks. The frontal lobotomy was believed to isolate the inappropriate signals from the frontal cortex.

The development of levodopa dramatically reduced the need for neurosurgical treatments for movement disorders. Likewise, the antipsychotic medications offered new hope for psychiatric patients. In addition, the cavalier implementation of frontal lobotomy for the seriously mentally ill turned public acceptance away from neurosurgery for psychiatric conditions. It was many years before invasive neurosurgical treatments regained partial favor for these sorts of disorders, and the number of ablative neurosurgeries done for psychiatric patients remains fewer than 1,000 per year worldwide (Spangler et al. 1996).

The recent resurgence of interest in direct manipulation of the brain as a viable treatment for movement and psychiatric disorders is the result of two developments. First, pharmacologic treatments were found to be imperfect and often complicated by side effects. Second, the development of small, battery-operated, programmable stimulation devices allowed treatment without destroying tissue.

The first implantable cardiac pacemaker was installed in 1958 in Sweden (Nicholls 2007). Although originally designed to simply increase the pace of a bradycardic heart, it has evolved into a device that can sense inappropriate rhythms and respond accordingly. In 1980, the first cardioverter defibrillator was implanted. Such devices detect tachycardias and shock the heart back into a normal rhythm. Many of these are silent, except when they detect an abnormal electrocardiogram (ECG) pattern. This concept is called *responsive stimulation.*

In the mid-1980s, Benabid and his colleagues in France were using brain stimulation to map the best location to remove the Vim for PD and essential tremors. Like Penfield before them (see Chapter 1, Introduction), they used brain stimulation to locate the most appropriate section to remove. They noted that acute

stimulation of the ventral intermediate nucleus at frequencies above 60 Hz suppressed the tremors (Benabid et al. 1993). Furthermore, the effects were lost when the stimulation was stopped. In 1987, they began pilot studies of chronic stimulation for patients who had already been thalamotomized on one side. Having obtained positive results, they began bilateral stimulation, and this approach is now approved by the U.S. Food and Drug Administration (FDA).

The FDA also approved deep brain stimulation (DBS) in 1997 as a treatment for essential tremor. The FDA has since expanded the approval to include DBS as a treatment for PD and dystonia. (The indication for dystonia is only a "compassionate use" indication.) DBS allows reversible neurosurgical interventions with fewer neurologic complications than ablative resection. Theoretically, if the stimulation does not work, you can simply withdraw the thin wire and things are largely unchanged; obviously, you cannot undo resective surgery.

How Is It Done?

DEEP BRAIN STIMULATION

DBS devices are made up of three components: the impulse generator, the extension, and the electrode (Figure 7–1). The impulse generator is a battery-operated device placed subcutaneously, usually below the clavicle (although some generators are small enough to rest in a cavity in the skull). As with the vagus nerve stimulation (VNS) device, a clinician can externally calibrate the generator to optimize the benefits and minimize the side effects. The extension transmits the electrical signal from the impulse generator to the electrodes. The probes are usually placed bilaterally in subcortical regions of the brain where they emit the electrical stimulation.

Typically, but not always, the neurosurgery to implant the device is performed under a combination of general and local anesthesia. The reason for local rather than generalized anesthesia is to allow the patient to participate in the proper placement of the electrode. For example, with essential tremor, the neurosurgeon
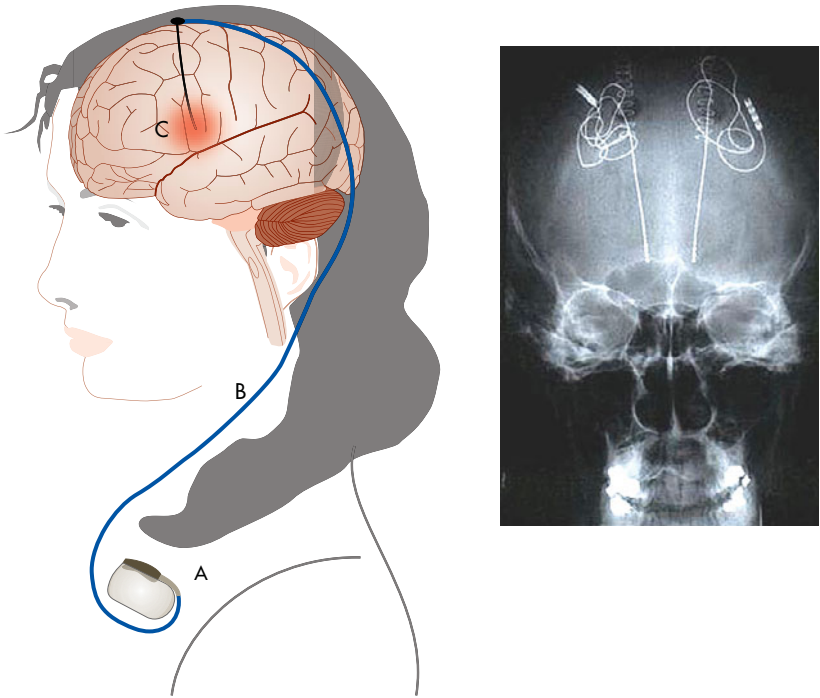
FIGURE 7–1.   Deep brain stimulation.

The impulse generator (A), the extension (B), and the electrode implanted into subcortical regions of the brain (C).

Source.   X-ray image on right provided by Helen Mayberg. Used with permission.
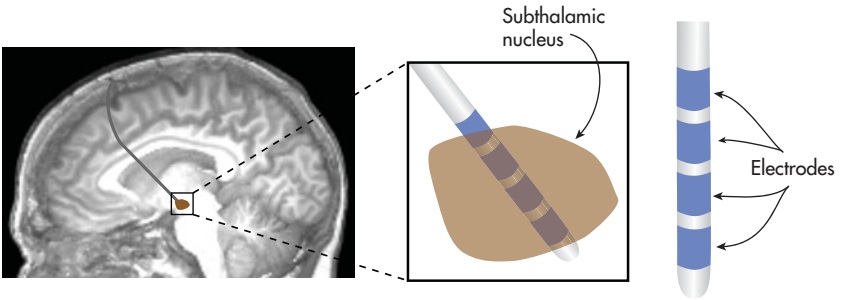
FIGURE 7–2. DBS electrode placed in the subthalamic nucleus to treat Parkinson's disease.

The lead of the probe has polyurethane insulation spaced around the four potential active electrode sites.

wants to find the location that maximally quiets the tremors. However, with dystonia, for which DBS can take months to show benefits, the placement is done under general anesthesia. The electrode is simply placed in the best possible anatomic location.

The active portion of the probe actually contains four electrodes that can emit electrical signals. Figure 7–2 shows an example of a probe placed in the subthalamic nucleus as treatment for PD. The four sites on the lead of the probe can be controlled to optimize the effect on the target site.

By adjusting which electrodes emit a signal, clinicians can mold the DBS effect. Figure 7–3 shows how activation of different electrodes in the probe changes the electrical signal, which in turn changes the parts of the brain stimulated, and ultimately determines the effect of DBS on the patient.

There are many other variables that can be adjusted in DBS, not just which electrode emits a current. Voltage, pulse width, and frequency are three other variables that can be adjusted in DBS. For example, a possible setting could be 3.5 volts, pulse width of 0.1 millisecond, and a frequency of 130 Hz. Changing these variables can alter the effects of the stimulation.

RESPONSIVE NEURAL STIMULATION

Numerous alternative ways to directly stimulate the brain are continuously being explored. One can barely keep up with the new reports. Two techniques have risen to the top and are currently being studied. One is called *responsive neural stimulation (RNS)*. This entails the addition of a microprocessor designed to sense the brain's electrical signals (through electroencephalography (EEG) or, more accurately, electrocorticography) and deliver pulses when abnormal activity is detected (Figure 7–4). A large, multisite clinical trial is under way to evaluate the effectiveness of RNS as a treatment for epilepsy; the study is designed to address FDA approval requirements.

