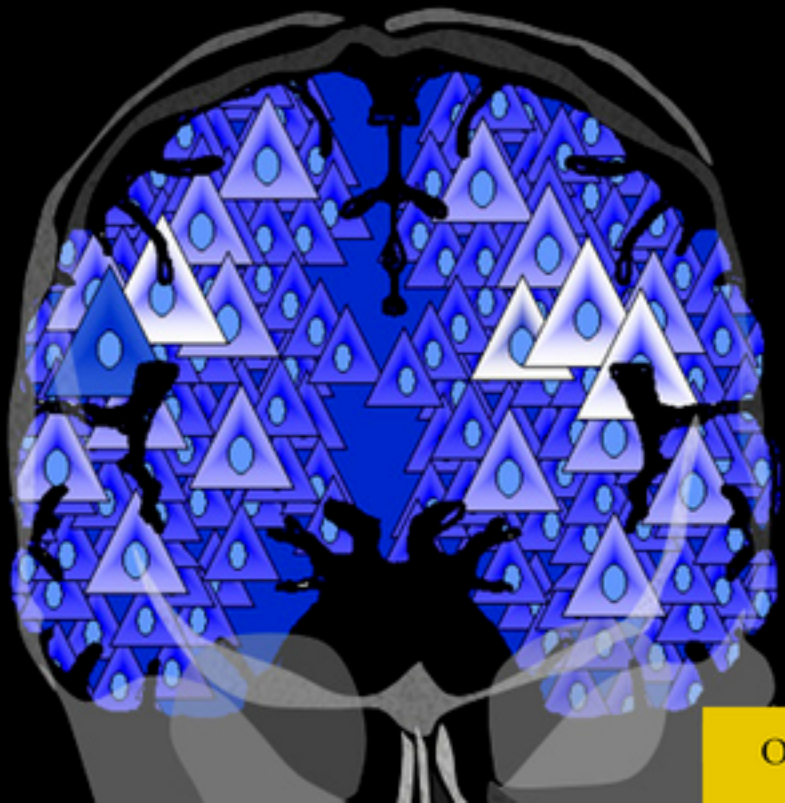
INTRAOPERATIVE NEUROPHYSIOLOGICAL MONITORING FOR DEEP BRAIN STIMULATION

Principles, Practice, and Cases

ERWIN B. MONTGOMERY, JR



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Erwin B. Montgomery Jr., MD

Medical Director
Greenville Neuromodulation Center

The Greenville Neuromodulation Scholar in Neuroscience and Philosophy
Thiel College

Greenville, PA

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To Lyn Turkstra, my love and partner in all things, and
Gary I. Allen, who taught me to listen to neurons.

CONTENTS

PREFACE

A remarkable therapy, deep brain stimulation (DBS) has helped many thousands of patients who, other therapies having failed them, otherwise faced great hardship. Numerous neurological and psychiatric disorders are amenable to DBS, and many more promise to become so. Reasons exist as to why this amenability is increasing.

The brain is essentially an electrical device. Within it resides neurotransmitters that convey information between neurons. Neurotransmitters are the messenger and not the message. The conveyance of information is accomplished by virtue of their use rather than any inherent property. Specifically, spatial and temporal patterns of neurotransmitter release, which are ultimately determined by the neurons' electrical activities, convey information. Neurotransmitters are like electrons flowing through the computer: Nothing inherent to an individual electron perforce implies information. Like electrons in action in computer circuits, patterns and pulses determine neuronal operations. If a computer fails, one does not simply lift the lid and dump a bunch of electrons onto the computer motherboard. Deep brain stimulation targets neurons' electrical activities.

The spatial and temporal specificity of DBS admits of few pharmacological equivalents, its accuracy and precision in some regions of application currently measured in sub-millimeter units. Thus, the spatial and temporal resolution of information processed in the brain is on the order of sub-millimeters and milliseconds. Whereas pharmacological agents act over the whole brain, at least over wide areas with similar neurotransmitter receptors, and act on the order of hours.

None of this is meant to denigrate neuropharmacology. Indeed, further research in neuropharmacology and its foundational sciences is sorely needed. Because it has its basis in neurotransmitter physiology, neuropharmacology will continue to prove quite effective in treating a wide range of neurological and psychiatric disorders. Though medications may produce many more side effects than does DBS, and do so more frequently, their reversibility recommends them over surgical therapies. Yet, the

fact remains that an increasing number of patients will need DBS as pharmacological approaches fail to produce desired benefits. The number of centers offering DBS will therefore increase to meet this need.

Clinical success of DBS depends on accurate placement of leads, which house the electrical contacts for stimulation. The ability to change the patterns of electrodes used for stimulation and the various properties of the stimulation—frequency of stimulation pulses, pulse width, current, and voltage—offer means of tailoring DBS to each patient's unique anatomy in the vicinity of the DBS leads. Misplacement by even a millimeter, however, spells the difference between success and failure.

Thanks to remarkable advances in image-based surgical navigation, DBS surgery has become safer and easier. Targets never actually seen directly by the surgeon may be reached by aid of current technology, which is capable of placing DBS leads with precision and accuracy on the order of a millimeter. The critical question becomes how the target is "seen," if not by the unaided eye, then by some other method, such as magnetic resonance imaging (MRI) or other imaging techniques. However, effectiveness depends on whether the target "contrasts" with its neighbors in terms of the physics underlying the imaging.

In a way, the very terms used in DBS confuse the issue. For example, one speaks of DBS of the subthalamic nucleus (STN), which presumes or implies that it is stimulation of the STN that actually provides the therapeutic benefit. Consequently, one only has to be able to see the STN, relative to its neighbors, to successfully direct the DBS lead to the target. However, this is false on several accounts. First, it is not the STN that is the target of STN DBS. Rather it is the sensorimotor region of the STN with the limbic and associative regions of the STN avoided. Current MRI and other imaging methods cannot visualize these other regions in the STN. Consequently, there is no contrast detectable by these methods that differentiate the sensorimotor region from the limbic and associative regions. When the descriptive term is DBS of the sensorimotor region of the STN, or the sensorimotor region of the globus pallidus interna or the arm region of the ventral intermediate nucleus, the issues regarding targeting become more realistic.

Even with the clarifying specification of DBS of the sensorimotor STN, misunderstanding can be conveyed. For example, it is not clear that actually stimulating neurons in the sensorimotor region of the STN is responsible for the therapeutic benefit. Rather, there is evidence that stimulation of the cortical projections to or in the vicinity of the sensorimotor neurons of the STN is critical to the therapeutic mechanisms. Thus, one might better speak of DBS of the axons in the vicinity of the STN. At the least, this is a more honest expression of the current state of knowledge and does not

have the effect of reinforcing misplaced presumptions. Paraphrasing Claude Bernard, father of modern physiology, "we are more often fooled by things we think we know than things we do not."

The problem becomes, then, one of context; a target deemed optimal for radiological purposes may not be optimal for clinical purposes. For this reason, surgeons rely on additional means of determining the best target. The earliest days of stereotactic functional neurosurgery involving electrocautery or radio-frequency lesioning saw employment of stimulation through the lesioning electrode and other electrophysiological means of assuring best targeting. Cases in which test stimulation through the lesioning electrode confer observable benefit serve to bolster a surgeon's confidence that future lesioning will meet with success and reduced risk.

Microelectrode and semi-microelectrode recordings of extracellular action potentials generated by neurons, local field potentials, test stimulation through the DBS leads—the range of electophysiological means of identifying the optimal DBS target are numerous and varied. Nearly every surgeon uses test stimulation through the DBS leads. Thus, whatever opinion one has of other forms of electrophysiological studies, she must understand fully test stimulation through DBS leads. Many, if not most, surgeons and neurologists appreciate the importance of supplementing excellent image-guidance and DBS test stimulation with additional neurophysiological methods. In one study of 144 STN DBS surgeries, for example, 30% of cases required more than one trajectory of microelectrode recordings, because the initial image-guided trajectories failed to meet the criteria for a physiologically defined optimal target (Montgomery 2012). This observation suggests that imaging alone proved insufficient.

Failure to encounter the physiologically defined optimal target in the image-guided trajectory, for example determined by microelectrode, semi-microelectrode recordings, or DBS test stimulation, leaves the intraoperative neurophysiologist wondering in which direction and distance she ought to move the microelectrode, semi-microelectrode or DBS lead. Image guidance brings her no closer to that decision. The development of MRI and CT and other intraoperative imaging may be of aid, but whether they will supplant electrophysiology based studies remains uncertain. Only electrophysiological means employed interoperatively provide an answer. It thus behooves those involved in DBS lead-placement surgery to gain expertise in electrophysiology based methods even if just for intraoperative DBS test stimulation. All of these methods are based on fundamental properties of biophysics, electricity, and electronics.

The development of turnkey commercial systems for intraoperative neurophysiological monitoring has been both a boon and bane; these systems may leave one with

the impression that intraoperative neurophysiological monitoring is routine, when it is anything but. In the abovementioned study 30% of participants needed two or more microelectrode recording trajectories to locate the target. One must therefore acquire a measure of expertise in order to determine whether the microelectrode trajectory is acceptable. If she deems it unacceptable, then she must know the fundamental principles of neurophysiology and neuroanatomy to help her to decide her next course of action. This presupposes that she will be able to identify whether intraoperative neurophysiological monitoring systems work properly, without artifact and electrical noise, to guide her. Distinguishing artifact and noise, as a preliminary to removing them, requires advanced knowledge of biophysics, electricity, and electronics.

