Deep brain stimulation (DBS) is a widely used therapy for movement disorders such as Parkinson's disease, essential tremor, and dystonia. Its therapeutic success has led to the application of DBS for an increasing spectrum of conditions. However, the fundamental relationships between neural activation, neurochemical transmission, and clinical outcomes during DBS are not well understood.

Drawing on the clinical and research expertise of the Mayo Clinic Neural Engineering Laboratories, this book addresses the history of therapeutic electrical stimulation of the brain, its current application and outcomes, and theories about its underlying mechanisms. It reviews research on measures of local stimulation–evoked neurochemical release, imaging research on stimulation–induced neural circuitry activation, and the state of the art on closed-loop feedback devices for stimulation delivery.
Deep Brain Stimulation
Deep Brain Stimulation
Indications and Applications

edited by
Kendall H. Lee
Penelope S. Duffy
Allan J. Bieber
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Preface

The success of deep brain stimulation (DBS) as a restorative neurosurgical treatment for certain intractable, neurologically based movement disorders has led to its consideration for a rapidly expanding list of neurologic and psychiatric conditions. Many of these newer applications are at the investigational stage but hold promise as an efficacious means of managing a wide variety of treatment-resistant conditions. These advances have led to increased and expanded efforts to understand the molecular, neural network, and behavioral effects of DBS. Clinical and preclinical DBS research is focused on improving patient care by deepening our understanding of pathologic and normal brain function. It encompasses not only investigations of the effects of DBS on neural activity, patient behavior, and outcomes, but also methods of improving electrode implantation and surgical targeting, techniques to trace the neurochemical and neural network effects of stimulation, engineering improved electrodes and new stimulation devices, such as closed-loop systems that use physiologic feedback to adjust stimulation delivery, and the design and implementation of carefully controlled clinical trials. Such wide-ranging yet integrated research and development efforts require input from the medical disciplines of neurology, neurosurgery, and psychiatry, but also from a variety of scientific disciplines such as engineering, computer science, applied mathematics, imaging science, neurochemistry, neurobiology, neurophysiology and experimental and behavioral psychology.

The need for an interdisciplinary approach to DBS research thus draws on the expertise of those who may be unfamiliar with the clinical application of DBS or with the science behind it or both. This book is intended as a handbook or introduction to the field for professionals and students who are new to DBS or to particular aspects of it. It grew out of work conducted at the Mayo Clinic Neural Engineering Laboratory, which is investigating DBS mechanisms and ways to improve its clinical application and outcomes. For students in graduate programs or medical school, we hope this
book serves not only as an overview of the field but as a source of inspiration to contribute to it. We hope that established clinicians and seasoned scientists from related and disparate fields, whose expertise is needed in basic or translational DBS research, will find it a useful resource.

We have divided the book into three major sections. The **Introduction** serves as an overview of the fundamentals of DBS. **Chapter 1** covers the somewhat tumultuous history of early uses of DBS in psychiatry to its present day applications to both neurologic and psychiatric disorders and provides the basic mathematics of stereotactic surgery, without which DBS would not be possible. It also introduces the reader to the standard DBS surgical procedure and discusses ethical issues that should be taken into account in clinical DBS practice.

To appreciate the therapeutic effects of clinical DBS, it is necessary to understand something about the electrophysiological basis of electrical stimulation and its effects on neural tissue. Thus, **Chapter 2** explores the principles of extracellular stimulation, neural excitability, interactions at the electrode-electrolyte tissue interface, and the electrochemical properties that affect the safety and therapeutic benefits of clinical DBS.

It is understood that DBS has effects not only at the stimulating electrode implantation target site but also in areas distal to the stimulated target that are structurally or functionally connected to it. To help the reader understand how neural networks are affected by pathology and DBS, **Chapter 3** reviews the basal ganglia-corticothalamic circuitry as represented by Parkinson's disease. It will help readers appreciate the complexity of the circuitry and its implications for DBS target structures that are part of it.

Neuroimaging is critical not only to surgical targeting of deep brain structures but also to research on the circuitry and neural network effects of DBS. **Chapter 4**, on imaging in DBS, provides a brief overview of fundamentals of magnetic resonance imaging and positron emission tomography and reviews the use of and advances in functional brain imaging for the study of DBS-evoked global changes in neural activation. **Chapter 5** reviews critical ethical issues in the use of DBS in patients with conditions commonly treated by DBS and those with conditions for which DBS is in the investigational stage.
The second section of the book, Clinical Applications, explores clinical impact of DBS for a wide range of neurologic and psychiatric conditions. Each of Chapters 6 through 15 describes a specific disorder, the deep brain structures that have been targeted to treat it, the rationale behind the DBS target choices, and clinical outcomes to-date. Chapter 16 describes the use of electrical stimulation to restore function following spinal cord injury. Although it does not involve DBS, specifically, it shares the goal of functional restoration by means of electrical stimulation. The chapter reviews the present progress in applying electrical stimulation systems that are transcutaneous and those that stimulate peripheral nerves or muscle fibers, as well as implanted epidural and intraspinal systems that stimulate the spinal cord directly.

The last section, Research on Mechanisms of DBS and Neuromodulation, has six chapters that cover theories and methods for studying the neurobiological effects of DBS. Chapter 17 reviews past and present hypotheses about the neuronal, metabolic, and physiologic mechanisms that underlie the therapeutic effects of DBS. Chapter 18 focuses on the understudied role of astrocytes and their potential contribution to DBS effects and mechanisms. Chapter 19 reviews the methods of measuring real-time DBS-evoked neurochemical changes in the brain, specifically in vivo voltammetry. These alterations in neurotransmitter release hold promise as a source of physiologically relevant information for future closed-loop feedback devices, which could fundamentally alter the delivery of DBS to minimize adverse effects and accentuate therapeutic outcomes. Chapter 20 provides the reader with an appreciation for the intricacies and complex design considerations of creating DBS stimulating and recording electrodes, including their size, shape, biocompatibility, electronic impedance, and surface chemistry. A biocompatible and durable chronic recording electrode can be considered the holy grail of future devices designed to use neurochemical or neurophysiologic feedback to control stimulation delivery. An explanation of closed-loop control systems for DBS, including electrophysiologic and neurochemical techniques and mathematical modeling, is provided in Chapter 21. The final chapter in the book, Chapter 22, explores another avenue of
neuromodulation: advances in molecular and cellular restoration that rely on biologic therapies to repair central nervous system dysfunction. It focuses primarily on spinal cord injury, but serves to alert the reader to the spectrum of scientific efforts in promoting functional restoration of central neural structures.

We would like to thank our contributors, each of whom has brought his or her individual expertise and experience to the task. Together we hope this book serves to introduce the reader to the clinical and basic science foundations and the advances and challenges of DBS, as well as to its history and its future as a means of advancing improved patient care through neuromodulation.

Kendall H. Lee, MD, PhD, Editor
Penelope S. Duffy, PhD, and Allan J. Bieber, PhD, Co-editors