CORTICAL BRAIN STIMULATION

Another promising technique is cortical brain stimulation (CBS). (This could almost be called "superficial" brain stimulation, in
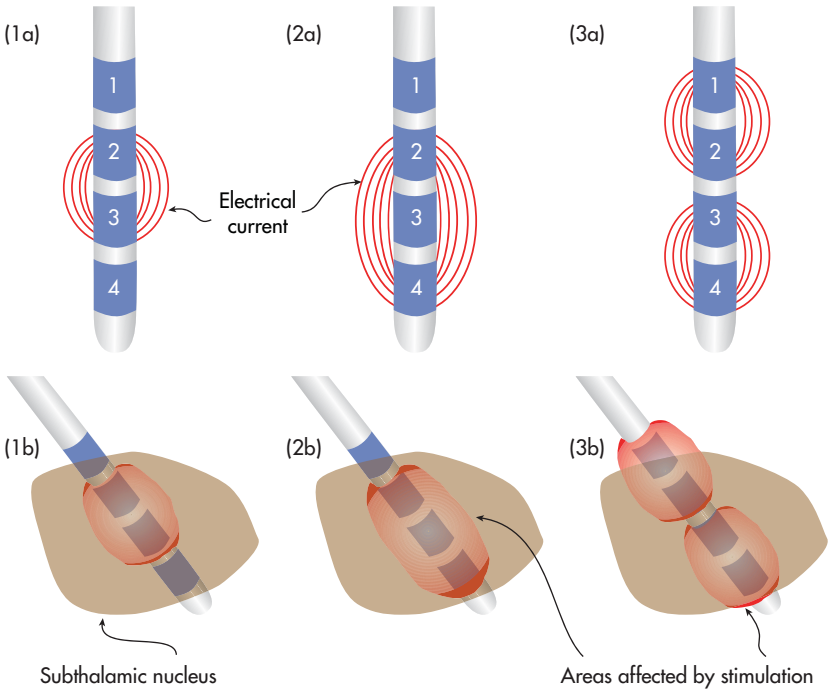
FIGURE 7–3. Electrical current production in DBS.

Electrical current can be produced from any two of the four electrodes. (1a) shows the current between electrodes 2 and 3. (1b) shows how much of the nucleus is stimulated with these settings. (2a) and (2b) are between electrodes 2 and 3. (3a) and (3b) are between electrodes 1 and 2 and 3 and 4.

Source. Modified from Butson and McIntyre 2008.
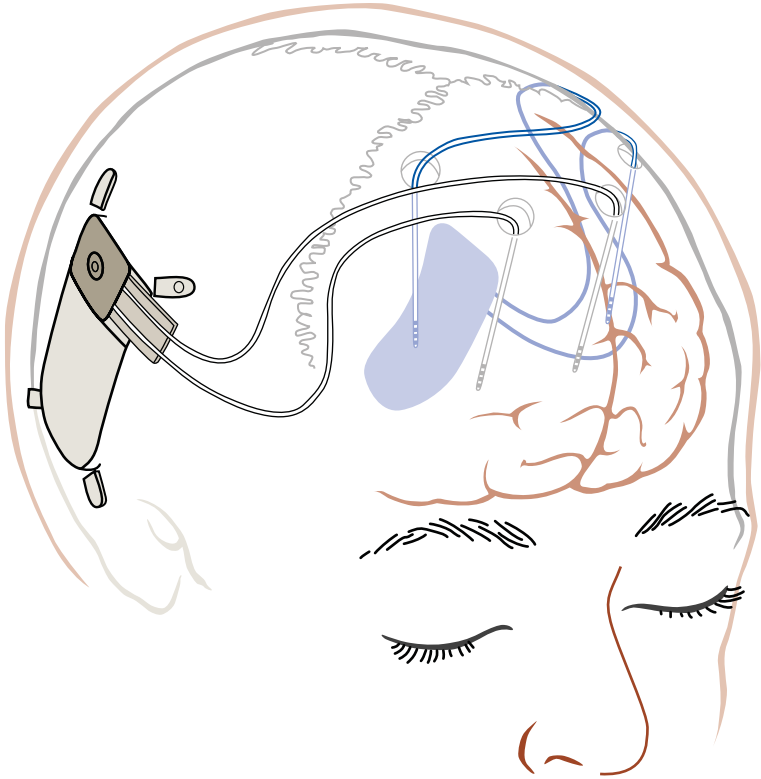
FIGURE 7–4.   Responsive neural stimulation.

Bilateral impulse generators can detect abnormal electrical activity and respond with appropriate stimulation (patient's left side generator, behind the brain, is in blue). Electrodes can be placed deep into subcortical structures as shown, or left superficially on the surface of the cortex (cortical brain stimulation).

contrast to "deep" brain stimulation.) In this case, the electrodes are placed directly on the surface of the cortex. This is a useful option for problems that arise from disorders in cortical gray matter, for example when a seizure focus is in the cortex. To minimize infections and other side effects, the electrodes are placed below the skull but on top of the dura mater (see Figure 3–6 for reference).

What Does DBS Do to the Brain?

The mechanisms of DBS are incompletely understood (Kern and Kumar 2007). However, it is known that the frequency of the stimulation is important. Frequencies of greater than 100 Hz seem to be most effective, whereas frequencies of less than 50 Hz are of no benefit. The stimulation remains localized (about 2–3 mm) because the intensity of the current is small. The pulse width may determine the parts of the neuron that are affected. Longer pulse widths influence the cell body, whereas shorter pulse widths have more effect on the axons. These parameters (frequency, intensity, pulse width, etc.) can be modified to influence effects and side effects.

The ultimate effect of constant high-frequency DBS is reversible inhibition of the stimulated site. This is clear because it has been shown that the effects are similar to ablative surgery. Exactly how high-frequency stimulation "shuts down" the target site remains a mystery. The following theories attempt to explain the mechanism by which DBS operates:

1. "Neuronal jamming," such that signals emitting from the site are incomprehensible and ineffective downstream
2. Activation of inhibitory GABA neurons
3. Stimulation of reciprocal inhibitory neurons

PARKINSON'S DISEASE

The most common utilization of DBS is for treatment of Parkinson's disease that is resistant to medication. A brief review of the current understanding of PD provides a better understanding of how DBS affects the brain. The pathology of PD is centered on the
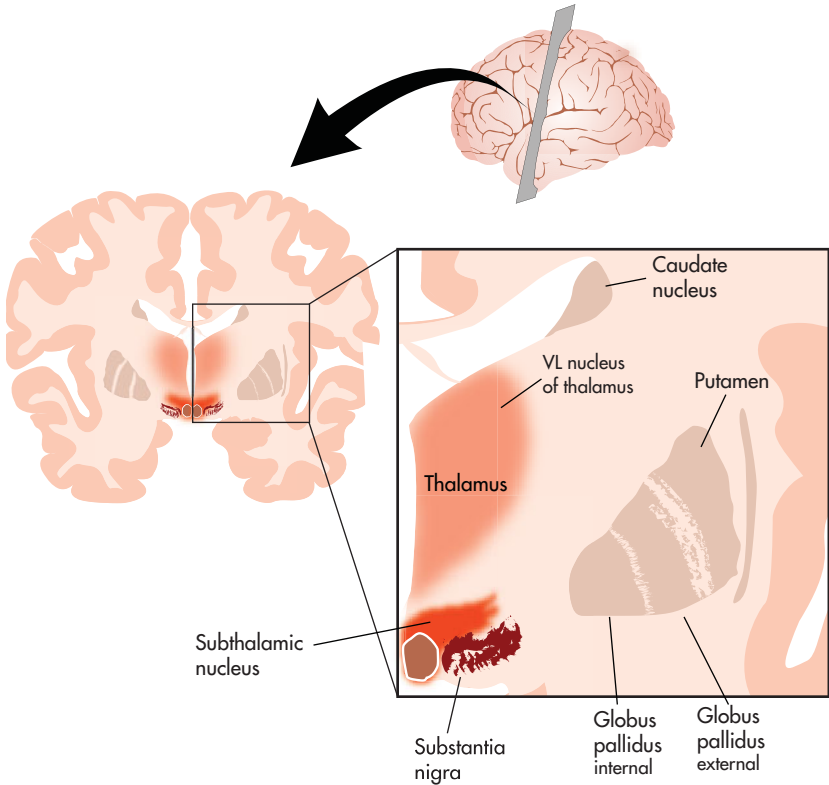
FIGURE 7–5.   The basal ganglia.

The basal ganglia is made up of the caudate nucleus, putamen, subthalamic nucleus, and substantia nigra. VL=ventrolateral.

Source.   Adapted from Bear et al. 2006.

basal ganglia (Figure 7–5). The disease process starts with gradual destruction of the substantia nigra, which in turn has devastating effects on the other nuclei of the basal ganglia (Bear et al. 2006). This occurs subclinically without external symptoms, because the system has some reserve and is able to compensate for mild losses.

The downstream effect of a diminished signal emanating from the substantia nigra is enhanced signals flowing from other nuclei. This has the effect of putting the brakes on movement. Figure 7–6 outlines what may be occurring in the basal ganglia of individuals with PD (Purves et al. 2004). Increased signals from the subthalamic nucleus and globus pallidus interna result in increased inhibition of the ventrolateral nucleus of the thalamus.

The goal of DBS treatment is to inhibit the enhanced inhibiting signals. In other words, high-frequency DBS (or ablative surgery) "releases the brakes," thus allowing movement to occur more normally. The two best locations for DBS for treating PD are the subthalamic nucleus and the globus pallidus interna. By inhibiting these nuclei with a DBS electrode, the brakes are removed and movement flows.