The present writing endeavors to maximize the probability of excellent outcomes in DBS. Yet one seldom gains expertise solely by reading, no matter how expert the text in question may be. Those already engaged in intraoperative neurophysiological monitoring for DBS will find in this book ample material for ongoing discussions. Those planning to engage in intraoperative neurophysiological monitoring—or in any other diagnostic or therapeutic method based on electrophysiology, for that matter—may regard this book as a primer.

Many chapters repeat certain material (the chapters related to specific DBS targets, for example). This repetition is wholly intentional; certain chapters are intended to serve as stand-alone references.

Algorithms also appear in this book. These help the reader to interpret the information obtained from microelectrode recordings and other intraoperative neurophysiological monitoring. The reader should regard these algorithms as assisting rather than dictating the intraoperative neurophysiologist and surgeon's respective actions. Because no algorithm anticipates every individual patient's circumstances, intraoperative neurophysiologists and surgeons bear responsibility for how they apply any information herein to their patients' care.

Every attempt has been made to provide evidence and reason for the various algorithms, procedures, and claims made. However, this is not to claim that every claim or suggestion has been subjected to randomized controlled prospective investigation, nor could they. One could take this lack of evidence-based medicine level 1 evidence as an excuse to dismiss the claims and recommendations or to hold that in the absence of level 1 evidence one has license to do as one chooses. This would be an exercise in solipsism (see http://ReasonBasedMedicineAndScience.com) and would not be in the best interests of patients or advancing DBS therapies. The current state of affairs is that no two surgeons perform DBS implantation surgeries exactly the same. The high degree of variability leads to the question whether all of the different techniques cannot be the

best or whether the differences matter little in the outcome. These important questions cannot be resolved if each surgical team isolates themselves by avoiding discussion and debate. While many readers may disagree with the claims and recommendations offered here, it is hoped that this will be an invitation to discussion and debate that is widely accepted.

The book presents a number of actual cases. Each case's intraoperative microelectrode recordings appear as they did in the operating room at the time they were made. Interpretive commentary follows the presentation of microelectrode recordings for each trajectory. Finally, there appear postoperative imaging studies that demonstrate the monitoring results, some of which may contain errors or complications. The author included these errors and complications because he believes that one often learns more from failure than success. The reader should not gather from these inclusions that complications happen frequently. Provided one follows proper surgical techniques, taking care especially to prevent brain shift from air entering the skull, complications occur but rarely.

Indeed, DBS has met with such remarkable success that it risks leaving one with the impression that the procedure is easy. Most of the time, the procedure goes smoothly and brings the patient the desired benefit. The value in extended experience-based training of intraoperative neurophysiologists owes to those rare moments when the procedure meets with complication and the neurophysiologist's mettle is tested. For this reason, the author recommends that a training period comprise ten surgeries of each type of DBS; it affords the trainee opportunity to gain experience in difficult cases.

This author's own training would have been impossible were it not for the many others whose fellowship inspired, enlightened, and encouraged him. Among them is Dr. Gary I. Allen, under whose guidance this author first eavesdropped, via microelectrode recordings, on the incredible "conversations" neurons have with each other. Dr. Allen sacrificed many evenings to mentoring the author, including the evening of his tenth wedding anniversary. The kindness Dr. Allen showed is difficult to repay, but is just as difficult to forget.

This author owes a debt to the following individuals: Dr. Lyn Turkstra, whose love and support through years of marriage have sustained him; Steven Buchholz, who collaborated with him in early studies of neuronal activities in the basal ganglia–thalamic-cortical system in nonhuman primates; Drs. Doug Stuart and Thomas Hixon, who advised and protected his research; Dr. John Gale, former technician and now colleague and friend, whose uncommon enthusiasm recharges this author's intellectual "batteries" whenever they run low; He Huang, who began his association with this author as a computer programmer but over the years has become an excellent fellow

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Erwin B. Montgomery Jr., MD

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/// 1 /// IMPORTANCE OF INTRAOPERATIVE NEUROPHYSIOLOGICAL MONITORING

INTRODUCTION

An evolving therapy for neurological and psychiatric disorders, Deep Brain Stimulation (DBS) succeeds where all manner of medications and brain transplants fail. Though currently in an early stage of development, gene therapy has yet to match DBS's benefits, which outstrip those of the best medical therapy. In addition to the risks attending DBS surgery, the difficult task of placing the stimulation electrodes accurately and precisely means a premium attaches to getting it right the first time.

Not at all a foregone conclusion, precise and accurate placement of stimulating electrodes remains the subject of ongoing debate. The diverse methods employed by physicians share a common element, namely, use of some manner of neurophysiological monitoring in the operating room, if for no other reason than to confirm the absence of adverse effects.

Experience and the present state of technology have led this author to favor the use of microelectrode recordings for optimal placement of DBS leads, which house the stimulating electrodes for therapy. Yet this preference does not diminish the continued importance of macrostimulation through the DBS lead, a form of intraoperative neurophysiological monitoring that all physicians utilize to some extent. By discussing both microelectrode recordings and macrostimulation through the DBS lead, the author hopes to make his book useful to physicians partial to either method.

THE GROWING IMPORTANCE OF DEEP BRAIN STIMULATION AND INTRAOPERATIVE NEUROPHYSIOLOGICAL MONITORING

The best outcome possible for patients guides the purpose of intraoperative neurophysiological monitoring, and the best outcome depends on proper placement of DBS leads, which neurophysiological monitoring helps to ensure. Intraoperative neurophysiological monitoring admits of several techniques: microelectrode recordings for purposes of identifying and analyzing extracellular action potentials; electrical stimulation via the microelectrode (microstimulation); local field-potential recordings via macroelectrodes (DBS leads, for example); and macrostimulation via DBS leads or the indifferent electrode in some bipolar microelectrodes. This book discusses each technique.

Though these techniques differ in terms of the roles they play in identifying the clinically optimal stimulation target, their effectiveness depends on a single factor: an understanding of the biophysical properties, physiological characteristics, electronics, and regional anatomies of structures surrounding DBS targets. This book focuses on providing such an understanding.

Intraoperative microelectrode recordings of extracellular action potentials generated by neurons, which have assisted surgical procedures for decades, were initially made before lesioning (ablating) the target structure. The diminution of benefit over time and the significant risk to speech and swallowing consigned these surgical procedures to rare use. Early in its development, DBS reduced these risks, and surgical procedures came to enjoy a revival as various movement disorders and psychiatric conditions recommended themselves for such intervention. As the number of eligible patients has increased, the need for persons trained in intraoperative neurophysiological monitoring has also increased.

That for many disorders DBS surpasses the best medical therapies owes to its remarkable effectiveness. Early in its development, DBS brought relief to patients who faced surgery because all other reasonable medical and psychological therapies had failed. So impressively has DBS succeeded, in fact, that the US Food and Drug Administration (FDA) has approved it for the following notable indications: Parkinson's disease (unilateral thalamic); essential tremor (unilateral thalamic); primary dystonia in patients aged seven years or more; and obsessive-compulsive disorder (via a humanitarian device exemption [HDE]). A number of "off-label" uses have come to be considered standard and accepted therapy for the following notable conditions: Parkinson's disease (bilateral thalamic); essential tremor (bilateral thalamic); Tourette's syndrome; secondary dystonia owing to perinatal injury; tardive dystonia; tardive dyskinesia; Huntington's disease; and multiple sclerosis. Also underway are clinical trials of DBS in

the treatment of epilepsy, depression, Alzheimer's disease, tinnitus, and stroke, among others. The vast number of therapeutic applications—actual and potential—augurs a substantial increase in the need for intraoperative neurophysiological monitoring.

Randomized controlled trials pitting DBS against the best medical therapies in Parkinson's disease have shown that patients undergoing the former experienced greater relief than did patients undergoing the latter, peculiarities in definitions of acute adverse effects related to the former notwithstanding (Weaver, Follett, Stern et al. 2009; Weaver, Follett, Stern et al. 2012). Physicians who treat Parkinson's disease recognize that, with the number of available medications, the number of possible drug combinations has increased exponentially. They therefore confront a question similar to the one epileptologists ask themselves, which is how many anticonvulsants they must prescribe before these drugs' benefits grow fewer than those to be gained from surgery. Epileptologists realize that, whether tested alone or in combination with other drugs, a new medication faces a long trial period—a period, one hastens to add, during which patients continue to face uncontrolled seizures, mounting side effects from currently prescribed medications, and other risks. Compounding the epileptologist's dilemma is the fact that, though a degree of risk attends many surgical procedures, they can cure certain patients. A similar dilemma confronts neurologists and psychiatrists in treating disorders amenable to DBS.

DEEP BRAIN STIMULATION'S FUNDAMENTAL DIFFERENCE FROM PHARMACOLOGICAL THERAPIES

Fundamentally different from, and therefore an important supplement to, available pharmacological treatment, DBS represents a sea change in therapeutics for neurological and psychiatric disorders. The difference lies in the specificity of action at particular spatial and temporal scales. Though pharmacological treatments, whose risks relative to surgery are modest, ought to endure as the initial treatment option, DBS does possess unique virtues enough to win it appreciation in its own right. As this appreciation grows, so grows the need for intraoperative neurophysiological monitoring and for future basic, translational and clinical DBS-related research.

Increasingly, neurological and psychiatric disorders are being appreciated as the consequence of misinformation rather than excess or insufficient neuronal activity. This means that most neurological and psychiatric disorders result from worsening of the signal-to-noise ratio, misinformation, or other reduced or degraded information. The question then becomes how potential therapies affect changes in the misinformation. The basis for most pharmacological treatments, neurotransmitters do not constitute

messages; they are the messengers whose message originates by other means. Patterns of intraneuronal and interneuronal electrical activity mediate information in the brain. Though neurotransmitters form the basis for most interneuronal communication (gap junctions are the exception), viewing such communication as owing solely to the flux of neurotransmitters represents an instance of the commission of a particular error in reasoning, essentially reductionist in nature, that is characterized by one's deeming a quality or function of a part as applying also to the whole. This error, known as the mereological fallacy, can lead to a loss of knowledge. Reducing brain function to neurotransmitter levels and neuropathophysiology to the relative excess or deficiency in the quantity of neurotransmitters (the so-called neurohumoral paradigm) risks missing the complexity and thus, the most relevant level of analysis and intervention. For the same reason that one cannot infer from an electron the function of a computer or a telephone, one cannot infer from the chemical nature of dopamine its function in the brain or the effects of its diminishment, as happens with Parkinson's disease.

