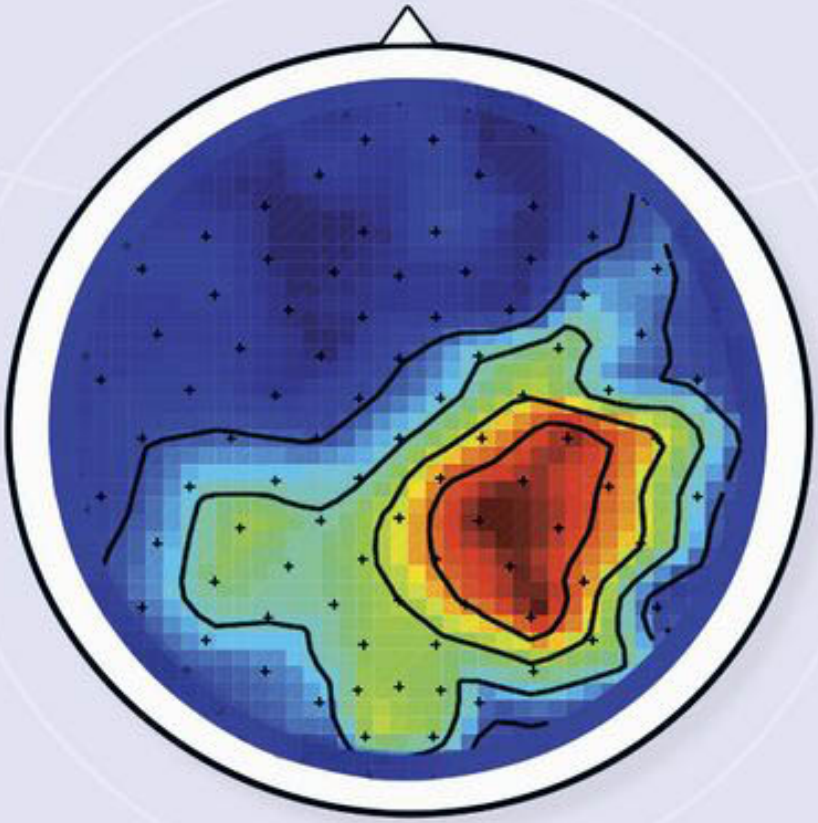

# BRAIN-COMPUTER INTERFACES

## PRINCIPLES AND PRACTICE

EDITED BY
JONATHAN R. WOLPAW
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OXFORD

# BRAIN–COMPUTER INTERFACES

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## PRINCIPLES AND PRACTICE

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Dedicated to
Michael, Sarah, Eliana, Vered, Maya, and Gabriella,
children of the 21st century

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# PREFACE

The possibility that signals recorded from the brain might be used for communication and control has engaged popular and scientific interest for many decades. However, it is only in the last 25 years that sustained research has begun, and it is only in the last 15 that a recognizable field of brain–computer interface (BCI) research and development has emerged. This new field is now populated by some hundreds of research groups around the world, and new groups are appearing continually. The explosive growth of this field is evident in the fact that a majority of all the BCI research articles ever published have appeared in the past five years.

This surge in scientific interest and activity arises from a combination of three factors. First and most obvious is the recent appearance of powerful inexpensive computer hardware and software that can support the complex high-speed analyses of brain activity essential to real-time BCI operation. Until quite recently, much of the rapid online signal processing used in current and contemplated BCIs was either impossible or extremely expensive. Now, hardware and software are no longer limiting factors: given the appropriate expertise, almost any promising BCI design can be implemented quickly and inexpensively.

The second factor is the greater understanding of the central nervous system (CNS) that has emerged from animal and human research over the past 50 years, particularly the voluminous new information about the nature and functional correlates of brain signals such as EEG activity and neuronal action potentials. Along with this new understanding have come improved methods for recording these signals, in both the short-term and the long-term. The continuing increases in basic knowledge and improvements in technology are enabling and guiding steadily more sophisticated and productive BCI research. Particularly important is the veritable revolution in the appreciation of the brain's remarkable capacity for adaptation, both in normal life and in response to trauma or disease. This new appreciation is a stunning change from the conception of the hardwired CNS that prevailed only 20 or 30 years ago. It generates enormous excitement about the possibilities for using these adaptive capacities to create novel interactions between the brain and computer-based devices, interactions that can replace, restore, enhance, supplement, or improve the brain's natural interactions with its external and internal environments.

The third factor is new recognition of the needs and abilities of people disabled by disorders such as cerebral palsy, spinal cord injury, stroke, amyotrophic lateral sclerosis (ALS), multiple sclerosis, and muscular dystrophies. Home ventilators and other life-support technology now enable even the most severely disabled people to live for many years. Furthermore, it is now understood that people who have very little voluntary muscle control can lead enjoyable and productive lives if they can be given even the most basic means of communication and control. BCIs, even in their currently limited state of development, can serve this need.