Safety/Adverse Events

The most serious potential risk associated with DBS is from the neurosurgical procedure, particularly bleeding and stroke (Kern and Kumar 2007). This risk generally ranges from 1%–3%. If a stroke occurs, it usually happens during or within a few hours of surgery. Another risk is infection, which develops in about 4%–5% of patients. If an infection arises it is usually not life-threatening, but it may require immediate removal of the entire DBS system. It is important to realize that DBS, virtually alone among the brain stimulation treatments, has a small but nevertheless real risk of death: <1% depending on the location and type of electrodes used. (Because it requires repeated anesthesia, electroconvulsive therapy also has a theoretical risk of death, but this occurs in only about 1 in 50,000 inductions.)

DBS may lead to neuropsychiatric problems (Wichmann and DeLong 2006). Some patients have developed paresthesias or involuntary movements. Others have experienced cognitive side
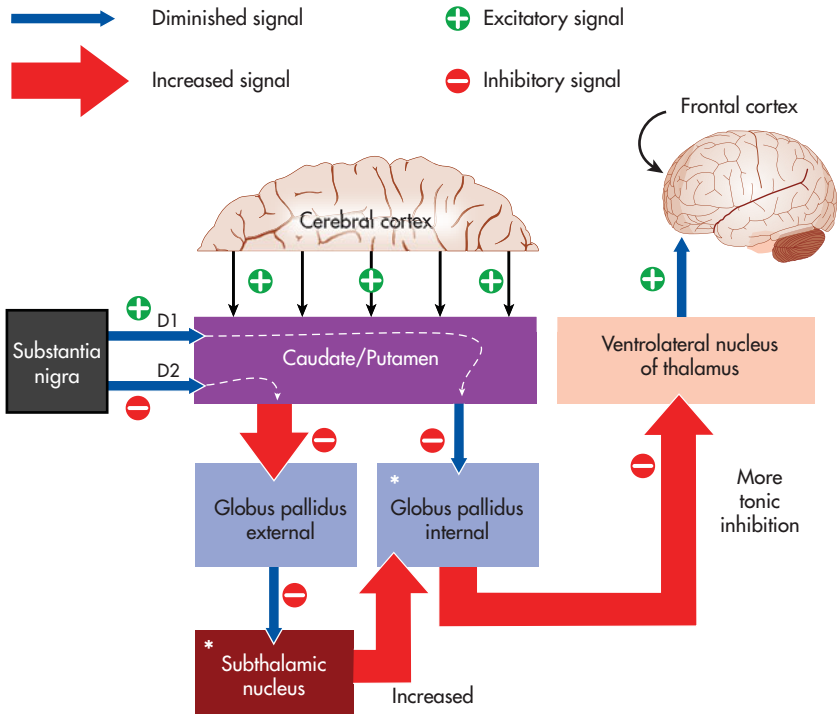
FIGURE 7–6.   Signal enhancement and movement inhibition in Parkinson's disease.

Parkinson's disease starts with diminished output from the substantia nigra, which results in enhanced signals coming out of the subthalamic nucleus and globus pallidus interna. DBS electrode placement in either of these nuclei (*) reduces the inhibition on movement.

Source.   Adapted from Purves et al. 2004.

effects or mood changes that range from disinhibition to gambling or even suicide. Most of these problems can be eliminated with adjustments to the stimulating parameters, but they are important to watch for.

Postmortem analyses of brains from patients treated with long-term DBS have revealed some subtle findings. Mild gliosis (the inflammatory cells of the brain) have been found around the electrode. Moderate cell loss proximal to the electrode tip has also been found.

Impulsive Behavior

The dopaminergic medications used to treat PD have been reported to increase impulsive behavior such as pathological gambling (Dodd et al. 2005). A group at the University of Arizona recently demonstrated with a computer game that DBS will also increase impulsiveness (Frank et al. 2007). Their research suggests that the subthalamic nucleus sends a "hold your horses" signal to other parts of the brain to allow more time to weigh attractive choices. The DBS patients were quicker to rush their choices when their stimulators were on, temporarily blocking the subthalamic nucleus brakes.

Critical Review of DBS in Neuropsychiatric Applications

PARKINSON'S DISEASE

The medications for PD are generally effective, but problematic. As the disease progresses, medications lose their effectiveness in most patients. Thus, patients on long-term treatment struggle with three phases of response through any day:

1. *On*: moving easily
2. *Off*: stiff, difficult movement
3. *On with dyskinesias:* experiencing involuntary movements similar to tics or chorea

DBS is a viable alternative for patients with drug-induced motor fluctuations or those with intractable tremor (Wichmann and DeLong 2006). The best candidates are patients who respond to levodopa and are free of dementia or psychiatric disorders. Choosing the right time to implant a device is part of the clinical challenge.

The pivotal trials testing DBS treatment for patients with PD were conducted at 18 centers in the late 1990s (Deep-Brain Stimulation for Parkinson's Disease Study Group 2001). Although no patients received a sham implantation, double-blind assessments were conducted at 6 months by assessing motor function with the stimulator "on" and again when "off."

Two sites for implantation were used in the original studies: subthalamic nuclei and the globus pallidus interna. Although no head-to-head trial has been conducted, the subthalamic nucleus has become the preferred site for most surgeons. Figure 7–7 shows unblinded assessments of motor function pre-DBS and post-DBS and with and without medication. Likewise, patient diaries of waking hours in "on," "off," or dyskinesias are included. Note that the DBS does not significantly improve the motor score compared with medications alone, but does improve the amount of time patients spend with good mobility.

Since the publication of the pivotal studies, further research continues to support benefits from DBS for the movement disorders associated with PD. A 5-year follow-up of the first 49 patients to receive bilateral stimulation of the subthalamic nucleus found continued improvement in motor function (Krack et al. 2003). Researchers conducting a meta-analysis of 45 studies concluded that motor function improved by 54% in patients with subthalamic nucleus stimulation and 40% in patients with globus pallidus interna stimulation (Weaver et al. 2005).

More recently, a randomized study compared DBS with medical management in 37 cohorts of PD patients (Deuschl et al. 2006). The authors reported superior motor function, as well as improved quality of life for the patients receiving stimulation and medication compared with medication only. This study also provided a better assessment of adverse events. Although the patients receiving just medication experienced greater overall
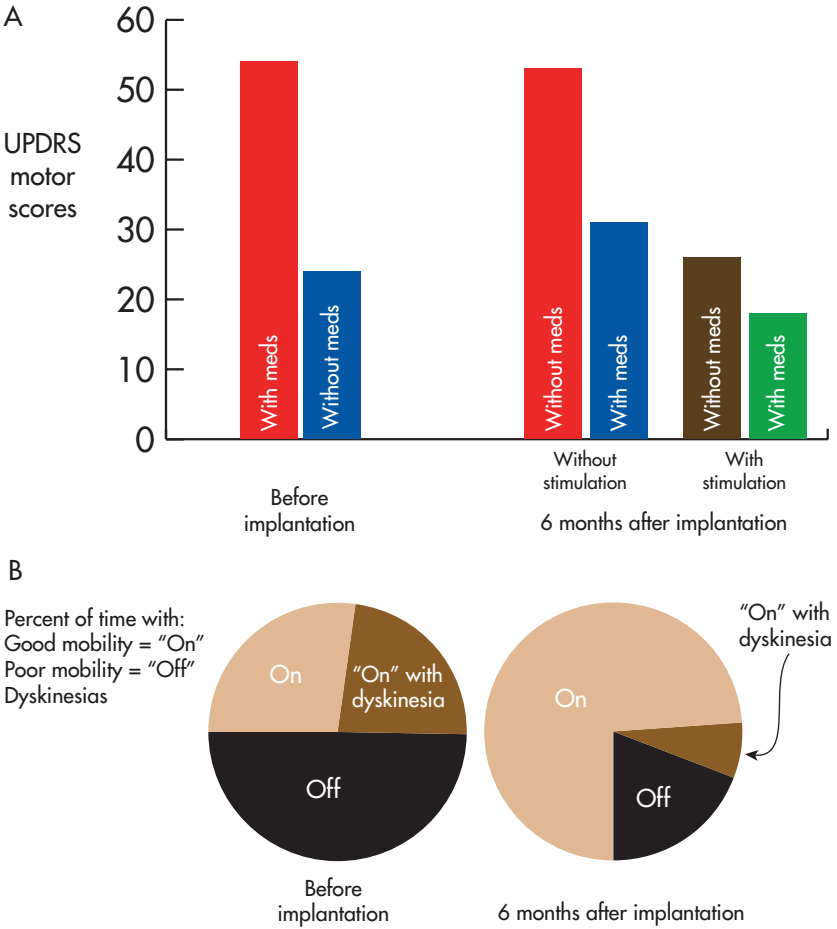
FIGURE 7–7. Patient responses to DBS placed in the subthalamic nucleus.

(A) Unified Parkinson's Disease Rating Scale (UPDRS) motor scores before and after implantation, and with and without medications. (B) Patient diaries before and after implantation, reporting percentage of time in each state of mobility.