Electrical activity occurs in neurons and between them, and this activity from other neurons converges in the next neurons' dendrites, cell bodies, and, in some cases, axo-axonal connections. From the pattern of convergence within a neuron then results a pattern of extracellular action potentials that are transmitted down axons to make contact on subsequent neurons at the synapse. The pattern of electrical activity that reaches the synapse contains the information and determines the pattern of neurotransmitter release. The information is not inherent in the neurotransmitter but in the pattern of neurotransmitter release. The applications of neurotransmitters (or agents that block neurotransmitters) without regard to the temporal dynamics at the time scales of electrical activities within neurons is not likely to replicate and restore normal physiology. Deep brain stimulation acts at the level of the electrical patterns within and between neurons.

Deep brain stimulation enjoys over most pharmacological approaches a significant advantage in terms of spatial or anatomical specificity of action. Because most pharmacological agents depend on specific types of neurotransmitter receptors, the selectivity of action for the pharmacological agent depends on the receptors' spatial or anatomical distribution, which, in the case of most brain neurotransmitters, is wide. Side effects occur when neurotransmitter replicants (agonists) or blockers (antagonists) reach receptors occupying areas outside the desired targets. Dopamine receptors in the motor areas of the caudate nucleus and striatum, for example, probably mediate the therapeutic effect of dopaminergic agents in the treatment of the motor symptoms of Parkinson's disease. Thus, it is likely that many psychological and cognitive DBS side effects proceed from two phenomena: (1) stimulation of dopamine receptors

in areas that interact with the limbic and cognitive systems and (2) inadvertent activation of dopamine receptors in the cortical and limbic systems. The vastly smaller volume of tissue affected by DBS (approximately 2.5 mm in radius) may account for the fewer long-term adverse events observed in patients with Parkinson's disease who underwent DBS than in those who received best medical therapy (Weaver, Follett, Stern et al. 2009).

Remarkable advances in pharmacology made since the mid-twentieth century have benefited countless patients. Remarkable advances in pharmacological treatments for Parkinson's disease, particularly, have benefited countless neuroscientists. These advances led to the development of theories of pathophysiology that assign critical significance to neurotransmitters—the theory of cholinergic/dopaminergic imbalance popular in the 1970s, for example. The current theory of globus pallidus interna overactivity as causal to Parkinson's disease rests on a fundamentally pharmacological notion. The fact that neurotransmitter function–based pharmacological therapies met with considerable success conceals the post hoc nature of the undergirding reasoning, which proceeds from an incorrect inference, drawn from improvements observed in a variety of neurological and psychiatric disorders.

The ad hoc reasoning undergirding pharmacological theories of pathology has subtending it a second error in reasoning that instances what is known as the fallacy of pseudotransitivity. In the 1920s scientists applied acetylcholine to an isolated heart preparation, which slowed the heart rate just as electrical stimulation of the vagus nerve did. From these phenomena scientists drew the inference, which subsequent research validated, that acetylcholine must mediate the effects of the vagus nerve (Valenstein 2005). Again, such validation obscures the fact that the inference as to synonymity between neurotransmitters and neuronal activity rests on a fallacy—in this case, the fallacy of pseudotransitivity—which assumes the following formal expression: *If a implies c and b implies c, then a implies b*. Though stimulation of the vagal nerve (*a*) slows the heartbeat (*c*) and the application of acetylcholine (*b*) slows the heartbeat (*c*), it does not *necessarily* follow that electrical stimulation of the vagus nerve (*a*) implies acetylcholine (*b*). Happily, subsequent research demonstrated acetylcholine as the neurotransmitter of the vagus nerve. Thus, the fallacy employed served a constructive role in providing the hypothesis, subsequently demonstrated, but it would have been a disservice had the fallacy been taken as evidence or fact.

Though fallacious, the inference linking heart rate to the mediating effects of acetylcholine led to the development of a reasonable hypothesis that, once validated, advanced knowledge of acetylcholine and the vagus nerve. Yet there followed also an adverse consequence: From phenomena observed in the specific vagus

nerve–acetylcholine instance scientists derived the notion that one can explain all brain function in terms of neurotransmitters. Whatever success realized in that instance fails to translate to other situations. Dopamine replenishment, by medication or cell transplants, in brains of patients with Parkinson's disease often brings about no improvement in symptoms (Olanow, Goetz, Kordower et al. 2003). A nonpharmacological therapy, DBS succeeds in this respect, thus putting paid to the notion that neurotransmitters govern all brain function.

Understanding how DBS differs from pharmacological therapies depends on understanding the former's mechanisms of action. One notes two peculiar qualities of DBS's therapeutic effects: (1) they bear no relation to dopamine levels in the brain (Hilker, Voges, Ghaemi et al. 2003) and (2) they bear no relation to injected electrical charge alone but to the latter in combination with the timing of its pulse (Montgomery 2005). Attesting to the importance of timing is the fact that in some patients with Parkinson's disease DBS at 130 pulses per second (pps) proves effective, while DBS at 100 pps does not. A mere three milliseconds (3/1000 of a second) difference in the duration between electrical pulses, this difference makes all the difference and it offers a sense of the time scales at which DBS operates. Coupled with the importance of timing is that of dynamics (changes in state over time). Failure to account for dynamics explains the inadequacy of the neurohumoral paradigm informing current pharmacological and neurohumoral approaches as described above. On the order of 100 ms, the time course of dopamine release in the basal ganglia as represented by the discharge patterns of dopamine neurons in the substantia nigra pars compacta (Figure 1.1), for example, contrasts dramatically with the time course of the action of dopaminergic agents in the pharmacological treatment of patients with Parkinson's disease.

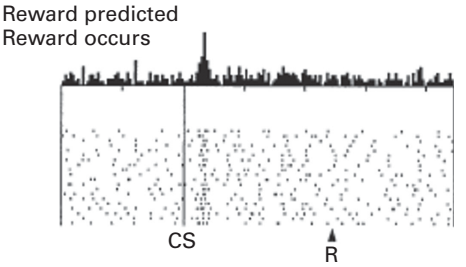

FIGURE 1.1 Raster and histogram, recorded over the time course of a behavior, of a dopamine neuron residing in the substantia nigra pars compacta of a nonhuman primate. The raster in the bottom of the figure shows a row for each trial of the task. Each dot represents the discharge of the dopamine neuron. The top graph shows the number of spikes at each bin of time summed across trials. CS is the condition stimulus that predicts a reward (R). One notes a large increase in the activity of the dopamine neuron related to the CS. The time course of the dopamine release is on the order of 100 ms (Schultz 1998).

IMPORTANCE OF TARGET LOCALIZATION AND THE ROLE OF INTRAOPERATIVE NEUROPHYSIOLOGICAL MONITORING

Though it would seem trivially obvious that the success of DBS depends on stimulating the correct target, the demands of the accurate placement of the DBS lead make the matter anything but trivial. Indeed, the complexity of stimulation of the desired targets and the avoidance of undesired targets places marked constraints on the methods available to achieve the necessary accuracy.

Some 13 mm in length and 6 mm in width, and roughly the shape of an American football, the subthalamic nucleus presents a small target (Yelnik and Percheron 1979). The challenge of reaching such a small target is compounded by the fact that a particular region of the subthalamic nucleus must be reached (Figure 1.2). This true target, the sensorimotor region, occupies approximately half of the subthalamus (Figure 1.3) and thus effectively doubles the accuracy requirements. Stimulation of other portions of the subthalamic nucleus having connections to the limbic system, the prefrontal cortex, and the orbital frontal cortex can result in significant mood and cognitive problems. Knowing the location of the sensorimotor region within the subthalamic nucleus is therefore imperative. Similarly, the posterior limb of the internal capsule, which occupies a lateral, anterior, and ventral position vis-à-vis the subthalamic nucleus, can experience tonic muscular contraction if stimulated. Posterior to the subthalamic nucleus lies the ascending medial lemniscus, the inadvertent stimulation

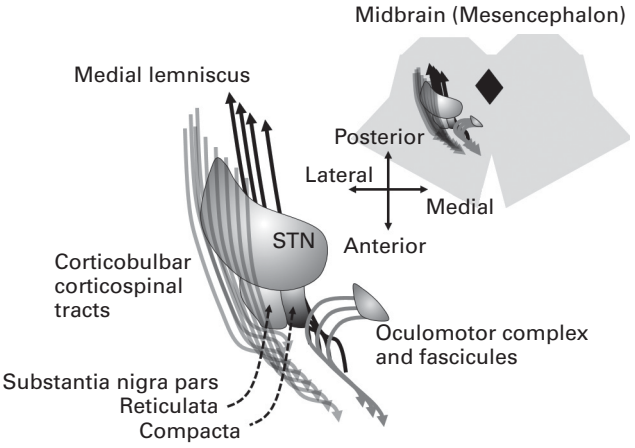

FIGURE 1.2 Schematic representation of the regional anatomy of the subthalamic nucleus through the midbrain (mesencephalon). The subthalamic nucleus (STN) lies above the substantia nigra pars reticulata and compacta with the reticulata lying more laterally. The corticobulbar and corticospinal tracts run lateral, anterior, and ventral to the STN, and the medial lemniscus fibers run posteriorly. The oculomotor complex with its exiting fascicles is medial.