The distinctive property of BCI research and development, beyond its remarkable recent growth, is that it is inherently and necessarily multidisciplinary. The sequence of operations that lead from the user's brain to the BCI's action indicates this clearly. Appropriate selection of the brain signals that a BCI uses depends on our understanding of neuroscience, both basic and applied. Recording these signals properly depends on the physical sciences as well as on electrical and materials engineering and sometimes on neurosurgery and tissue biology as well. Appropriate, efficient, and timely processing of the recorded signals requires computer science and applied mathematics. The design and operation of the algorithms that translate signal features into device commands that achieve the user's intent depend on systems engineering as well as on understanding of spontaneous and adaptive changes in brain function. The selection of appropriate user populations and the implementation of appropriate applications require clinical neurology and rehabilitation engineering and depend on expertise in assistive technology. Finally, management of the complex ongoing interaction between the user and the application device requires understanding of behavioral psychology and human factors engineering. All these disparate disciplines, and effective cooperation among them, are essential if BCI research and development are to be successful in their primary goal, to provide important new communication and control options to people with severe disabilities.

The multidisciplinary nature of BCI research was a major impetus for this book and is the first principle of its structure and content. The book is intended to provide an introduction to and summary of essentially all major aspects of BCI research and development. Its goal is to be a comprehensive, balanced, and coordinated presentation of the field's key principles, current practice, and future prospects. It is aimed at scientists, engineers, and clinicians at all levels, and it is designed to be accessible to people with a basic undergraduate-level background in biology, physics, and mathematics. In response to the inherently multidisciplinary nature of the field, it seeks to introduce people from the many different relevant disciplines to all aspects of BCI research and thereby enable them to interact most productively. Attention has been paid to ensuring that

the chapters mesh into a reasonably coordinated and logical whole, while at the same time preserving the sometimes differing views of the individual authors.

Each chapter tries to present its topic in a didactic format so that the reader can acquire the basic knowledge needed to work effectively with researchers and clinicians from the wide range of disciplines engaged in BCI research. For example, the chapters on signal processing (chapters 7 and 8) do more than simply review the various signal analysis methods that have been used in BCIs. They try to provide an accessible introduction to the broad range of signal analysis methods that might conceivably be applied to BCI use, and they outline the comparative advantages and disadvantages of these methods for specific BCI purposes. The goal is to enable the reader to participate actively in choosing from among alternative methods.

The book has six major parts. The Introduction stakes out the book's territory by carefully defining what is and what is not a brain–computer interface and it identifies six important themes that appear throughout the book. Part II introduces the different kinds of electrical and metabolic brain signals that BCIs might use; these chapters are necessarily long and challenging because they present many fundamental principles that underlie the subjects of all of the subsequent chapters. Part III proceeds through each of the components that constitute a BCI system, from signal acquisition to output commands, and discusses the applications that these commands control. Part IV reviews the principal kinds of BCIs developed to date and describes the current state of the art. Part V addresses the issues involved in the realization, validation, and dissemination of BCI systems useful to people with severe disabilities. Success in these difficult tasks is critical for the future of BCI technology. Part V also considers the possibilities for BCI uses that go beyond the assistive communication and control applications that have engaged the most attention up to the present; these further possibilities include BCI applications that could serve people with or without disabilities. In addition, Part V includes a chapter discussing the ethical issues associated with BCI research and development. Part VI, the Conclusion, considers the key problems that must be solved if BCIs are to fulfill the high expectations that so many people have for them.

Many people have contributed to this book. Each chapter is a unique and essential part of the whole. We hope that together they tell a coherent and exciting story and that therefore the whole is even greater than the sum of its parts.

Jonathan R. Wolpaw
Elizabeth Winter Wolpaw
Albany, New York
September 2011

# ACKNOWLEDGMENTS

Brain–computer interface research and development is a team sport and so has been the realization of this book. No single author could have written it. The contribution of every one of the chapter authors was essential to our goal of presenting a comprehensive view of this complex new field. Coming from a wide variety of disciplines, they are brought together here by their knowledge of and commitment to research in areas important to BCI research and development. In this volume, they share their expertise and the fruits of their own work and that of other researchers and clinicians all over the world. Some of the authors have been engaged in BCI research since its beginnings, others have joined the ranks more recently, and still others work in related fields. All of them have generously contributed to make this book possible. We thank them all for this generosity and for their patience through the numerous steps of the process.

We are indebted to the many experts who served as external reviewers. Their names are listed on pages xvii–xviii of this volume. They represent many different disciplines and hail from many different places. Their insightful comments and suggestions have made the chapters substantially better. We also thank our colleagues at the Wadsworth Center for their numerous helpful comments and suggestions; we are particularly grateful to Chadwick Boulay, Peter Brunner, Natalie Dowell-Mesfin, Markus Neuper, Jeremy Hill, and Stuart Lehrman for their excellent technical advice and assistance.

People disabled by neuromuscular disorders have been and remain the primary impetus for BCI development. Their courage in facing the difficult challenges of their lives is an inspiration to all of us. We thank them all for this inspiration and especially want to thank those who have participated in many of the studies reported here. They are truly partners in this work.

Many institutions, both public and private, located in many countries around the world, have supported the research that is the substance of these chapters. Without their generous and enthusiastic support, virtually none of the work reported in this book would have been possible.