Source. Adapted from Deep-Brain Stimulation for Parkinson's Disease Study Group 2001.

frequency of side effects (64% vs. 50%), the patients receiving DBS had a greater incidence of serious adverse events (13% vs. 4%), including one death from intracerebral hemorrhage. Psychiatric sequelae were common.

Finally, it is important to remember that DBS only improves motor function. The natural progression of akinesia, postural instability, and cognitive function are unaffected by DBS.

Listening for the Right Spot

Modern neurosurgeons use imaging scans and knowledge of neuroanatomy to place the electrode tip in the precise location. However, they also use the sound of the neuronal activity to help guide them. The electrode captures cell activity during placement. The sound can be amplified and played for the surgeon in the operating room. Experienced surgeons recognize the "sounds" of different tissue and use that to help them find the right spot.

TREMOR

The treatment of tremors was actually the first use of DBS and continues to be a major application of the device (Wichmann and DeLong 2006). Essential tremor is the most common type of tremor, but there are several other kinds of tremors that also respond to DBS: brain stem (Holmes) tremor and tremors associated with PD or multiple sclerosis. The ventral intermediate nucleus of the thalamus is the usual site for placement of the DBS electrodes. The stimulation of the Vim appears to be effective for most forms of tremor regardless of the etiology.

The pivotal trials of DBS for parkinsonian or essential tremor were conducted in Europe at 13 neurosurgical centers (Limousin et al. 1999). A total of 111 patients were implanted, and the results were reported at the 12-month follow-up. Patients' upper and lower limb tremors were significantly reduced in 85% of the patients. Postural tremors were reduced in 89%.

Numerous subsequent studies continue to demonstrate beneficial effects for essential tremor treated with DBS (Wichmann

and DeLong 2006). Specifically, the procedure improves quality of life and the benefits persist. However, investigators in one small follow-up study found tolerance developing in some patients with essential tremor.

Figure 7–8 shows some perplexing results from functional imaging studies conducted with 10 patients receiving DBS for essential tremor (Perlmutter et al. 2002). Patients were scanned with the stimulator "on" and "off," and the results were averaged for the group. Areas of increased blood flow during stimulation are shown in color. Note that the stimulation actually increases blood flow to the thalamus (where the electrodes are placed) and to the supplementary motor area.

These results were unexpected because DBS of the Vim seems to have the same effect as ablation. How can removing the Vim and increasing the activity of the Vim (as shown with increased blood flow) have the same effect? These results accentuate the limited understanding we have of what DBS is doing to the brain, and of the relationship between blood flow and regional activity.

DYSTONIA

Dystonia is characterized by twisting, repetitive movements or abnormal postures caused by irregular muscle contractions (Wichmann and DeLong 2006). Dystonia can be primary (inherited or birth-related) or secondary such as that caused by neuropsychiatric medications. Dystonia is classified into two forms: generalized and focal. The focal form can usually be managed with botulinum toxin injections, but the generalized form is less responsive to medications. Some patients are almost completely incapacitated by the movements.

Earlier work involving ablation of either the globus pallidus interna or the thalamus led others to try DBS for dystonia. The globus pallidus interna has become the most common site of stimulation. Pivotal trials were never conducted because it was believed the eventual market demand for DBS treatment of dystonia was insufficient to justify industry funding of such a study. However, remarkable individual responses with DBS led the FDA to grant approval on a "compassionate use" basis. For example, patient Kari Weiner had been afflicted with dystonia for
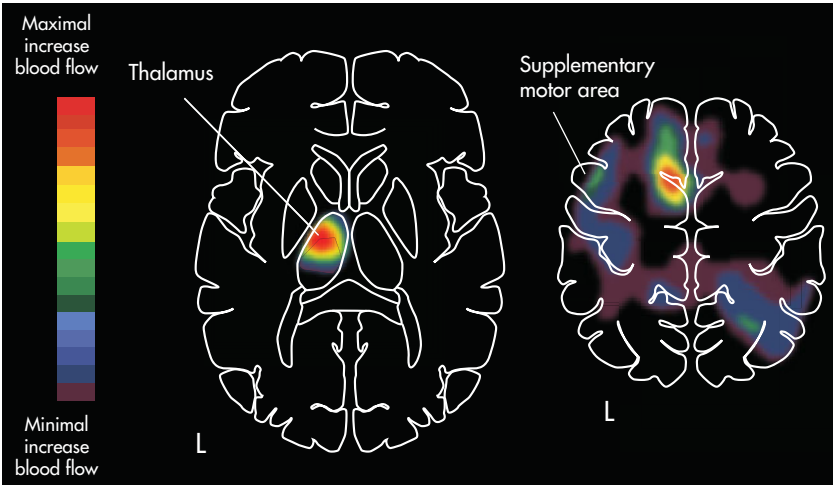
FIGURE 7–8.   Effects of DBS on the brain.

Positron emission tomography (PET) scans of patients with DBS for essential tremor. The color shows areas of increased blood flow during times of stimulation.

Source.   Adapted from Perlmutter et al. 2002.

7 years and was using a wheelchair by age 13 (Horgan 2005). Since receiving DBS she has been able to walk without assistance.

In a randomized European study of 40 patients with primary-segmental or generalized dystonia (Kupsch et al. 2006), half the patients had the stimulation started immediately and the other half had treatment delayed by 3 months. At 3 months, patients were blindly rated on the basis of video exams and were compared to baseline. Patients who received stimulation had significant improvements in movement scores (39%) and disability (38%). Patients in the sham arm had small, nonsignificant improvements.

CHRONIC PAIN

There is a long history of neurosurgical interventions to relieve chronic pain. It is intuitively appealing to sever the connection between the offending site and the area that perceives the pain in the brain. Unfortunately, it is not that straightforward. The results are often temporary and symptoms frequently return. Brain stimulation offers a way to adapt the treatment to match the dynamic and evolving nature of the pain condition. The frequency, pulse width, and intensity of stimulation can be altered as the pathology changes.

Treatment of pain may have been the first use for brain stimulation (see Figure 1–2). DBS for chronic pain has been studied sporadically for over 50 years, although only in the past 20 years have we had the technology for continuous stimulation (Kringelbach et al. 2007). There are numerous small studies that follow the effects of stimulation of various regions for various different forms of pain. In general, it is believed that stimulation of the periventricular/periaqueductal gray matter is best for nociceptive pain, whereas stimulation of the sensory thalamic nuclei is best for neuropathic pain (Kern and Kumar 2007). The reports seem encouraging. However, as with the ablation studies, these results are not so straightforward.

In the 1990s, researchers at Medtronics (the manufacturer of the DBS device) conducted two multicenter trials of DBS for chronic pain at the same time they were conducting studies for PD

and essential tremor (Coffey 2001). The results of the pain studies were disappointing (high dropout rate and poor efficacy); the manufacturer abandoned the studies and did not apply for FDA approval. To date, a definitive large, randomized, multicenter trial establishing sufficient efficacy has not yet been conducted.

Cortical Stimulation. Another option for chronic pain entails stimulation of the motor cortex. In this procedure the electrodes are placed directly on the dura mater over the motor cortex where the pain is located. This use is not FDA approved, but it is relatively common (Birknes et al. 2006). At our institution (Medical University of South Carolina) the neurosurgeon asks for a transcranial magnetic stimulation evaluation of the motor cortex prior to surgery so as to better understand the location of the section of the motor cortex that is to be stimulated.

DEPRESSION

Subgenual Cingulate. The use of DBS in patients with treatment-resistant depression has been widely reported in the lay press. Although DBS is an exciting new option for depressed patients for whom all other therapies are ineffective, the enthusiasm is perhaps premature. To date, very few patients have been treated (<30 in the world) and properly blinded studies have not been conducted. To make matters even more confusing, the various groups employing this technique are using different technologies while also stimulating different sites in the brain.

The most widely cited study on treatment of depression with DBS has been that of Helen Mayberg and her group in Toronto (Mayberg et al. 2005). Mayberg, like many other researchers, conceptualizes depression as a systems disorder. That is, she posits that the network modulating mood becomes out of synch in patients with depression. It had been noted that patients with depression showed greater activity in the subgenual cingulate cortex, also called Brodmann area 25, compared with control subjects (George et al. 1997; Wu et al. 1992). More recently, research by a different group replicated and extended these insights (see Figure 7–9) (Greicius et al. 2007). In this study, the resting activity in the subgenual cingulate correlates with the duration of the
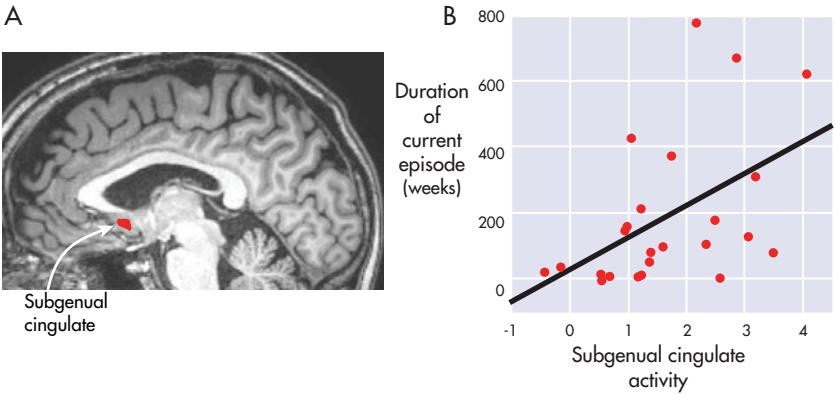
FIGURE 7–9. Subgenual cingulate activity and depression.