FIGURE 1.3 Schematic representation of the spatial accuracy and precision required for DBS of the subthalamic nucleus. Shown is a sagittal section showing the subthalamic nucleus (indicated by tip of the ballpoint pen). The actual target for stimulation, the sensorimotor region, lies in the subthalamic nucleus. The size of the sensorimotor region relative to the tip of a ballpoint pen offers an idea of the accuracy required.

of which by suboptimal currents may result in intolerable side effects. Medial to the subthalamic nucleus lie nerve fascicules (roots) of the oculomotor nerve. Stimulation of these can produce double vision. The region of the brain physicians must navigate to place DBS leads is not only exceedingly small but also fraught with difficulties.

The methods one can use to identify the actual target depend on whether one can distinguish the target from other regions that, as a consequence of their proximity, DBS may inadvertently affect. One approach rests on the fact that such white-matter structures as the posterior limb of the internal capsule and the medial lemniscus differ from such gray matter structures as the subthalamic nucleus in terms of proton density, radiodensity, and electrical resistivity. Thus, one can differentiate these structures by use of magnetic resonance imaging (MRI), computerized tomography (CT scan), and measurements of electrical impedance, respectively. In their present form, however, none of these methods can differentiate areas within a gray-matter structure. Whether employed preoperatively or intraoperatively, these methods also cannot differentiate the sensorimotor region within the subthalamic nucleus from those parts within the subthalamic nucleus where inadvertent stimulation could produce serious side effects, such as regions projecting to the limbic and frontal cortical systems. At best, currently, these methods only identify the neighbors to the target and not the actual target. Microelectrode and semi-microelectrodes specifically identify the

sensorimotor regions and consequently define the optimal target. The question that must be addressed by those who do not use microelectrode or semi-microelectrode recordings is whether identifying the neighbor is sufficient.

The same issues apply to DBS surgery for the thalamus and the globus pallidus interna. The methods described above do not differentiate the ventral intermediate nucleus of the thalamus (the DBS target) from any of the nuclei of the ventral and lateral region of the thalamus. Similarly, these methods do not differentiate the sensorimotor region of the globus pallidus interna from nonmotor regions.

Compounding the demands on accuracy is that for some targets merely identifying the sensorimotor region is insufficient. Rather, one must identify specific homuncular (body) representations within the sensorimotor regions (Figure 1.4). Thalamic DBS

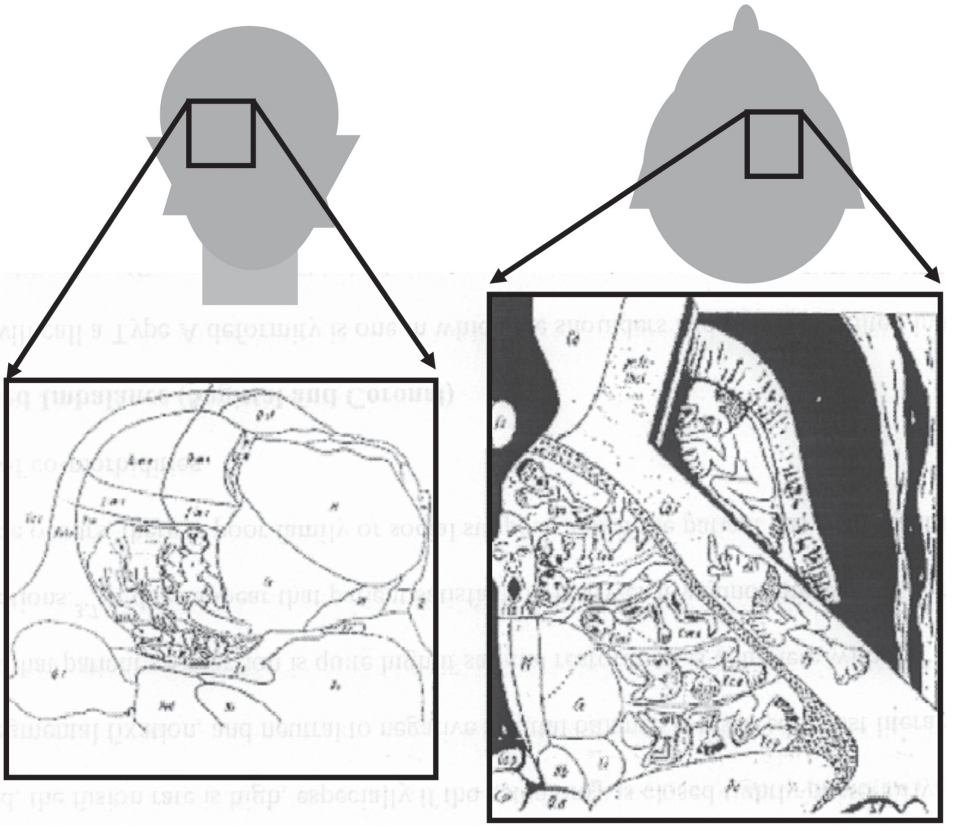

FIGURE 1.4 Sensorimotor anatomy (homunculus) of the ventral intermediate nucleus of the thalamus. The view of the coronal plane, to the left, shows the homuncular representation as layers where the lower extremity is lateral and then sweeps ventrally. Just medial and superior is the upper extremity with the head representation the highest. The medial-to-lateral organization also is seen in the axial view. *Source:* Reproduced with permission from Hassler R in Schaltenbrand and Wahren (1977).

presents a useful example. It involves a homuncular representation consisting of the following correspondences: the medial region, the homuncular head; the lateral region, the lower extremity; and the region between, the upper extremity. A DBS lead placed too close to the head region can, once stimulation occurs, increase risk of impaired speech, language, and swallowing ability. This makes identifying the head representation important.

Targeting the upper extremity representation in the thalamus in patients who experience predominantly proximal or distal extremity tremor requires that one distinguish the proximal extremity representation from the distal upper extremity representation. Targeting the distal upper extremity representation brings the DBS lead even closer to the head representation and thus increases the required degree of accuracy. Some patients with predominately lower extremity tremor, such as in primary orthostatic tremor (a variant of Essential tremor), require targeting of the lateral region of the ventral intermediate nucleus. This targeting brings the DBS lead close to the posterior limb of the internal capsule and thus risks causing tonic muscle contraction, which limits therapeutic benefit.

When attempting to assess the clinical response to micro- or macrostimulation, one cannot use the distribution of the reported paresthesias for localization within the homunculus as means of so doing. Studies combining microelectrode recordings with subsequent microstimulation demonstrate the difficulty. Discordant responses are those where the distribution of the paresthesias from microstimulation is not the same as the regions of the body that drive neuronal responses; concordant responses are when there is an overlap. Discordant responses were found in approximately 50% of the stimulated and recorded sites (Grill, Simmons, Cooper et al. 2005). It is possible that the discordant stimulation occurred in axons that, though they pass in the vicinity of the microelectrode, project to a different homuncular representation. The paresthesias would be referred to the homuncular representation being stimulated distant from the site of the stimulation (see Figure 1.5).

A similar situation involves the globus pallidus interna, a structure whose homuncular region covers a larger spatial and anatomical area relative to the effective radius of the volume of tissue activated by DBS. The lower extremity representation is anterior, medial, and dorsal to the head representation, which resides in the posterior, lateral, and inferior region of the globus pallidus interna. The upper extremity representation lies between the two (Figure 1.6). Targeting within the sensorimotor region of the globus pallidus interna thus varies according to the region of the body affected—cervical region from upper or lower extremity segmental dystonia, for example. Figure 1.6 shows the homuncular representation whose spatial extent, which is approximately 2.5 mm, exceeds the usual radius of effective DBS (Butson, Cooper, Henderson et al.

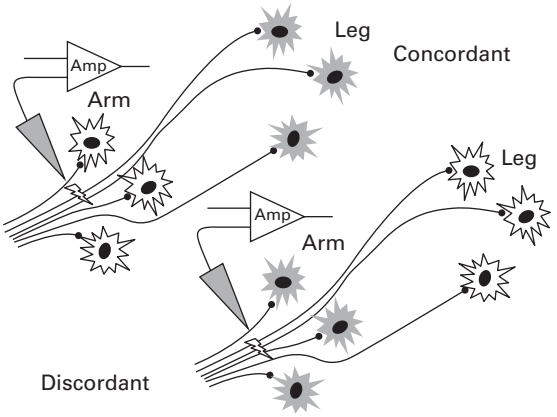

FIGURE 1.5 Possible mechanism of discordant and concordant paresthesias in response to stimulation. In the case of concordant responses, microelectrodes recorded activity changes correlated with movement of the arm but not with movement of the leg. Thus, there is relative certainty that the microelectrode is within the arm homuncular representation. Microstimulation (represented by the spark images) at the same site activates local neurons (white cartoons of neurons). This activation patients experience as paresthesias of the arm. In the discordant response, the microelectrode continues to record changes in neuronal activity with movement of the arm but not with movement of the leg. Hence, the microelectrode is within the arm homuncular representation. However, microstimulation activates axons that pass through the site as they project to the leg representation. Stimulation of these axons as they pass through the arm representation causes paresthesias referred to the leg.