Finally, we would like to thank our editors at Oxford University Press. It has been a pleasure to get to know and work with Craig Allen Panner, Associate Editorial Director for Neuroscience, Neurology, and Psychiatry, who encouraged us to embark on this project in the first place. We thank him heartily for giving us this opportunity and for his wise guidance and unfaltering patience throughout the process. We thank Assistant Editor Kathryn Winder for her enthusiasm and for her unerring attention to detail in seeing this project through to completion. We also thank Production Editor Karen Kwak, and Viswanath Prasanna, Elissa Schiff, and the rest of Oxford's production team for their extraordinary care in turning the manuscript into a polished product.

It has been a privilege to work with all of these remarkable people, and we are grateful to have had the chance to do so. We hope that this volume provides a valuable foundation, framework, and resource for those engaged, or involved in any other way, in BCI research and development.

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# PART I. | INTRODUCTION

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# 1 | BRAIN–COMPUTER INTERFACES: SOMETHING NEW UNDER THE SUN

JONATHAN R. WOLPAW AND ELIZABETH WINTER WOLPAW

In 1924, Hans Berger, Professor of Psychiatry at the University of Jena in Germany, discovered that electrical signals produced by the human brain could be recorded from the scalp. After five years of further study, Berger published the first of 14 articles that established electroencephalography (EEG) as a basic tool for clinical diagnosis and brain research (Berger, 1929). In 1938, just as his work had begun to receive international recognition, the German government closed his laboratory and forced him into retirement. The year was momentarily brightened for him by a holiday greeting from Herbert Jasper, a young North American neuroscientist at the start of a stellar career. Jasper sent to Berger the drawing shown in figure 1.1. It implies, albeit in a fanciful way, that EEG signals could also be used for communication.

This possibility—that people could act through brain signals rather than muscles—has fascinated scientists and nonscientists alike for many years. Now, nearly a century after Berger's epochal discovery, possibility is becoming reality. Although the reality is new and tentative and very modest, its excitement and potential are driving the burgeoning field of brain–computer interface research (fig. 1.2). This book is about that field—the principles that underlie it, its achievements so far, the problems that confront it, and its prospects for the future.

## WHAT IS A BRAIN–COMPUTER INTERFACE?

As currently understood, the function of the central nervous system (CNS) is to respond to events in the outside world or the body by producing outputs that serve the needs of the organism. All the natural outputs of the CNS are neuromuscular or hormonal. A brain–computer interface (BCI) provides the CNS with new output that is neither neuromuscular nor hormonal. *A BCI is a system that measures CNS activity and converts it into artificial output that replaces, restores, enhances, supplements, or improves natural CNS output and thereby changes the ongoing interactions between the CNS and its external or internal environment.*

Understanding this definition requires an understanding of each of its key terms, beginning with *CNS*. The CNS is comprised of the brain and the spinal cord and is distinguished from the peripheral nervous system (PNS), which is comprised of the peripheral nerves and ganglia and the sensory receptors. The structures of the CNS are distinguished by their location within the meningeal coverings (or meninges), by their unique cell types and histology, and by their function in integrating the many different sensory inputs to produce appropriate motor outputs. In contrast, the PNS is not within the meninges, lacks the unique CNS histology, and serves mainly to convey sensory inputs to the CNS and to convey motor outputs from it.

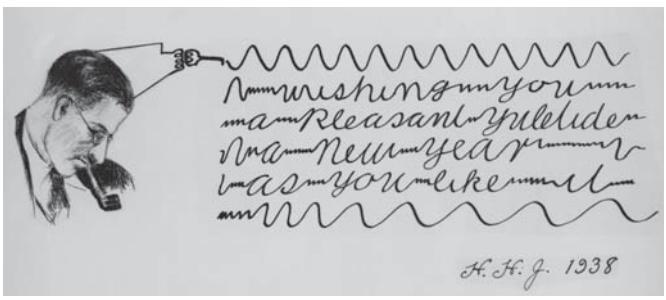


***Figure 1.1*** *This drawing was included in a holiday greeting that Herbert Jasper sent to Hans Berger in 1938. It is an early rendering of what is now called a brain-computer interface. (© Photo Deutsches Museum, Munich.)*

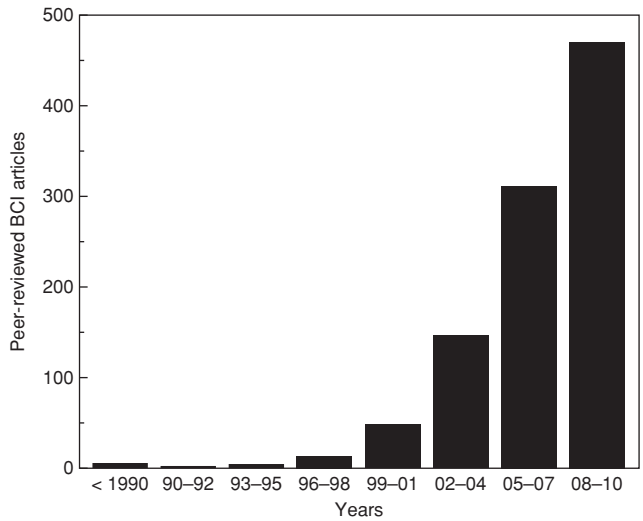


***Figure 1.2*** *BCI articles in the peer-reviewed scientific literature. In the past 15 years, BCI research, which was initially limited to a few isolated laboratories, has emerged as a very active and rapidly growing scientific field. The majority of research articles have appeared in the past five years. (Updated from Vaughan and Wolpaw, 2006.)*