Activity in the subgenual cingulate (A) correlates with duration of the current episode of depression (B).

Source. Adapted from Greicius et al. 2007.

episode of depression. Other research had shown that patients with depression who respond to treatment show a decrease in activity in the hyperactive subgenual cingulate (Wu et al. 1992).

With this background in mind, the Toronto group implanted bilateral electrodes in six patients with treatment-resistant depression. (Actually, the electrodes were placed in the white matter tracts next to the subgenual cingulate because the latter is hard to reach.) Remarkably, all patients, while in the operating room, spontaneously reported acute positive effects of the stimulation they experienced, such as a "sudden calmness" or "disappearance of the void." At 6 months, four of the six patients still experienced positive response to the stimulation (symptoms cut in half), but very few reported they were totally free of symptoms (remission). Positron emission tomography (PET) scans of the responders showed decreased activity in the subgenual cingulate. These positive results have spurred further studies.

Patenting the Brain?

> One of the more interesting (and troubling) developments spinning off from DBS research is that several scientists are patenting regions of the brain for therapeutic stimulation. Whether or not these patents are legally permissible, we worry that this is not a good development for advancement of the field.

Nucleus Accumbens. Schlaepfer and his group in Germany have experimented with stimulating the nucleus accumbens—what is sometimes called the brain's pleasure center (Schlaepfer et al. 2007). They postulate that activity in the nucleus accumbens is insufficient in depressed patients, which may explain the anhedonia and lack of motivation these patients experience. Schlaepfer's group implanted DBS electrodes in three patients suffering from extremely resistant forms of depression. They reported that clinical ratings improved for all three patients when the stimulator was on and worsened when it was turned off.

Although the study is small and of short duration, it is of particular interest because of its similarities to the work Heath

conducted in the 1950s and 1960s (see section on Emotional Pacemaker in Chapter 1, Introduction). Heath also implanted stimulating devices to enhance pleasure in depressed patients. Ultimately, he found the benefits dissipated with time. It will be important to establish whether modern DBS has enduring efficacy as a treatment for depression.

Another multisite research group is implanting the electrodes in a manner that interrupts the white matter tracts connecting the cingulate to the orbitofrontal cortex. The tip of these electrodes abuts on the nucleus accumbens; the Food and Drug Administration calls this approach ALICNA (anterior limb of the internal capsule, nucleus accumbens). In this study, DBS was added to stable background medication for 15 treatment-resistant patients. The research group found that about half of the patients responded at 6 and 12 months, with less than one-third achieving remission (Dougherty et al. 2007). Although there was some worsening of suicidal thoughts, there were no suicide attempts.

A Word of Caution

It is important to remember that in their initial glowing assessment of the frontal lobotomy, Freeman and Watts (1950) reported that out of 711 lobotomies, 45% yielded good results and an additional 33% yielded fair results. Later studies revealed far more minimal effects, with major side effects. This stresses the importance of having outcome assessments conducted by independent observers and proceeding cautiously with new invasive technology.

OBSESSIVE-COMPULSIVE DISORDER

For patients with severe, unremitting obsessive-compulsive disorder, ablative neurosurgery has been an option. Small lesions made in the anterior capsule or anterior cingulate have been effective in about one-third of the patients. DBS offers the option of interrupting the obsessive circuitry without destroying tissue. However, only the findings of sequential case studies have been reported, and no large comprehensive study has been conducted. Green-

berg et al. recently published the best report (2006). They followed 8 patients for 36 months after implantation. Of these, 4 patients had improvements of >35% on the Obsessive-Compulsive Disorder Scale and an additional 2 had improvements of >25%.

Summary of Clinical Use

DBS is FDA approved and effective for treatment-resistant Parkinson's disease, and it is also used for dystonia and essential tremor. In addition, cortical stimulation over motor cortex has been used for many years by neurosurgeons for intractable pain. There are other exciting case series of DBS for depression or obsessive-compulsive disorder, but large randomized clinical trials are needed. For all disorders potentially treated with DBS, it is important to know if the effects seen are DBS-related or are caused by the insertion effect of the microtrauma of passing the wire. Given the history of the over-rapid adoption of frontal lobotomies, it is important to proceed cautiously with DBS for other conditions because there is potential for morbidity and even mortality associated with this treatment.

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CHAPTER 8

Transcranial Direct Current Stimulation

Introduction and History

Transcranial direct current stimulation (tDCS) is perhaps one of the simplest ways of focally stimulating the brain. Similar techniques were practiced almost immediately after practical applications for electricity began to be developed in the late 1880s. Passing a direct current through muscle, or the brain, was in vogue in Europe. For example, one of Charcot's residents, Georges Duchenne de Boulogne, traveled around Paris with a small generator and battery; he passed electricity through pa-

tients' muscles, examining its effects on numerous disorders and using it to better understand muscle-nerve innervations, particularly in the muscular dystrophies (Figure 8–1) (George 1994). Others began applying direct current through the brain. Because this technique showed no benefits, it was largely dropped as a treatment in Europe and the United States.

For reasons that are not clear, tDCS remained an area of active research in Russia during the 1940s and continues to be studied there. It was sometimes called "electrosleep therapy," because patients would sometimes nap or sleep during the 30-minute treatments. (Gomez and Mikhail 1978) Most of the tDCS done in Russia was not delivered in clinical trials and was largely anecdotally used for the treatment of alcoholism, pain, depression, or a combination of these (Feighner et al. 1973).

Dr. Walter Paulus and his group in Gottingen, Germany have led a recent resurrection of this technology, and there is now active investigation of tDCS, with over 100 articles published in the past 10 years in peer-reviewed journals. Clearly, tDCS has an effect on the brain—it can boost cortical excitability and improve memory in healthy people. Whether these effects can be used therapeutically remains to be determined.

How Is It Done?

Quite simply, tDCS involves passing a weak (usually ≤1 mA) direct current through the brain between two electrodes. The current enters the brain from the anode, travels through the tissue, and exits out the cathode (Figure 8–2). Some researchers refer to this as either cathodal tDCS or anodal tDCS, depending on which electrode is placed over the region that is being modified.

The administration of tDCS is relatively easy. Many researchers simply use damp sponges as the electrodes. These can be placed anywhere on the scalp and are held in place with an elastic headband.

FIGURE 8–1.   An early form of "something like" transcranial direct current stimulation (tDCS).

Duchenne de Boulogne passed direct current through the muscles of the face and stimulated the muscles involved in smiling. Duchenne wrote about the differences between a "false" and a "true" smile. Because he stimulated muscles and not the brain or nervous tissue, Duchenne's work is not technically tDCS.
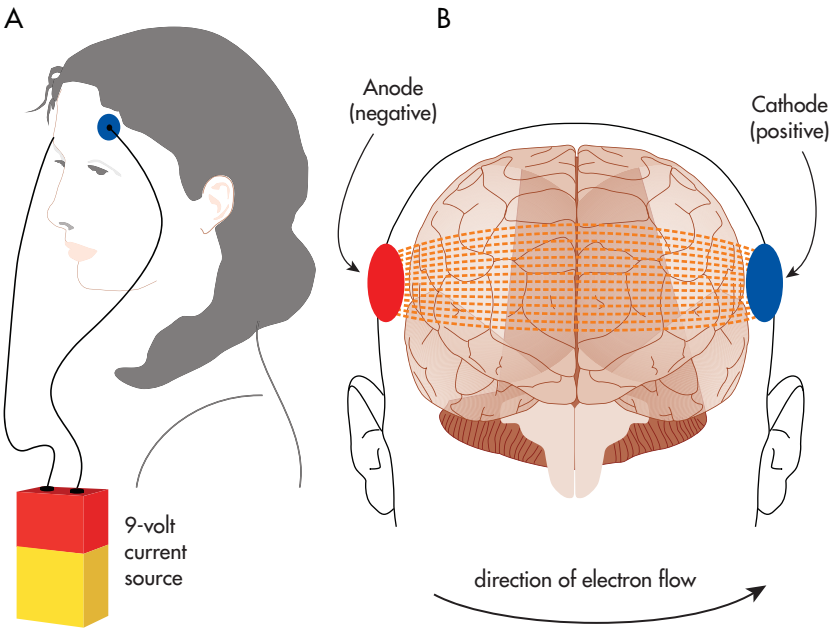
FIGURE 8–2.   Transcranial direct current stimulation.