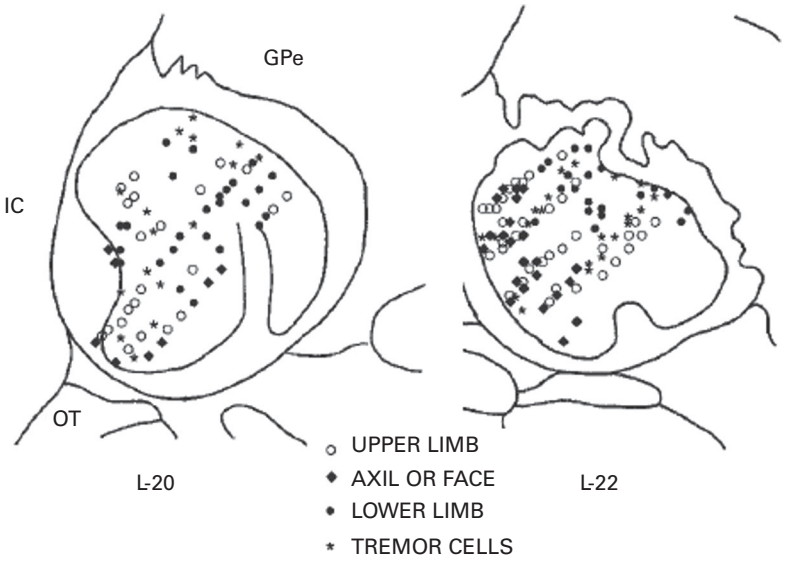

FIGURE 1.6 Sensorimotor anatomy (homunculus) of the globus pallidus interna. One notes a greater number of facial units (filled diamonds) situated posteriorally and laterally (L-22 indicating 22 m lateral to the AC-PC line) relative to 20 mm lateral to the AC-PC line (L-20), and a greater number of lower limb–related units (filled circles) situated medially and anteriorly. Upper extremity–related units (open circles) are interposed between. *Source:* Reproduced with permission from Guridi, Gorospe, Ramos et al. (1999).

2007). Simply by placing the DBS lead into the sensorimotor region of the globus pallidus interna one risks missing the most optimal region in patients with focal or segmental dystonia. The large spatial distribution of the sensorimotor homunculus relative to the volume of tissue activation with DBS presents a problem for patients with hemidystonia or generalized dystonia; a significant percentage of them require placement of multiple DBS leads in order to obtain satisfactory response.

Important also is the trajectory angle of the DBS lead, particularly with respect to the ventral intermediate nucleus of the thalamus (see chapter 11), because if it happens to be tangential rather than parallel to the long axis of the ventral intermediate nucleus of the thalamus, relatively few of the lead's stimulating electrodes may actually enter the ventral intermediate nucleus of the thalamus. Failure to enter this area reduces efficacy. The angle of the long axis of the ventral intermediate nucleus of the thalamus, moreover, may vary considerably relative to the Cartesian coordinate system of the most precise image-guided surgical navigation. As of this writing, no monitoring technique to determine the actual trajectory exists besides microelectrode and semi-microelectrode recording.

Neuroimaging targeting, which is performed prior to opening the patient's skull, complicates the accuracy issue, because the accompanying brain shift increases the former's inherent variability (inaccuracy). That is, it affects the degree of precision required reliably to pinpoint the appropriate target. Microelectrode and semi-microelectrode recordings can compensate for brain shift to some extent; and intraoperative MRI and CT scans, along with other methods, are being developed. But these techniques will not obviate the above-mentioned concerns about identifying sensorimotor regions or their corresponding homunculi. The magnetic field generated by MRI makes its adjunctive use in intraoperative neurophysiological monitoring difficult. Improved surgical techniques that reduce brain shift would also reduce the attractiveness of intraoperative MRI, because it would obviate the need for aided targeting and would therefore only interfere with microelectrode recordings.

THE EPISTEMIC STATUS OF MICROELECTRODE OR SEMI-MICROELECTRODE RECORDINGS

The different methods of intraoperative neurophysiological monitoring being explored—local field recordings made through macroelectrodes, for example, or electroencephalographic evoked potentials from test stimulation produced through DBS leads—are judged in light of the current use and concerns of microelectrode recordings. Many leading centers for DBS surgery make use of microelectrode recordings,

but this hardly means the latter have gained universal acceptance. Indeed, some centers may only make selective use of them, employing them for other targets but not for the ventral intermediate nucleus of the thalamus, for example. Some use a single microelectrode during monitoring and others an array of electrodes.

Most approaches owe to habit—habit acquired by one's own experience or in apprenticeship to a mentor, himself beholden to habit. The understanding underlying these approaches is thus little more than the result of various attempts at post hoc justification. This is apparent in the lack of prospective randomized controlled studies comparing the different forms of intraoperative neurophysiology.

This author maintains that nearly all discussion of intraoperative neurophysiology methodology consists of comparing one method's outcomes to published outcomes of previous studies performed typically by different surgeons and their staff. These studies contain many significant, indeed fatal, flaws. In several studies of DBS implantation surgery, for example, comparison is made between outcomes of surgery eschewing intraoperative neurophysiological microelectrode recordings and outcomes of surgery utilizing them. To the outcomes of either set these studies impute equal success, thus implying that ceteris paribus surgery eschewing intraoperative neurophysiological microelectrode recordings ought to be preferred on the basis of its reduced cost and risk.

Whatever evidence of equivalence discovered by these studies rests on a failure to find a statistically significant difference, a result that may owe less to absence than error. Specifically, the failure may owe to commission of a type II error (oversight of a truly existing difference), an insufficiently small sample size, or a highly variable outcome measure. More appropriate means exist for demonstrating noninferiority (Wellek 2010), but these see little if any use.

At present, no level 1 Evidence-Based Medicine data exist to determine which set of intraoperative neurophysiological monitoring methods necessarily and sufficiently optimizes outcomes. And the foreseeable future holds no promise of any such data coming to light. The question, then, is how to proceed. Physicians should not consider the lack of level 1 Evidence-Based Medicine data as license for nihilism or adventurism; doing so would be to commit the logical error of *argumentum ad ignorantiam*, or arguing from ignorance. The physician must continue to make responsible decisions according to the best available information and knowledge. A misconception prevails that Evidence-Based Medicine is only synonymous with randomized, controlled trials. Yet in its original formulation, Evidence-Based Medicine included expert consensus. Missing from this formulation is, of course, any sense of how best rationally to proceed, because the rationale behind expert consensus goes unstated.

By way of providing a rationale, this author proposes that, in the absence of level 1 Evidence-Based Medicine, one can proceed in a reasonable manner by appealing to fundamental anatomical and physiological principles. These principles, if logically applied, can aid rational consideration and decision-making. For example, a physiologically demonstrated DBS-effect radius of approximately 2.5 mm (discounted for the moment are the electrical inhomogeneities of tissues surrounding the DBS electrodes, which affect the shape of the volume of tissue activation) means that any targeting method must be able to place the DBS electrodes within some distance less than 2.5 mm of the appropriate target or more than 2.5 mm from any structure that when stimulated produces an adverse effect.

If one hews to the principle that the optimal target must be identifiable, his task becomes that of distinguishing optimal from nonoptimal targets. For example, CT scans differentiate structures according to each structure's respective radiodensity. Given this, one must establish whether the optimal target's radiodensity differs from those of nonoptimal, possibly contraindicated structures. Alternatively, establishing this difference may depend on the optimal target's location vis-à-vis other structures or neighbors—its distance from, say, the midpoint of the line connecting the anterior commissure to the posterior commissure. One must also expect that opening the patient's skull can cause the brain to shift and thus cause the optimal target to deviate from the position established preoperatively. The stability of the anterior-posterior intercommissural line's midpoint relative to external landmarks, in other words, becomes the issue.

Unfortunately, there exist no controlled direct comparisons of outcomes for patients who were randomized according to the use or nonuse of intraoperative microelectrode recordings. Difficult for a number of reasons, such studies also pose an ethical problem concerning participation, as well as a practical problem of achieving equipoise sufficient to enable randomization (Fins 2008). Reports have been limited, rather, to those made by physicians who, having forgone use of intraoperative microelectrode recordings, claim to have produced results no different from those presented in published reports by physicians who do use them (Zrinzo, Zrinzo, Tisch et al. 2008). Such claims typically rest on the failure to demonstrate statistically significant differences via standard hypothesis testing. Yet the truth is that the sample size was too small, and for this reason the reports containing them do not permit interpretation (Montgomery 2012). Patients having the same neurosurgeon were never randomized according to their microelectrode recording status. As a result, unfair becomes any comparison made between the results produced by neurosurgeons who make such recordings and the results of the neurosurgeons who do not, because the second category does not

exclude the possibility of better outcomes had the surgeon occupying that category made use of intraoperative microelectrode recordings.

Though imperfect and requiring acceptance of significant assumptions, one study attempts to shed light on the necessity of intraoperative microelectrode recordings by examining the spatial variability of the physiologically defined optimal location in the subthalamic nucleus. The physiologically defined optimal location possesses the following characteristics: it covers at least 5 mm of sensorimotor representation; microstimulation produces in it no adverse effects; and it is attended by improving symptoms in patients with Parkinson's disease. In order to translate the observations of the spatial variability of the physiologically optimal target to clinical meaningfulness, one must assume that the physiologically defined optimal target is a reasonable surrogate for the clinically optimal one. The results indicated that much larger than the volume of tissue activation by DBS was the 99%-confidence volume, that is, the volume of tissue DBS would have to activate in order to include 99% of the physiologically defined optimal target (Montgomery 2012). One therefore one needs to look within the 99%-confidence volume to find the physiologically optimal target for the individual patient (Figure 1.7) and that is best accomplished by microelectrode recordings.