*CNS activity* consists of the electrophysiological, neurochemical, and metabolic phenomena (e.g., neuronal action potentials, synaptic potentials, neurotransmitter releases, oxygen consumption) that occur continually in the CNS. These phenomena can be quantified by monitoring electric or magnetic fields, hemoglobin oxygenation, or other parameters using sensors on the scalp, on the surface of the brain, or within the brain (fig. 1.3). A BCI records these *brain signals*, extracts specific measures (or *features*) from them, and converts (or *translates*) these features into *artificial outputs* that act on the outside world or on the body itself. Figure 1.3 illustrates the five types of applications that a BCI output might control. For each of these five application types, it shows one of many possible examples.

A BCI output might *replace* natural output that has been lost as a result of injury or disease. For example, a person who can no longer speak might use a BCI to type words that are then spoken by a speech synthesizer. Or a person who has lost limb control might use a BCI to operate a motorized wheelchair. In these examples the BCI outputs *replace* lost natural outputs.

A BCI output might *restore* lost natural output. For example, a person with spinal cord injury whose arms and hands are paralyzed might use a BCI to stimulate the paralyzed muscles via implanted electrodes so that the muscles move the limbs. Or a person who has lost bladder function due to multiple sclerosis might use a BCI to stimulate the peripheral nerves that control the bladder, thus enabling urination. In these examples, the BCI outputs *restore* the natural outputs.

A BCI output might *enhance* natural CNS output. For example, a person performing a task that requires continuous attention over a prolonged period (e.g., driving a vehicle or serving as a sentry) might use a BCI that detects the brain activity preceding lapses in attention and then provides an output (e.g., a sound) that alerts the person and restores attention. By preventing the attentional lapses that periodically impair natural CNS output (and might cause traffic accidents), the BCI *enhances* the natural output.

A BCI output might *supplement* natural CNS output. For example, a person who is controlling the position of a computer cursor with a hand-operated joystick might use a BCI to select items that the cursor reaches. Or a person might use a BCI to control a third (i.e., robotic) arm and hand. In these cases, the BCI *supplements* natural neuromuscular output with an additional, artificial output.

Finally, a BCI output might conceivably *improve* natural CNS output. For example, a person whose arm movements have been impaired by a stroke involving the sensorimotor

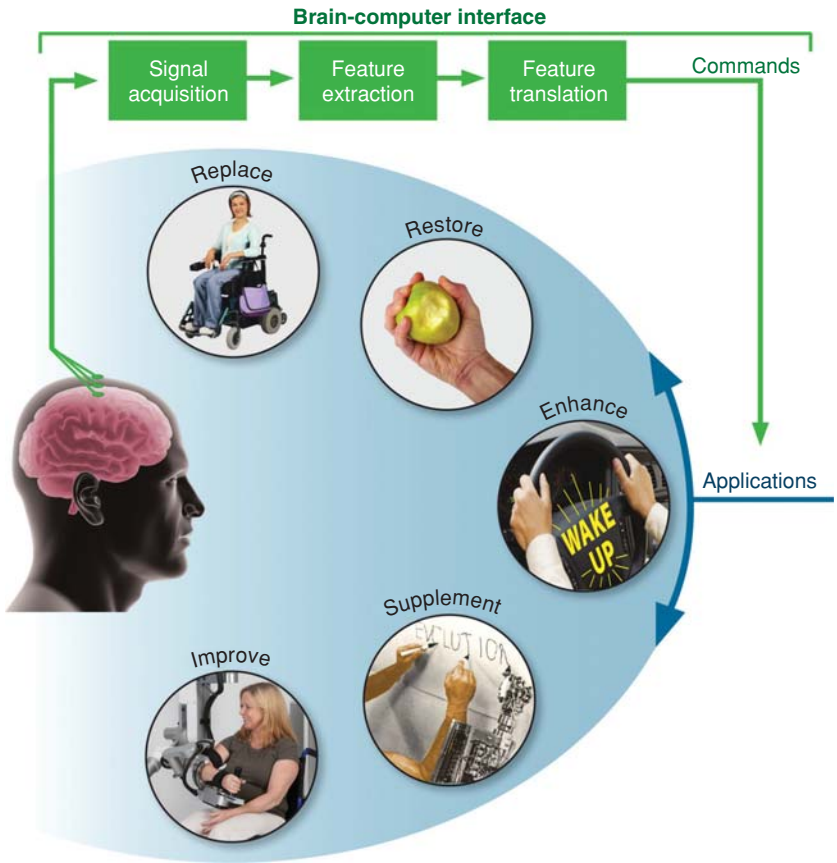


***Figure 1.3*** *The basic design and operation of a brain-computer interface (BCI) system. In this illustration, the BCI is shown in green. Electrical signals reflecting brain activity are acquired from the scalp, from the cortical surface, or from within the brain. The signals are analyzed to measure signal features (such as amplitudes of EEG rhythms or firing rates of single neurons) that reflect the user's intent. These features are translated into commands that operate application devices that replace, restore, enhance, supplement, or improve natural CNS outputs. (Modified from Wolpaw et al., 2002.) (Supplement image © Stelarc, http://stelarc.org; Improve image © Hocoma AG, www.hocoma.com.)*