The tDCS device encompasses attaching an anode and cathode from an energy source generating direct current (A). The passage of current through the brain induces changes that are believed to be therapeutic (B).

What Does tDCS Do to the Brain?

Exactly what happens to the brain during tDCS remains unknown. However, experiments with animals, humans, and even direct recordings from individual neurons offer a general explanation. Starting with the basics, the anode (which is negative; remember A-N, AN) is the place where electrons enter the brain. The cathode (which is positive) is where the electricity exits the brain. Thus, a negative charge builds up under the exiting cathode as the electrons line up to get on the exiting electrode (like passengers waiting to get on the subway, bunching at the door).

A smaller cathode can produce a more focal delivery of charge to a brain region as more charge lines up right below the exit door. Therefore, you can shape or influence the size of the brain region being affected by changing the size of the cathodal electrode (smaller size is more focused) or changing the size and location of the anodal electrode (Nitsche et al. 2007).

The behavioral effects of what happens under the exiting cathode are not necessarily as simple as one would hope. In most studies the area under the anode is more active (or excited) and the area under the cathode is more inhibited. For example, stimulation of the motor regions produces such results. This technique is being exploited as a possible treatment for stroke.

However, the brain is enormously complex, and there are studies that show the brain region under the anode is behaviorally *inhibited*. In one study researchers examined the latency of a visual evoked response: 10 minutes of anodal tDCS reduced visual evoked potential amplitudes, whereas 10 minutes of cathodal tDCS increased amplitudes for several minutes following stimulation. (Accornero et al. 2007). Thus, in this study there was behavioral inhibition under the anode and excitation under the cathode. It appears that the different regions of the brain with their different morphology, layering, and cellular composition can have different responses to direct current stimulation.

The human head is a poor conductor of electricity. Moreover, tDCS is extremely inefficient at stimulating the brain (as is ECT) because at least 50% of the current is lost to the surrounding tissue. That is why you can use much less electricity when you

tDCS Compared With ECT

In tDCS, small currents are used over 20–30 minutes. It is constant, and the brain has time to accommodate to the gentle current. By contrast, electroconvulsive therapy (ECT) uses a short, powerful, bidirectional current, which typically has a waveform that makes it resemble an alternating current. The brain cannot adapt to the ECT stimulus, and a seizure is induced. However, the total amount of electricity used in a session of ECT compared with a session of tDCS is not that different. It is significant that the brain reacts differently depending on the different types of the stimulus applied and the very different time-domains of application.

bypass the skull and touch neurons directly, as you do with DBS or TMS (in which the magnetic field passes through the skull).

Finally, as with all stimulation techniques, the ability to induce effects that will endure beyond the time of administration is essential for practical clinical applications. With tDCS, it appears that the focal and behavioral changes can persist after the electrodes are removed. In studies of tDCS on the motor cortex for example, tDCS-induced inhibition or excitation can last for several minutes to an hour or so. Whether therapeutic changes can endure for weeks or months remains to be determined.

FEAT AND FEAST

Theoretically, one could send electrical signals in an alternating current pattern, but unidirectionally. Then, electrical charge would distribute asymmetrically between the cathode and anode. This idea is called *transcranial alternating current stimulation* (tACS) or *focal electrical alternating current therapy* (FEAT) (Arana et al. 2008). As with many of the stimulation methods, you could massively increase the current and use this to create a powerful focal seizure. This has in fact been done in nonhuman primates. We call this method *seizure-producing tACS*. Others, including the pioneers of this method, refer to it as *focal electrical alternating current seizure therapy* (FEAST) (see Figure 8–3).
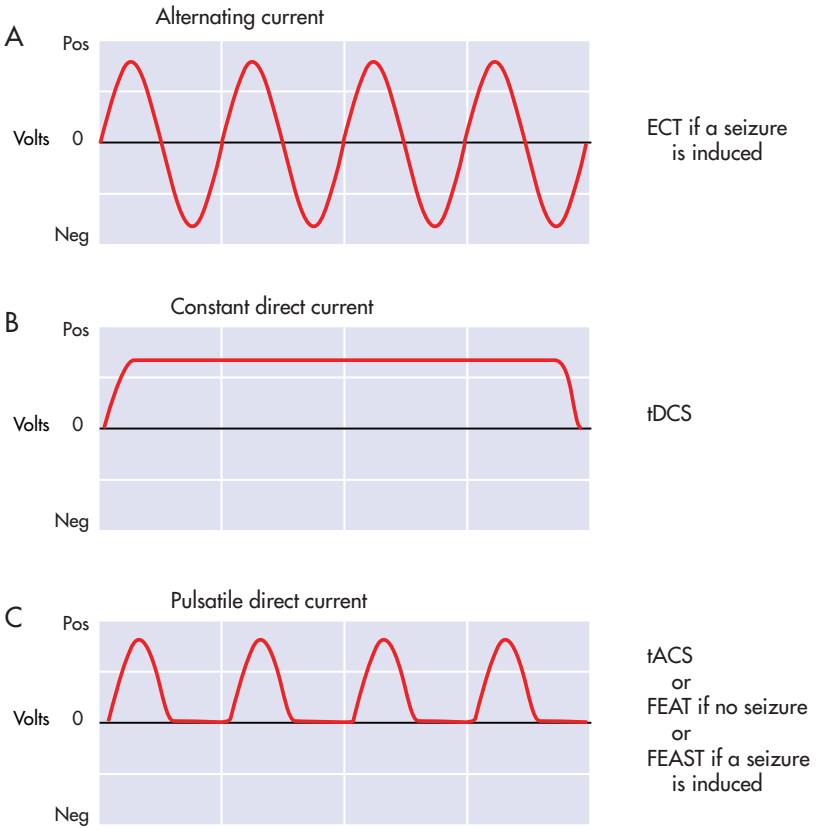
FIGURE 8–3. Waveforms for different techniques.

Different ways of delivering electrical current (and whether or not a seizure is induced) have different names in the literature.

Safety/Adverse Events

Side effects of tDCS depend on the placement of the electrode, whether it is anodal or cathodal, the intensity of the stimulation, and the length of time the patient is treated. In the older prefrontal treatment literature, it was reported that skin burns could occur, and some patients felt uncomfortable or even felt dizziness. Modern treatments are minimally troublesome at worst.

Paulus's group reported their results in 567 patients and subjects who had received tDCS in challenge studies over the motor, parietal, or occipital cortex (Poreisz et al. 2007). Remarkably, no patient requested the stimulation be terminated. About 70% of subjects noticed a mild tingling sensation under the electrode. One-third of subjects felt fatigue after treatment and one-third also felt itching under the electrode. Less frequently, headache (11%), nausea (3%), and insomnia (1%) were also reported.

Critical Review of tDCS in Neuropsychiatric Applications

Much of the most recent work with tDCS has not been focused on healing the sick. Rather, most of the reported studies have dealt with the behavioral effects of tDCS stimulation on healthy control subjects. Although it is beyond the scope of this book to review these more basic behavioral studies, it is clearly established that tDCS can focally excite or inhibit the brain. This impressive and growing body of research convinces us that there are perhaps clinical uses of tDCS yet to be discovered. This is why we have given tDCS a stand-alone chapter despite there being only a few large, well-conducted clinical trials with tDCS.

Stroke

Numerous small studies using healthy volunteers have shown that tDCS can enhance motor function and control. The next logical step is to apply the technique to patients whose motor control

has been damaged as a consequence of stroke. The unique qualities of tDCS offer possibilities beyond just stimulating the damaged tissue. Some research suggests that constraining the unaffected, healthy side of the brain actually improves healing. For example, constraining the good arm and forcing the patient to use the impaired arm improves recovery after a stroke affecting the upper limb.

Theoretically, tDCS could be able to mimic this therapeutic process. That is, one could excite the damaged side while inhibiting the healthy side. When the anode is placed over the injury, it should excite the neurons beneath it. Likewise, if the cathode is placed over the healthy side, it should provide some inhibition of those neurons. In summary, however, the research on tDCS as a treatment for stroke is still preliminary, and significant, clear-cut effects in well-conducted, sham-controlled trials are lacking (Alonso-Alonso et al. 2007; Fregni and Pascual-Leone 2007).

FUTURE POSSIBILITIES

As with all of the new stimulation techniques, there have been groups trying out the technology in many neuropsychiatric disorders. Single-site small-sample studies have suggested some positive effects of tDCS in pain, migraine, fibromyalgia, depression, and epilepsy. None of the studies were large or multisite, and the sample sizes have been small. Further work is needed to discover whether these early promising studies can be replicated.

Summary of Clinical Use

tDCS is an exciting new tool, but there are no clinically useful applications at the moment. Like many of the stimulation techniques, tDCS has followed the interesting pattern of discovery, overuse, misuse, and then a reawakening of interest with the advent of more modern approaches. tDCS is likely to become useful in the near future, especially when coupled with pharmacological and behavioral approaches to reshape circuit behavior in health or disease.