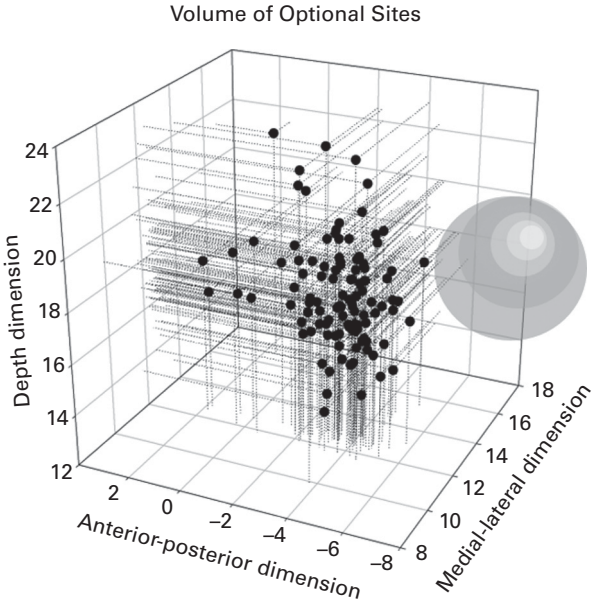

FIGURE 1.7 The volume and distribution of the 99%-confidence volume of the physiologically defined optimal target relative to the midpoint of the line connecting the anterior commissure (AC) and the posterior commissure (PC) in the anterior-posterior and medial-lateral dimensions. The radius was 4.5 mm. The sphere shows the approximate volume of typical tissue activation. *Source:* Modified from (Montgomery 2012).

Some argue that brain shift introduces the greatest variability in the vertical axis, and that one could compensate for this by adjusting the location of the volume of tissue activated by DBS via selection among the electrical contact. Though this assertion does hold some truth, it overlooks the fact that the variability in the plane orthogonal to the DBS lead remains greater than the radius of the volume of tissue activation (Figure 1.8). One thus finds himself obliged to search in the plane orthogonal to the long axis of the DBS lead.

Future developments in functional neuroimaging may allow neurosurgeons to identify the sensorimotor regions and their homuncular representations. These images they would obtain preoperatively and merge with intraoperative MRI and or CT, thereby obviating the need for some forms of intraoperative neurophysiological monitoring. Until such time, however, microelectrode recordings, risks posed notwithstanding, will remain necessary to optimal outcomes.

As this chapter seeks to establish, understanding the principles governing optimization of target localization depends on defining the latter's requirements according to anatomical and physiological principles. For example, one principle rests on the premise that treatment of cervical dystonia, or other dystonia affecting the head, requires activation of the region of the globus pallidus interna specific to the head's function.

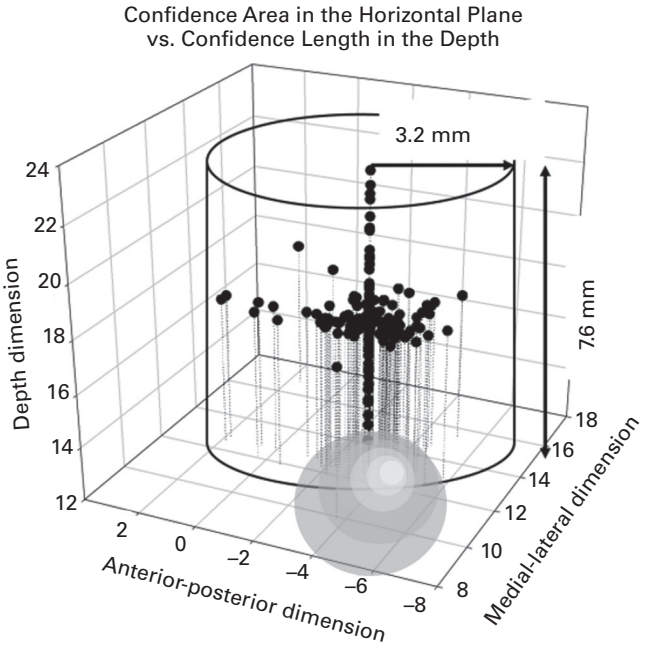

FIGURE 1.8 The area and distribution of the 99%-confidence volume of the physiologically defined optimal target ion viewed in the plane orthogonal to the long axis of the DBS lead and along the long axis of a trajectory for the DBS lead. The sphere shows the approximate volume of typical tissue activation. *Source:* Modified from (Montgomery 2012).

A second premise, which is derived from physiological experience and computational modeling, holds that the volume of tissue activation surrounding a single cathode (negative electrode) is approximately 2.5 mm. A third premise holds that, since the volume of the globus pallidus interna is extremely large relative to the volume of tissue activation by DBS, one must devise some method for identifying the homuncular representation of the head.

Indeed, even level 1 Evidence-Based Medicine data, if they existed, would not relieve one of having to reason from principles. Because they refer to populations and not individual patients, inferences from randomized controlled trials require that one extrapolate to the individual patient (Montgomery and Turkstra 2003), and this requires that she invoke physiological, anatomical, and other principles that exist independently of or do not derive from specific randomized controlled trials. Commitment to individual patient benefits therefore demands that physicians know these fundamental physiological and anatomical principles.

Issues will arise for which exist no data from randomized controlled trials or fundamental principles. Similarly, situations will arise in which principles oppose each other. Such instances and situations nonetheless require that one decide on a way to resolve them. The recommendations made here have evolved with many years' experience and have come to inform the author's practice. The experience of this author alone is not for or against alternatives not addressed. All recommendations in this book the author makes for educational purposes only. He does not intend that they should direct the care of any particular patient. Physicians and healthcare professionals should always base their care decisions on their individual assessment and judgment.

MICROELECTRODE AND SEMI-MICROELECTRODE RECORDINGS

Identifying and analyzing extracellular action potentials arising from individual neurons among a collection of neurons constitutes the primary purpose of microelectrode recordings. Pursuit of this purpose requires use of microelectrodes, such as those made with tungsten or a platinum-iridium alloy metal, whose fine-tip exposures are on the order of 20 microns (μm) and impedance—some 0.6 to 1 megaohms (semi-microelectrodes have impedances less than 0.1 megaohm). The difference between microelectrode recordings and semi-microelectrode recordings turns on the number of neurons whose extracellular action potentials are contained within the electrode recording (Garonzik, Hua, Ohara et al. 2002). The relatively few neurons involved in microelectrode recording allow one to identify the extracellular action potentials from distinct individual neurons and to recognize their individual behaviors, whereas

semi-microelectrode recordings generally do not allow such recognition, because the density of other neurons being recorded causes interference of a sort resembling that which one sees on electromyographic recordings.

The experience of standing in a sports stadium presents a useful example. The roar of the crowd one hears while thus situated is analogous to what one hears with use a semi-microelectrode, and the ability to isolate individual conversations amid the roar is analogous to what use of a microelectrode allows one accomplish. Each use has its advantage. On one hand, the semi-microelectrode's larger tip exposure and lower impedance allow for a larger volume of recording, albeit at a resolution lower than the resolution of which a microelectrode is capable. A semi-microelectrode, therefore, may not allow identification of specific thalamic nuclei or of neurons within a specific homuncular representation, and this places it at a disadvantage (Garonzik, Hua, Ohara et al. 2002). On the other hand, the semi-microelectrode's lower impedance makes it less prone to electromagnetic artifact. (Improvement in the quality of modern amplifiers, however, has reduced this advantage.)

LOCAL FIELD-POTENTIAL RECORDINGS

Because local field-potential recordings are not made for the purpose of identifying extracellular action potentials, their electrical recording characteristics are less demanding. Much larger electrodes—electrical contacts on DBS leads, for example—typically have much lower impedances, and they make contact with, and record from, a larger volume of tissue. This means they cannot record extracellular action potentials. Rather, local field potentials tend to function much like a filter by summing (average) activities over a wider volume of tissue. As such, they require that some phase synchronization occur among the sources of electrical currents being recorded. Two sine waves of equal frequency but opposite phases (Figure 1.9A and B), for instance, begin at zero volts. One initially increases (phase equal to 0 degrees), while the other initially decreases (phase equal to 180 degrees). The sum or average of these two signals would be zero everywhere. If such were the case in local field-potential recording, no signal would result. Two sine waves of equal frequency and phase (Figure 1.9C and D), however, produce a sum that is not zero everywhere. If such were the case in a local field-potential recording, a definite signal would result.

Local field potentials depend on synchronization and positive interactions, that is, interactions whose sum is greater than the constituents (as in Figure 1.9E). Interactions depend on the duration of the signals, which for postsynaptic dendritic potentials are longer—on the order of 10 ms—while extracellular action potentials are shorter: on the order of 1 ms. Multiple and spatially distributed, inputs onto dendrites from the

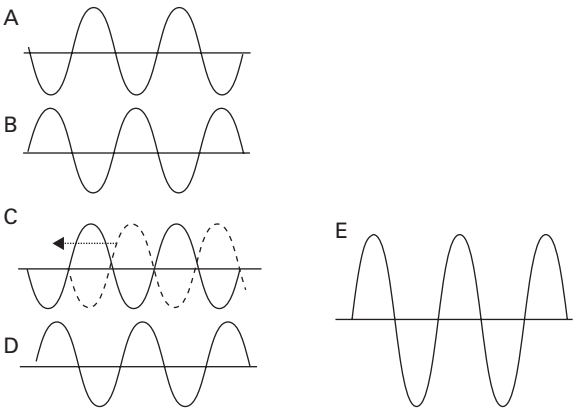

FIGURE 1.9 Schematic representation of the effects of synchronization on the local field potential. A and B show two anti-phase sine waves (phase difference of 180 degrees) that, when added together, render a sum of zero everywhere. Should sine wave A shift into phase (C) (phase difference of 0), the two sine waves (C and D) would combine to produce a larger amplitude sine wave (E). Synchronization of underlying oscillators thus produces positive resonance.

same source tend to result in increased synchronization and increased magnitude of the summed or averaged responses. Local field potentials consequently tend to emphasize presynaptic dendritic inputs over extracellular action potentials representing neuronal outputs.