cortex might use a BCI that measures signals from the damaged cortical areas and then stimulates muscles or controls an orthotic device so as to improve arm movements. Because this BCI application enables more normal movements, its repeated use may induce activity-dependent CNS plasticity that *improves* the natural CNS output and thereby helps the person to regain more normal arm control.

The first two types of BCI application, replacement or restoration of lost natural outputs, are the goals of most current BCI research and development, and examples of them appear many times throughout this book. At the same time, the other three kinds of BCI applications are also possible and are drawing increasing attention (chapters 22 and 23).

The last part of the definition states that a BCI *changes the ongoing interactions between the CNS and its external or internal environment*. The CNS interacts continuously with the outside world and with the body. These interactions consist of its motor outputs to the environment together with its sensory inputs from the environment. By measuring CNS activity and converting it into artificial outputs that affect the environment, BCIs change not only the CNS outputs but also the sensory inputs coming from the environment. These changes in sensory input are commonly referred to as *feedback*. Devices that simply monitor brain activity and do not use it to *change* the ongoing interactions between the CNS and its environment are not BCIs.

## BCI TERMINOLOGY

### PROVENANCE OF THE TERM BCI AND ITS PRESENT DEFINITION

Although an EEG-based BCI was demonstrated by Grey Walter in 1964 (Graimann et al., 2010a), the term *brain-computer interface* was apparently first used by Jacques Vidal in the 1970s. He applied the term very broadly, using it to describe any computer-based system that produced detailed information on brain function. Nevertheless, in the course of his work, Vidal developed a system that satisfies the narrower present-day meaning (Vidal, 1973, 1977). Vidal's system used the visual evoked potential (VEP) recorded from the scalp over the visual cortex to determine the direction of eye gaze (i.e., the visual fixation point) and thus to determine the direction in which the user wanted to move a cursor. Several years earlier, in the first neuron-based BCI, Eberhard Fetz and his collaborators had shown that monkeys could learn to use a single cortical neuron to control a meter needle to gain food rewards (Fetz, 1969; Fetz and Finocchio, 1971).

The BCI definition presented at the beginning of this chapter is based on the definitions and discussions in a number of reviews over the past decade (Donoghue, 2002; Wolpaw et al., 2002; Schwartz, 2004; Kübler and Müller, 2007; Daly and Wolpaw, 2008; Graimann et al., 2010a). It is intended to be comprehensive and definitive and, at the same time, to relate BCIs to the *sensorimotor hypothesis* (Young, 1990; Wolpaw, 2002), which is the theoretical foundation of modern neuroscience. The sensorimotor hypothesis is that the whole function of the CNS is to respond to external and internal events with appropriate outputs. In accord with this hypothesis, BCIs are defined as systems that translate brain signals into new kinds of outputs.

### SYNONYMOUS OR SUBSIDIARY TERMS

The term *brain-machine interface* (BMI) was used as early as 1985 to describe implanted devices that stimulate the brain (Joseph, 1985) but was not applied specifically to devices that provide new outputs until more recently (e.g., Donoghue, 2002). In practice the term BMI has been applied mainly to systems that use cortical neuronal activity recorded by implanted microelectrodes. At present, BCI and BMI are synonymous terms, and the choice between them is largely a matter of personal preference. One reason for preferring BCI to BMI is that the word "machine" in BMI suggests an inflexible conversion of brain signals into output commands and thus does not reflect the reality that a computer and the brain are partners in the interactive adaptive control needed for effective BCI (or BMI) operation.

The terms *dependent BCI* and *independent BCI* were introduced in 2002 (Wolpaw et al., 2002). In accord with the basic BCI definition, both use brain signals to control their applications, but they differ in their dependence on natural CNS output. A dependent BCI uses brain signals that depend on muscle activity. For example, the BCI described by Vidal (1973, 1977) used the amplitude of a VEP that depended on gaze direction and thus on the muscles that controlled gaze. A dependent BCI is essentially an alternative method for detecting messages carried in natural CNS outputs. Although it does not give the brain a new output that is independent of natural outputs, it may still be useful (e.g., Sutter, 1992) (chapter 14).