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CHAPTER 9

Other Techniques

We have reviewed the major brain stimulation techniques. However, there are numerous other ways of stimulating the nervous system that we still have not discussed. These other techniques all share in common that they electrically or magnetically stimulate the brain or peripheral nervous system. But not enough high-quality, critical studies have been conducted on some of these techniques for each to merit an individual chapter in this book. Although most of these applications are not part of mainstream medical treatment, clinicians will want to be aware of these techniques in case patients who are alert to alternative forms of treatment ask about them.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) units are some of the most widely used stimulation devices. Developed in the late 1970s, they are largely employed for pain relief. Like many of the other stimulation techniques, TENS was discovered serendipitously. Researchers were attempting to directly stimulate the spinal cord to achieve pain relief, but they needed a surface device to trigger the implanted device. They had to test tolerability of this surface electrode, and in doing so, they found that pain patients reported improved pain symptoms from the surface electrical stimulation alone.

How Is It Done?

TENS devices consist of a small battery-powered device attached to electrodes that are applied to the skin, typically over the low back or neck (Figure 9–1). Application of a cream is required to improve skin conductivity. The stimulation parameters can vary widely, but typically they are 40–150 Hz, pulse width of 10–1,000 microseconds, and amplitude 10–30 mA. The stimulation is usually constant and applied for 20–30 minutes. In some but not all patients the pain relief is quick and parameter- and dose-dependent.

What Does It Do to the Brain?

The most widely held theory concerning TENS follows the gate theory of pain, which posits that the skin electrical stimulation preferentially activates low-threshold, myelinated nerve fibers, which then inhibits propagation of nociception carried in the smaller unmyelinated C-fibers in the dorsal horn. Study results in animals support this idea.

Is TENS Safe?

TENS is relatively safe unless applied over other nervous tissue such as the eyes.
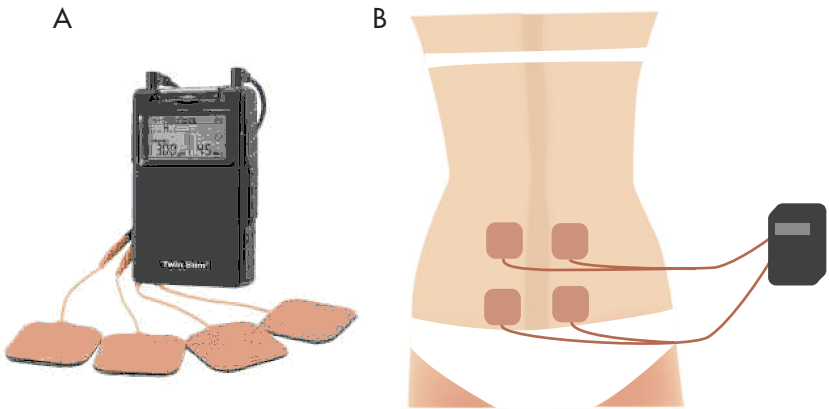
FIGURE 9–1. Transcutaneous electrical nerve stimulation (TENS).

The battery-powered TENS unit (A) generates high-frequency cycling direct current that passes through electrodes placed over the lower back (B) or any other peripheral location where the patient has been experiencing pain.

CRITICAL REVIEW OF CLINICAL APPLICATIONS

Interestingly, despite widespread use, the randomized clinical trial data on the use of TENS for low back pain are mixed and rather modest. For example, the conservative Cochrane Collaboration, which evaluates treatments, found mixed results for TENS as a treatment for low back pain (Khadilkar et al. 2005). One large study reported positive results, but another large study yielded negative findings (Khadilkar et al. 2005).

Electroacupuncture

Electroacupuncture is the application of electrical current to acupuncture needles. Acupuncture is a form of traditional Chinese medicine that seeks to restore health by inserting and manipulating needles in specific points along established ancient meridians. The effectiveness of acupuncture remains controversial in the scientific community, but the emergence of further randomized controlled trials is increasing our understanding of the benefits and limitations of this procedure. A review of studies utilizing acupuncture concluded that the procedure is effective for some but not all conditions (Ernst et al. 2007).

HOW IS IT DONE?

Electroacupuncture follows the same principles as traditional acupuncture, but with the application of a mild alternating electrical current flowing between two needles. The electrical pulses are generated by devices that send a small signal to the needles. The current is usually less than 0.6 mA, which is about the same as what is generated by a wristwatch battery. The voltage is usually between 40 V and 80 V, but can spike as high as 130 V. The duration of a treatment session is usually 10–20 minutes.

WHAT DOES IT DO TO THE NERVOUS SYSTEM?

Electroacupuncture is intended to provide continuous stimulation, which alleviates the need for the practitioner to constantly

manipulate the needles. However, exactly what electroacupuncture does to the nervous system remains unanswered.

IS ELECTROACUPUNCTURE SAFE?

Patients are aware of a sensation when electroacupuncture is applied. If the voltage is too high, patients can experience muscle twitching, numbness, and pain. One review of electroacupuncture devices noted that some of the output is erratic and beyond the manufacturer's specifications. The authors concluded that practitioners must be adequately trained to use the electrostimulators safely (Lytle et al. 2000).

CRITICAL REVIEW OF CLINICAL APPLICATIONS

There are numerous small studies reported in alternative medicine journals describing positive outcomes for electroacupuncture. Pain is the condition most commonly treated. The methodological limitations of these studies make it difficult to determine the utility of electroacupuncture for Western medicine.

The Cochrane Collaboration evaluated electroacupuncture as a treatment to control chemotherapy-induced nausea and vomiting, as well as for treatment of rheumatoid arthritis. In both cases, the reviewers concluded that there appeared to be some benefit, but not a robust effect. Likewise, the small size of the limited number of studies precludes recommending electroacupuncture for these conditions (Casimiro et al. 2002; Ezzo et al. 2006).

Cranial Electrotherapy Stimulation

Cranial electrotherapy stimulation (CES) is another form of electrical current applied to the peripheral skin in order to influence the brain. CES is sometimes called *electrosleep*, or *cranial electrosleep*, because it can make a user sleepy or "spacey" during the stimulation.

One device is commercially marketed in the United States as Alpha-Stim and has received a great deal of publicity recently.

The devices are FDA-approved for anxiety, insomnia, or depression because they were grandfathered in when the Medical Device Act was passed in 1979. CES, like electroconvulsive therapy, which was also grandfathered in, has not been examined the way vagus nerve stimulation, transcranial magnetic stimulation, or the antidepressant medications have been studied. Unlike electroconvulsive therapy, CES has not been subjected to any large multicenter randomized, blinded studies.

How Is It Done?

CES involves applying a pulsed, low-amplitude electrical current to the head using electrodes clipped to the earlobes (Figure 9–2). The current comes from a battery source that looks like a TENS device but has a high-frequency cycling design. Thus, using the nomenclature adopted for this book, CES is a specific type of transcranial alternating current (because the pulse is bidirectional). The user can increase the intensity from 10 up to 500 millionths of an ampere, but the frequency is set at 0.5 Hz. Since CES generates an alternating bidirectional current, it does not matter which ear is the anode or cathode. The standard session lasts 20 minutes per day, but a session can go as long as 60 minutes if needed.

What Does CES Do to the Brain?

Promotional descriptions of CES show the current flowing between the electrodes and traveling through the brain stem, where it stimulates the release of important neurotransmitters. This is more speculation than actual science. However, in a series of studies, Shealy and Wilky (1989) found that in patients with treatment-resistant depression, CES was associated with significant elevations in plasma serotonin. Likewise, in nondepressed volunteers, 20 minutes of CES produced significant increases in cerebrospinal fluid serotonin and β-endorphins, as well as increases in plasma endorphins (Shealy and Wilky 1989).