Local field potentials share with the semi-microelectrode the advantage of recording from a larger volume, which presents few problems with regard to electronics. Yet, local field-potential recording encounters problems regarding spatial resolution. Multipolar recordings (simultaneously recording from multiple electrodes) and other techniques exist that allow one to increase the spatial resolution in such instances where phase reversals in the local field potentials help to localize the source. What remains in question, however, is whether these techniques achieve the needed degree of spatial resolution.

The uniqueness of the local field-potential signal relative to the structures encountered in the electrode trajectory also remains in question. Undoubtedly unique is the pattern of extracellular action potentials in the various structures encountered in the trajectories to the specific DBS targets (chapters 9–11 contain detailed discussion of this uniqueness). It has been suggested that increased beta band–frequency power in the local field potentials correlates with Parkinson's disease. This correlation recommends itself as a useful marker for the clinically optimal target. It remains unclear, however, whether the sensorimotor region emits a unique signal vis-à-vis the nonsensorimotor region. The ability to differentiate the sensorimotor from nonsensorimotor regions of DBS targets perhaps depends on evoked potentials that derive from local field-potential recordings and that are time-locked to behavioral activations.

Those who do not use microelectrode or local field-potential recordings must rely on effects of stimulation—effects of macrostimulation through the DBS lead, typically—to guide their inferences as to optimal location. Situations arise, however, in which the effects, particularly improvements in symptoms indicative of proper placement, are unavailable. Improvement in symptoms with the passage of a recording or stimulating electron through the target is known as a "micro-otomy" effect, such as a micro-subthalamotomy effect in the case of subthalamic DBS, and it occurs prior to or absent any electrical stimulation. Simply passing electrodes through the subthalamic nucleus, for example, can result in remarkable yet temporary improvement of symptoms. Similarly, a micro-subthalamotomy effect can impose a "ceiling" above which subsequent stimulation fails to result in further improvement. When such an effect results, the intraoperative neurophysiologist or neurologist can no longer infer the proper location of the DBS electrode based on symptom improvement; all she can observe are adverse effects. Absent the use of microelectrode or local field potentials, the neurophysiologist or neurologist must relieve any adverse motor effects—tonic contraction owing to the electrical current's spreading to the corticospinal fibers in the posterior limb of the internal capsule, for example—because patients are typically under anesthesia. From occurrence of tonic contraction the neurophysiologist or neurologist can infer a subthalamic DBS lead's too-anterior placement. As to a too-medial or too-posterior placement, however, she remains in the dark.

MICROSTIMULATION

One can accomplish microstimulation by passing an electrical current through a microelectrode. A microelectrode, however, must be sturdy enough to withstand the stimulation effects. Platinum-iridium microelectrodes tend better to withstand stimulation effects than do tungsten ones. Current practice involves constant stimulation with a current of less than 100 microamps. Microstimulation admits of a variety of uses. Some use it to predict the clinical effects of subsequent DBS by using stimulation parameters similar to those used in clinical DBS. Others use it for purpose of identifying the physiological location of the microelectrode.

Extremely small by several orders of magnitude, the volume of tissue activation may render ineffective the use of microstimulation in predicting subsequent clinical DBS effect. Experience with microstimulation in the vicinity of the optic tract in globus pallidus interna DBS surgery suggests that 100 microamps activates a volume of tissue approximately 500 μm in radius (effects of inhomogeneities in the regional tissue resistivity aside), and that subsequent clinical DBS produced

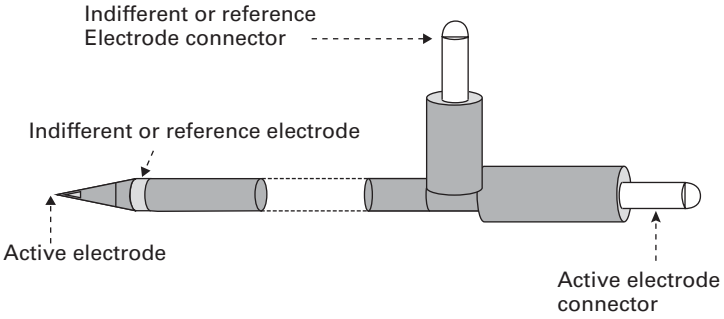

FIGURE 1.10 Schematic representation of a bipolar microelectrode. The active electrode is the tip, and the indifferent electrode is the band of conductive material (typically metal) appearing approximately several mm from the tip.

gratifying benefit, even if microstimulation had failed to do so. This author therefore views with skepticism the use of microstimulation in predicting clinically optimal target sites.

In cases involving use of bipolar microelectrodes (Figure 1.10), stimulation via the indifferent contact becomes possible. Because the contact is larger than other types of contact, it resembles macrostimulation more than it does microstimulation. The large contact area could mean activation of a large tissue volume. Yet, such activation remains unclear as to its prediction of subsequent clinical response.

Microstimulation is also used to drive physiological responses that indicate structures in the vicinity of the microelectrode. Production of paresthesias with microstimulation during subthalamic DBS microelectrode recordings, for example, suggests a trajectory too close to the ascending medial lemniscus and too posterior. When used for this purpose the stimulation parameters characteristic of clinical DBS are not optimally effective. Offering more effective stimulation parameters, high frequencies—on the order of 300 pps, typically—take advantage of temporal summation, a phenomenon in which the effects of each subsequent stimulation pulse build on the lingering effect of the previous stimulation (chapter 8 contains detailed discussion of temporal summation). False localization, which results from stimulation of axons in the vicinity of the target as the microelectrode passes them, confounds microstimulation employed for the purpose of identifying the sensorimotor homunculus (Figure 1.5).

Three issues limit one's using the larger indifferent electrical contact, for example on a bipolar microelectrode, Figure 1.10, to drive physiological responses: (1) the achievement of large-volume tissue activation, though it increases the probability of a physiological response, sacrifices spatial resolution; (2) the position of the indifferent electrode, which is typically several millimeters from the recording tip,

requires that one advance the indifferent electrode to the microelectrode recording site in order to correlate with the latter the effects of microelectrode and semi-microelectrode recordings; and (3) indifferent electrodes vary in size and structure as a result of different manufacturer's specifications, and therefore make necessary some calibration of the effective radius of the volume of tissue activation (chapter 8 contains discussion of this need for calibration).

MACROSTIMULATION

In the context of intraoperative neurophysiological monitoring, macrostimulation typically is performed through the implanted DBS lead by use of stimulation configurations, that is, the arrangement of active cathodes (negative electrical contacts) and anodes (positive electrical contacts). The purpose is to mimic, for purposes of prediction, the results of subsequent clinical DBS. In the course of so doing there arise two challenges: (1) demonstration of efficacy and (2) occurrence of adverse effects.

Important considerations challenge the use of such intraoperative macrostimulation. First, time pressures in the operating room severely constrain the range of electrode configurations and stimulation parameters (the combination of stimulation voltage or current, pulse width, and frequency) that are available for use in testing and relevant to postoperative care. Though the stimulation parameters used in the operating room may prove ineffective, others discovered during the course of subsequent outpatient DBS may produce a satisfactory benefit.

Second, quite a different electrical context may develop during subsequent outpatient clinical DBS than attended DBS in the acute phase. Marked changes in DBS electrode impedances can have a marked effect on the amount of electrical current introduced into the brain via a constant voltage stimulator (Montgomery 2010). For example, changes in interstitial fluids associated with the acute microtrauma—cytotoxic or vasogenic edema, for example—can significantly affect tissue impedance (chapter 8 contains discussion of these effects on tissue impedance).

Capacitance at the electrode-brain interface can also affect the electrical current in the event that an altered stimulation pulse waveform is introduced (chapter 8 contains discussion of these effects). Indeed, the acute changes in impedance described above may affect capacitance as readily as it may affect resistivity (the converse of permittivity) or the dielectric constant determining capacitance. These terms and concepts are explained in detail chapter 3.

Use of constant current stimulation helps to mitigate the effects of changes in impedance and capacitance (see Montgomery, 2010, and the discussion in chapter 3). The primary factor in neuronal activation is the current delivered. Inhomogeneities in the regional resistivity, however, complicate the situation. Specifically, significant distortions in the shape, size, and current densities—which acute changes associated with microtrauma only make more severe—can appear as a consequence of the combinations of gray and white matter present in the vicinity of the stimulation, thus making difficult prognostication from DBS macrostimulation, even in such instances where constant current stimulation is applied. Chapter 12 discusses inferences and clinical judgment concerning particularly the issue of where to move a DBS lead if the original placement produces side effects.

ETHICAL CONCERNS

When making any medical decision, one must weigh the benefits against the risks in the context of alternatives. And, unfortunately, no rubric exists that provides means of deciding each individual patient's case in those terms. Indeed, an already complex medical decision faces further complication at the hands of the physician, who might favor her own ethical convictions over the patient's wishes or the wishes of the patient's family members. These convictions might rest on implicit—perhaps even unacknowledged—biases. One common implicit bias, Omission bias, involves deeming errors of omission worse than errors of commission. The well-known "Runaway Trolley Car dilemma" illustrates this bias in action (Thomson 1976). It involves a situation in which a trolley has gotten free of its driver's control and is speeding downhill toward a group of five unsuspecting pedestrians. There is a switch that can divert the trolley, but there is a single pedestrian on that track who would be killed. A bystander observes that, if she acts quickly, she can save five of the endangered pedestrians; the other one will have to perish. Most persons would pull the lever to throw the switch. Consider another scenario where the agent is standing on a bridge over the tracks. Standing next to her is a large man with a large backpack. The agent knows that if she pushed the large person over the bridge, the large person would land on the tracks, derailing the trolley, saving the five pedestrians but at the death of the large person on the bridge. Most persons would not push the large person off the bridge. The net result, in terms of lives lost, is the same and the agent cannot argue that her actions did not determine the results. Somehow there is something very different about throwing a switch and pushing a large person off the bridge. In some ways, the dilemma described above

plays a role in a physician's approach to DBS. Chapter 14 contains detailed discussion of ethical issues related to intraoperative neurophysiological monitoring.