In contrast, an *independent BCI* does not depend on natural CNS output; in independent BCIs, muscle activity is not essential for generating the brain signals that the BCI uses. For example, in BCIs based on EEG sensorimotor rhythms (SMRs) (chapter 13), the user may employ mental imagery to modify SMRs so as to control the BCI output. For people with severe neuromuscular disabilities, independent BCIs are likely to be more useful. At the same time it is important to recognize that most actual BCIs are neither purely dependent nor purely independent. The output of a steady-state VEP-based BCI may reflect the user's degree of attention (in addition to the user's gaze direction) (chapter 14). Conversely, most SMR-based BCIs rely on the user having sufficient visual function (and thus gaze control) to watch the results of the BCI's output commands (e.g., cursor movements).

The recent term *hybrid BCI* is applied in two different ways (Graimann et al., 2010b). It can describe a BCI that uses two different kinds of brain signals (e.g., VEPs and SMRs) to produce its outputs. Alternatively, it can describe a system that combines a BCI output with a natural muscle-based output (chapter 23). In the latter usage, the BCI output supplements a natural CNS output (e.g., as illustrated in fig. 1.3).

Another recent term, *passive BCI*, is applied to BCI applications that use brain signals that are correlated with aspects of the user's current state, such as level of attention (Zander and Kothe, 2011). For example, a BCI might detect EEG features preceding lapses in attention and produce an output

(e.g., a sound) that alerts the user and restores attention (Chapter 23). The term *passive* is meant to distinguish these BCI applications from those that provide communication and control (i.e., *active* BCIs). However, *passive* and *active* are subjective terms that lack clear neuroscientific definitions. Furthermore, continued use of a passive BCI might well induce CNS adaptations that improve its performance, so that the term *passive* becomes no longer applicable. Thus, it seems preferable to categorize BCI applications simply as shown in figure 1.3, in which case passive BCIs will generally fit into the *enhance* or *supplement* category.

### RELATED NEUROTECHNOLOGY

The recent explosion of BCI research is part of a surge of interest in a broad spectrum of new technologies and therapies that promise unprecedented understanding of and access to the brain and its disorders. These include structural and functional imaging methods of high resolution and specificity, chronically implanted devices for stimulating specific structures, molecules and particles that can encourage and guide neuronal regeneration and reconnection, cells that can replace lost tissues, and rehabilitation regimens that can restore useful function. A number of these new methods *act directly on the brain*, and thus contrast with BCIs, which, as defined here, allow the brain to *act directly on the world*. At the same time, some of these methods (e.g., direct stimulation of cortical or subcortical sensory areas) are likely to be incorporated into future BCI systems to improve their performance (chapters 5 and 16).

Direct input methods, together with BCIs (which provide direct outputs), fit into the general class of brain interfaces. Whether direct input methods will someday acquire their own designation (e.g., computer-brain interfaces [CBIs]) remains to be seen. The BCI definition described here recognizes the novel nature of devices that provide new CNS *outputs*.

## SIX IMPORTANT THEMES

The rest of this chapter introduces six themes that we believe are important for understanding BCI research and development. These themes arise explicitly or implicitly many times in this book, and they are introduced here to emphasize and clarify their importance.

### BCIs CREATE NEW CNS OUTPUTS THAT ARE FUNDAMENTALLY DIFFERENT FROM NATURAL OUTPUTS

The natural function of the CNS is to produce muscular and hormonal outputs that serve the needs of the organism by acting on the outside world or on the body. BCIs provide the CNS with *additional artificial outputs* derived from brain signals. Thus, they require the CNS, which has evolved to produce muscular and hormonal outputs, to now produce entirely new kinds of outputs. For example, the sensorimotor cortical areas, which normally interact with subcortical and spinal areas to control muscles, are now asked instead to control certain brain signals (e.g., neuronal firing patterns or EEG rhythms). The profound implications of this requirement become apparent when BCI use is considered in terms of how the CNS normally operates. The research of the past 200 years, and especially of recent decades, has revealed two basic principles that govern how the CNS produces its natural outputs.

The first principle is that *the task of creating natural outputs is distributed throughout the CNS, from the cerebral cortex to the spinal cord.* No single area is wholly responsible for a natural output. As illustrated in an extremely simplified form in figure 1.4A, the selection, formulation, and execution of actions such as walking, speaking, or playing the piano are achieved through collaboration among cortical areas, basal ganglia, thalamic nuclei, cerebellum, brainstem nuclei, and spinal-cord interneurons and motoneurons. For example, while cortical areas initiate walking and oversee its progression, the rhythmic high-speed sensorimotor interactions needed to ensure effective locomotion are handled largely by spinal-cord circuitry (McCrea and Rybak, 2008; Ijspeert, 2008; Guertin and Steuer, 2009). The end product of this widely distributed CNS activity is the appropriate excitation of the spinal (or brainstem) motoneurons that activate muscles and thereby produce actions. Furthermore, although activity in the various CNS areas involved often correlates with motor action, the activity in any one area may vary substantially from one trial (i.e., one performance of a particular action) to the next. Nevertheless, the coordinated activations of all the areas ensure that the action itself is very stable across trials.