CES treatment also alters electroencephalographic (EEG) readings (Kirsch and Smith 2000). In studies of macaque monkeys, alpha EEG waves were slowed following CES; the slowing was associated with a reduction in adverse reactions to stressful
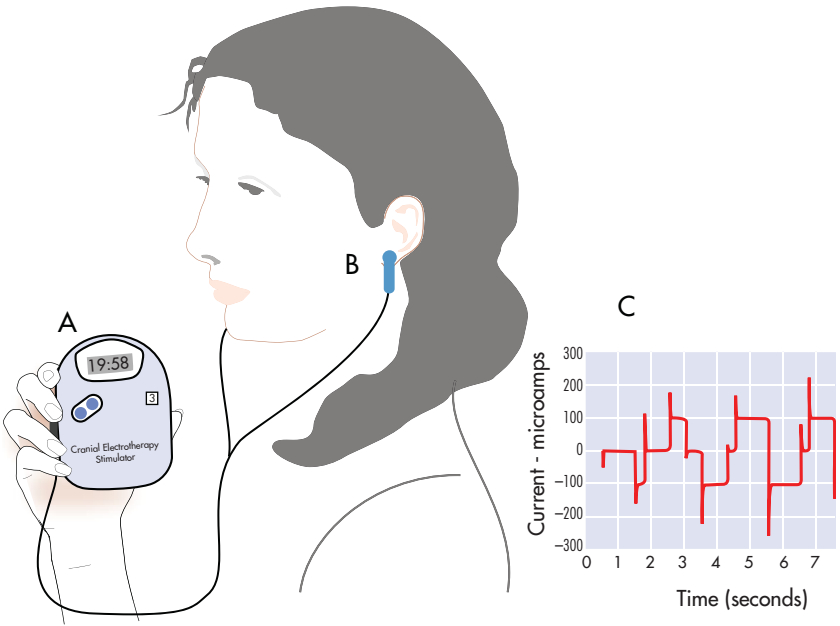
FIGURE 9–2. Cranial electrotherapy stimulation (CES).

The CES device (A) sends the stimulation to the electrodes attached to the patient's ear lobes (B). The stimulation is an alternating current measured in microamps (C).

stimuli (Jarzembski 1985). Schroeder and Barr (2001) conducted a double-blind study on EEG changes in 28 healthy male subjects who underwent sham CES, 0.5-Hz CES, and 100-Hz CES treatment in random order (Schroeder and Barr 2001). Both active CES treatments resulted in a downward shift in the alpha-mean frequency, with the 100-Hz treatment producing more overall effect and additionally decreasing the beta power fraction.

Is CES Safe?

Many patients will experience mild dizziness, vertigo, and sometimes anxiety or nausea when they start the device. These effects are dose-dependent, and treatment is usually applied at a setting that is tolerable. In some CES studies, patients have noted headache, skin irritation (e.g., burns), and lightheadedness or vertigo during or following treatment. Activation is described as a potential side effect in the device brochure, but frank mania and hypomania are not mentioned.

Critical Review of Clinical Applications

It is difficult to provide a measured assessment of the clinical studies conducted on the CES device, because there are numerous small-study reports in nontraditional journals regarding a maddeningly wide variety of psychiatric and neurological conditions. In general, the device seems to promote "stress reduction." As such, the best uses of the device may be for anxiety, depression, and insomnia. However, there are reports of CES benefiting fibromyalgia, headaches, tremor, ADHD, cognitive dysfunction, and substance abuse withdrawal.

Although the results of many studies on CES have been published in the past 30 years, most investigators have used relatively small samples in which only a dozen or so patients received the active treatment. In addition, the frequency and duration of CES treatment has not been established for specific conditions. Although short-term CES (e.g., 1–5 treatments of 23–30 minutes each) may help with acute anxiety, some researchers

argue that chronic conditions may require longer periods of treatment (Jarzembski 1985), and that effective therapy for patients with clinical depression or anxiety disorders may only result from 2–4 weeks of daily CES.

The dearth of studies reporting negative effects is troublesome. With the possible exception of exercise or getting a pet, few interventions in medicine are uniformly effective. Either this device is the next aspirin or some bias is distorting the reports.

To our knowledge, Klawansky and coworkers (1995) have published the only meta-analysis of CES—and that occurred more than a decade ago. They reviewed randomized controlled trials of CES for anxiety, brain dysfunction, headache, and insomnia. Eight trials on anxiety were combined and analyzed using effect sizes to compare outcome measures. Overall, CES was found to be significantly more effective than sham treatment (effect size = 0.62), although placebo effects may have been a factor, given that 30% of patients who received sham therapy also improved (Klawansky et al. 1995).

SUMMARY OF CLINICAL USE

A simple stress-reducing device that patients can use at home would be a welcome addition to modern medicine. CES seems appealing, with numerous positive study results described for a wide range of disorders. The technique is relatively inexpensive, easy to operate, and apparently safe. However, the studies have been small and of poor quality. It is hard to know whether the treatment is truly effective or a modern snake oil. Rigorous academic studies are needed.

Other Interventions

We will close this book with a quick review of some other techniques about which the informed clinician should be aware.

Sacral nerve stimulation (SNS; also named Interstim) is a technique used to control fecal or urinary incontinence. The stimulating electrodes are placed in the spinal cord (S3 foramen) near the sacral

Stimulating Spiritual Growth?

Sometimes it is hard to separate the wheat from the chaff in this dynamic field of brain stimulation. However, we think this next device goes too far. Dr. Persinger has developed a device (the 8-coil Shakti) that generates a weak magnetic field over the temporal lobes (Figure 9–3). The magnets alternate between the green and blue coils, which generates a changing magnetic current over the brain. Remarkably, this device is supposed to induce spiritual growth and well-being. We will await the results of the randomized controlled trial before purchasing ours.

nerve, and the generator is placed subcutaneously in the buttock. Generally, physicians perform a challenge or screening stimulation before implanting the full device into the nerve. It is not known exactly how SNS improves overall control of incontinence, other than by resetting tone and spinal cord control over voiding or defecation.

Research suggests, but has not proven, that percutaneous tibial nerve stimulation (PTNS), might also be effective in treating incontinence. In an open-label study, researchers in the Netherlands and Italy found that for 35 patients, 12 weeks of once-weekly treatment reduced incontinence. The stimulation was applied using needle electrodes to the posterior tibial nerve in the shank at 20 Hz for 30 minutes per session. Fully 63% of the patients found this helpful and chose to continue the treatment after the formal trial ended. The recent work builds on prior work done by a now-defunct company called Urosurge.

Another class of interventions that fits under some definitions of brain stimulation is that of devices that employ very low-level electrical stimulation. These are basically TENS devices operating at very low amplitude. They are known as MENS (microcurrent electrical neuromuscular stimulator) or tLVMAS (transcutaneous low-voltage microamperage stimulation). There are really no reliable studies regarding their efficacy in any conditions. They are likely to be generally safe, however. They are also used occasionally to promote bone regeneration or other forms of healing.
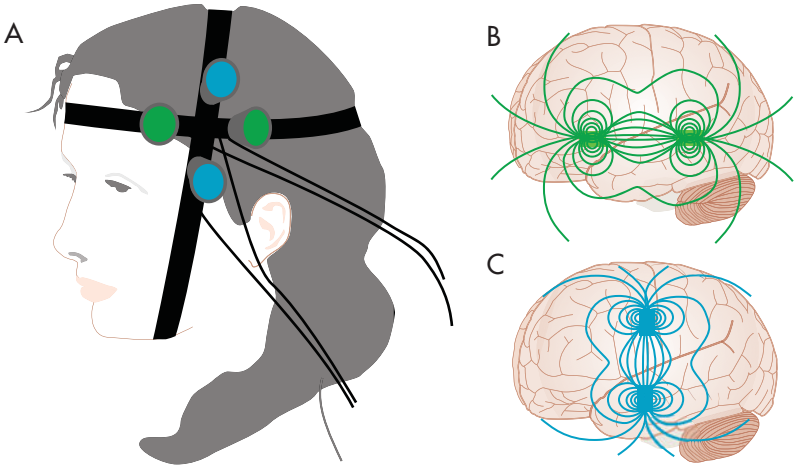
FIGURE 9–3.   Shakti device.

The 8-coil Shakti device consists of four magnets strapped to each side of the head (A). The magnetic signal alternates between the green and the blue, which generates different magnetic fields over the brain (B and C). This device is promoted as enhancing religious experiences, although there are no large clinical trials.

One-Stop Shopping

Some clinicians have fantasized about stimulating and scanning the brain at the same time. After all, the powerful magnetic fields generated during a magnetic resonance imaging (MRI) scan actually produce "zingers" or sharp electrical pains around the arms in some patients. Could an MRI scan also stimulate the brain? Perry Renshaw and colleagues while at MacLean Hospital in Boston noted that their bipolar depressed patients reported improved mood after undergoing MRI brain scanning as part of a study (Rohan et al. 2004), in which they used a special MRI technique, echoplanar functional MRI (EPI-fMRI). A follow-up animal study replicated the findings. Only more studies will tell whether patients can be scanned and treated at the same time using a single device.

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Appendix by Disease

Disease	Class 1 evidence of therapeutic benefit	Some data, but not convincing evidence
Anxiety		CES, TMS, VNS, electroacupuncture
Catatonia		ECT
Depression	ECT, TMS	DBS, VNS, CES, EPI-fMRI, MST, tDCS
Dystonia		DBS
Epilepsy	VNS	DBS, TMS, ECT
Headache		TMS
Incontinence	SNS, PTNS	
Mania	ECT	
Muscle rehabilitation		MENS, tLVMAS
Pain, acute	TMS	
Pain, chronic		CBS, electroacupuncture
Parkinson's disease	DBS	ECT, TMS, tDCS
Schizophrenia		TMS, ECT

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Appendix by Stimulation Method

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