Whereas the microelectrode's sharp tip cuts tissue in its path, the blunt end of the DBS lead tends to dissect any tissue and push it away. One might conclude from this that microelectrode recording increases the risk of hemorrhagic complications. Though such an assumption is consistent with the author's observation that most hemorrhages occur during the microelectrode's final 25-mm traversal, the length through which the microelectrode moves, this risk must be weighed against the risks of DBS leads' poor placement and need for subsequent surgical revisions.

Subtler risks await patients, physicians, and healthcare professionals after surgery. Patients, physicians, and healthcare professionals experience what is known as the "tyranny of partial improvement," that is, a less-than-expected benefit in cases where the DBS lead was otherwise optimally placed. As with most symptomatic therapies, the potential benefit relates directly to the severity of the symptoms weighed against the probability of success. An improperly placed DBS lead that slightly improves symptoms reduces the potential benefit of a revised and properly placed lead and thus reduces also the likelihood of a misplaced DBS lead's replacement. Compounding this problem is a patient's reluctance to undergo any subsequent surgery. Her confidence shaken, the patient may simply choose to abide the poor results and continue a regimen of medications whose failure led her to seek surgical treatment in the first place.

Physicians and healthcare professionals providing postoperative care may also have their confidence shaken when confronted with less-than-satisfactory responses in patients. While puzzling over these responses, physicians and healthcare professionals might wonder whether they simply did not find the right combination of electrode configurations and stimulation parameters (these combinations number in the thousands) and pursue further programming or did not place the DBS lead in the optimal location (this second error makes future effort and expense incidental to pursuing the desired result unjustified). Physicians and healthcare professionals' confidence in proper DBS lead placement remains highly important. Every effort must be made intraoperatively to ensure this confidence.

Lack of strenuous effort made to ensure such confidence smacks of complacency. Complacency is an ethical issue, and physicians and healthcare professionals bear the responsibility of recognizing and forfending against any risk of slipping into it. Decades of experience with intraoperative neurophysiological monitoring (microelectrode recordings included) and the excellence of many of the devices and systems for intraoperative neurophysiological monitoring together constitute a social

hazard. In the past, most DBS surgeries and their attendant intraoperative neurophysiological monitoring were performed at university-affiliated medical centers primarily by academic clinician-scientists whose already substantial interest in the subject motivated a deeper understanding of methods and the science. Today, an increase in the number of centers offering such surgery and monitoring has led to an increase in the number of patients who stand to benefit, as well as an increase in the responsibility borne by the physicians and healthcare professionals involved. Where scientific and academic interest is lacking ethical obligation must suffice, which means that intraoperative neurophysiologists must gain the expertise of their academic clinician-scientist colleagues. As Alexander Pope wrote in his famous poem "An Essay on Criticism" (1709), "A little learning is a dang'rous thing." Insufficient understanding engenders risk. Preventable problems arise unforeseen. Habit passes for knowledge, and some undesirable outcome goes unrecognized or is dismissed as an anomaly for which the physician bears no responsibility. All of this culminates in the defeat of any effort toward quality control.

Indeed, even when efforts meet with success and little complication, complacency can result. Localization of the physiologically defined optimal target location based on image-guided navigation, for example, is on the order of 70% accurate (Montgomery 2012). Of 144 cases of subthalamic DBS studied, 100 involved instances in which the first trajectory led to the physiologically defined optimal target, as suggested by the image-guided navigation. Though this finding leads one to conclude that more complicated microelectrode recordings could be avoided for a majority of patients, macrostimulation through the DBS lead and other types of intraoperative neurophysiological monitoring should nonetheless be done, because for 30% of patients the image-guided navigation would fail to direct the DBS lead to the physiologically defined optimal target. Admittedly, this analysis cannot ensure that one need necessarily place the DBS lead at the physiologically defined optimal target in order to produce an optimal clinical outcome. The absence of any other predictive measure, however, recommends targeting for the physiologically defined optimal target as a reasonable procedure.

Having established that the initial trajectory, as suggested by image-guided navigation, does not reach the physiologically defined optimal target, and that microstimulation does not produce adverse effects, one must choose her next move. The intraoperative neurophysiological monitoring in the study described above is based on two items: (1) intraoperative microelectrode recordings and (2) an algorithm devised to determine, in cases of errant initial trajectory, the target's probable location (Baker, Boulis, Rezai et al. 2004). Of the 44 cases involving an errant initial trajectory, 30 cases

required a single additional pass of the microelectrode, 11 required two, and 2 required three. (One patient was excluded because an intraoperative hematoma prevented further recordings.)

Reasonably robust, the algorithm used to determine where to search next for the target is based on two items: (1) an understanding of the physiological anatomy in the vicinity of the subthalamic nucleus and (2) the use of microelectrode recordings. Understanding of the regional physiological anatomy thus recommends itself, though it depends on the interpretation of the microelectrode recordings. Only a deep understanding of the making and interpretation of those recordings inspires one to have confidence in them.

Microelectrode recordings may also occasion complacency. Microelectrode recordings must contend with the issue of whether the signal's rising above the background indicates a real extracellular action potential or an artifact. This author's experience has shown him that rare is the case in which this issue does not arise. Indeed, one commonly must modify the electrical environment in order to minimize artifact and noise. Otherwise, the surgery cannot proceed. One can accomplish this rather easily (chapter 6 contains discussion of how this is done). Yet more frequently than one might imagine there arise problems of greater complexity, and these require investigation aided by a deep understanding of biophysics and electronics.

Though efficient and robust, turnkey systems—systems consisting of seamlessly integrated components (Figure 1.11)—conceal a certain danger. Currently available

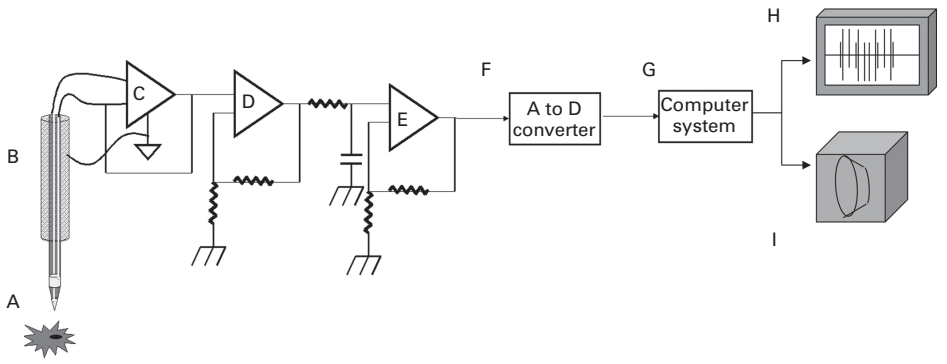

FIGURE 1.11 Schematic of a typical microelectrode and semi-microelectrode recording system. A represents the source of the neural signals, B is the electrode, C the high-impedance probe (unity gain amplifier) used for impedance matching (discussed in chapter 5), D the amplifier, E the filtering systems, F the analog to digital (A to D) converter (note in systems using digital signal processing systems, the A to D conversion occurs before much of the filtering, which is done digitally), G the computer system for analyses, H the visual display, and I the audio presentation.

commercial FDA-approved systems improve considerably on the "home-built" systems in use during the early days of intraoperative neurophysiological monitoring for DBS surgery. Yet, "home-built" systems possessed the distinct virtue of being familiar to those individuals who made them and who could therefore identify and fix their problems. Manufacturers' response to problems with their turnkey systems, as prompt and expert as this might be, is no substitute for the situation of having the engineer who designed the system on hand during surgery to address any problems.

The intraoperative neurophysiologist must adopt a healthy but respectful critical attitude toward the neurosurgeon, whom she should consider simply another instrument. As such, precision, accuracy, failure rate, and other concerns apply to the neurosurgeon as much as to any other instrument. (For their part, the neurosurgeon and the patient's treating nonsurgical physician ought to adopt exactly the same attitude toward the intraoperative neurophysiologist.) Correct image-guided navigation is something that the neurosurgeon cannot simply assume, because it greatly affects the neurophysiologist's ability to interpret the intraoperative neurophysiological monitoring. As discussed in chapters 9 and 10, microelectrode recordings of the globus pallidus interna are nearly identical to those of the subthalamic nucleus. Incidents have happened in which image-guided surgical navigation determined an initial trajectory situated on the wrong side of the posterior limb of the internal capsule. This led to the subthalamic nucleus's being mistaken for the globus pallidus interna. Other incidents have occurred in which exactly the opposite mistake was made. In those cases, microstimulation, macrostimulation, and other clues produced results directly opposite to those one would expect had the electrode entered the subthalamic nucleus instead of the globus pallidus interna. Beginning anew after many hours of surgery would thus prove difficult. The intraoperative neurophysiologist must therefore understand all of the various aspects of DBS surgery and must be able to recognize the signs of any potential mishap.

SUMMARY

So important is intraoperative monitoring that one finds the idea of performing DBS without it difficult to conceive. Though this monitoring may only take the form of macrostimulation through the DBS lead, it nonetheless requires considerable knowledge in order to ensure an optimal outcome. Fundamental scientific principles inform all methods of intraoperative neurophysiological monitoring, and an understanding of these principles enables the intraoperative neurophysiologist to offer her patient the greatest hope for benefit.