The second principle is that *normal CNS outputs (whether they be walking across a room, speaking specific words, or playing a particular piece on the piano) are mastered and maintained by initial and continuing adaptive changes in all the CNS areas involved*. In early development and throughout later life, neurons and synapses throughout the CNS change continually to acquire new actions (i.e., new skills) and to preserve those already acquired (e.g., Carroll and Zukin, 2002; Gaiarsa et al., 2002; Vaynman and Gomez-Pinilla, 2005; Saneyoshi et al., 2010; Wolpaw, 2010). This activity-dependent plasticity is responsible for acquiring and maintaining standard skills such as walking and talking as well as specialized skills such as dancing and singing, and it is guided by the results that are produced. For example, as muscle strength, limb length, and body weight change with growth and aging, CNS areas change so as to maintain these skills. Furthermore, the basic characteristics of the CNS (i.e., its anatomy, physiology, and mechanisms of plasticity) on which this continuing adaptation operates are the products of evolution guided by the need to produce appropriate actions, that is, to appropriately control the spinal motoneurons that activate the muscles. In figure 1.4A, to emphasize that this adaptation occurs and that it is directed at optimizing the natural CNS outputs (i.e., muscle activations), all of the CNS areas are shown in the same color as the muscles.

In light of these two principles—the many areas that contribute to natural CNS outputs and the continual adaptive plasticity in these areas—BCI use is a unique challenge for a CNS that has evolved and is continually adapting to produce the natural CNS outputs. Unlike natural CNS outputs, which are produced by spinal motoneurons, a BCI output is produced

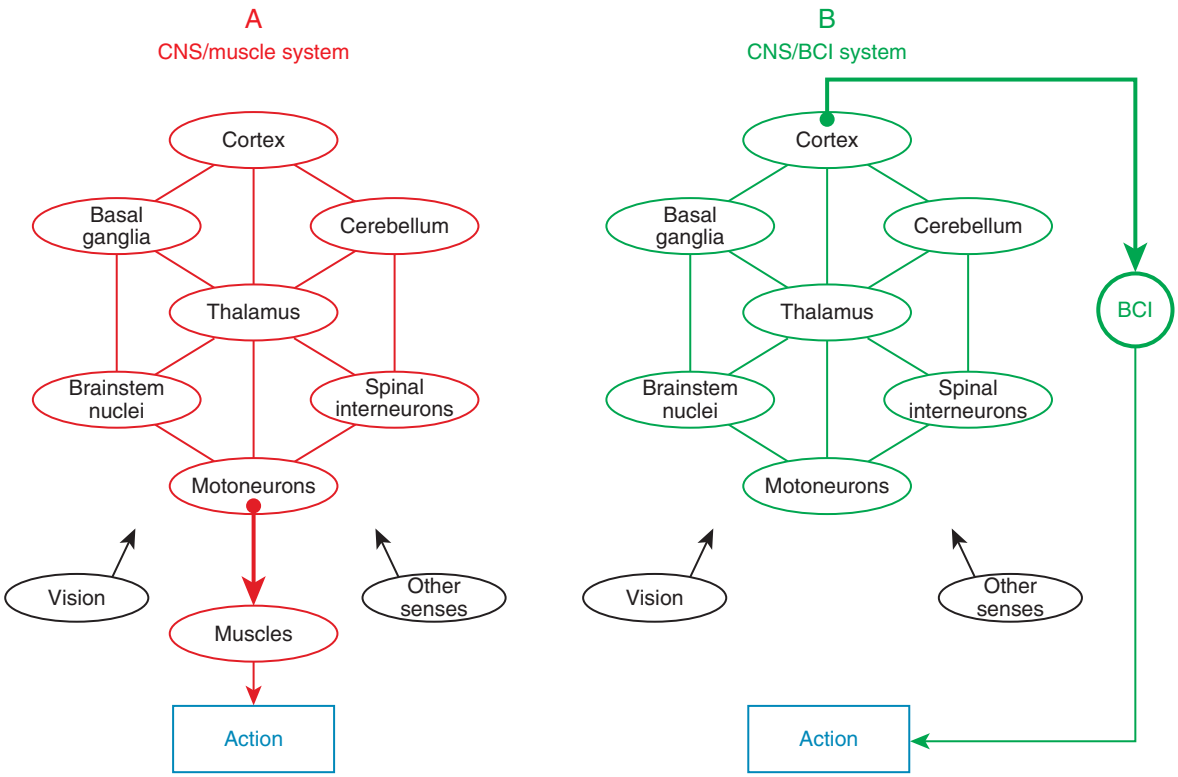


***Figure 1.4*** *CNS production of a muscle-based action versus CNS production of a BCI-based action. (A) This greatly simplified diagram shows the production of a normal motor action by the many CNS areas that collaborate to control spinal (or brainstem) motoneurons and thereby activate muscles. The red color indicates that all the CNS areas adapt to optimize muscle control. (B) This diagram shows the production of a BCI-mediated action by the same CNS areas, which now collaborate to optimize the control by the cortical area that produces the brain signals that the BCI translates into its output commands. The BCI assigns to the cortex the output role normally performed by spinal motoneurons and thereby asks that the CNS areas adapt to optimize an entirely new kind of output. This change in the target of CNS adaptation is indicated in this illustration by the fact that the color of all these areas (green) now matches the color of the BCI. (Modified from Wolpaw, 2007.)*

not by motoneuron activity but, rather, by signals that reflect activity in another CNS area (e.g., motor cortex). Normally the activity in this other area (e.g., motor cortex) is simply one of many contributors to natural CNS output. However, when its signals control a BCI, this activity actually *becomes* the CNS output. Figure 1.4B illustrates this fundamental change. The area that produces the signals that the BCI uses (i.e., the cortex in this illustration) takes on the role normally performed by spinal motoneurons. That is, the cortex produces the final product—the output—of the CNS. How well the cortex can perform this new role depends in part on how well the many CNS areas that normally adapt to control spinal motoneurons (which are downstream in natural CNS function) can instead adapt to control the relevant cortical neurons and synapses (which are largely upstream in natural CNS function). Figure 1.4B indicates this change in the goal of adaptation by now showing the CNS areas in the same color as the BCI, which, instead of the muscles, now produces the action.

For example, a BCI asks the cerebellum (which normally helps to ensure that motoneurons activate muscles so that movement is smooth, rapid, and accurate) to change its role to that of helping to ensure that the set of cortical neurons recorded by a microelectrode array produces patterns of action potentials that move a cursor (or a prosthetic limb) smoothly, rapidly, and accurately. The degrees to which the cerebellum and other key areas can adapt to this new purpose remain uncertain. The ultimate capacities and practical usefulness of BCIs depend in large measure on the answers to this question.

The evidence to date shows that the adaptation necessary to control activity in the CNS areas responsible for the signals used by BCIs is certainly possible but that it is as yet imperfect. BCI outputs are in general far less smooth, rapid, and accurate than natural CNS outputs, and their trial-to-trial, day-to-day, and week-to-week variability is disconcertingly high. These problems (particularly the problem of poor reliability) and the various approaches to addressing them, are major concerns in BCI research, and they are discussed often in this book.

## BCI OPERATION DEPENDS ON THE INTERACTION OF TWO ADAPTIVE CONTROLLERS

Natural CNS outputs are optimized for the goals of the organism, and the adaptation that achieves this optimization occurs primarily in the CNS. In contrast, BCI outputs can be optimized by adaptations that occur not only in the CNS but also in the BCI itself. In addition to adapting to the amplitudes, frequencies, and other basic characteristics of the user's brain signals, a BCI may also adapt to improve the fidelity with which

its outputs match the user's intentions, to improve the effectiveness of adaptations in the CNS, and perhaps to guide the adaptive processes in the CNS.

Thus, BCIs introduce a second adaptive controller that can also change to ensure that the organism's goals are realized. BCI usage therefore depends on the effective interaction of *two adaptive controllers: the user's CNS and the BCI*. The management of this complex interaction between the adaptations of the CNS and the concurrent adaptations of the BCI is among the most difficult problems in BCI research. The challenges it poses arise at many points throughout this book.

## CHOOSING SIGNAL TYPES AND BRAIN AREAS

Brain signals recorded by a variety of different electrophysiological and metabolic methods can serve as BCI inputs (chapters 12–18). These signals differ considerably in topographical resolution, frequency content, area of origin, and technical requirements. Figure 1.5 shows the range of electrophysiological methods from EEG to electrocorticography (ECoG) to intracortical recording and indicates the multiple scales of the brain signals available for BCIs, from the centimeter scale of EEG through the millimeter scale of ECoG to the tens-of-microns scale of neuronal action potentials. All of these electrophysiological methods have been used for BCIs and warrant continued evaluation, as do the metabolic methods discussed in chapters 4 and 18. Each has its own advantages and disadvantages. Which methods will prove most useful for which purposes is as yet unknown, and the answers will depend on a host of scientific, technical, clinical, and commercial factors.

On the one hand, the role of neuronal action potentials (spikes) as basic units of communication between neurons suggests that spikes recorded from many neurons could provide numerous degrees of freedom and might thus be the best signals for BCIs to use. Furthermore, the strong relationships between cortical neuronal activity and normal motor control

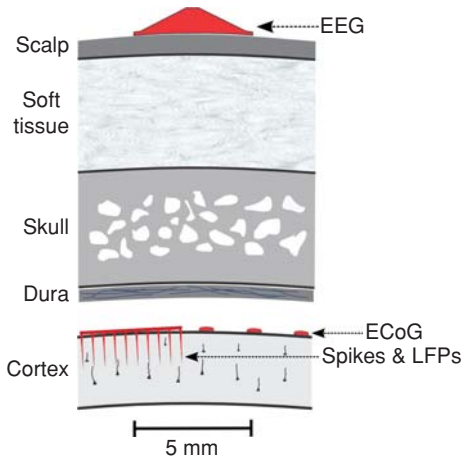


***Figure 1.5*** *Recording sites for electrophysiological signals used by BCI systems. EEG is recorded by electrodes on the scalp. ECoG is recorded by electrodes on the cortical surface. Neuronal action potentials (spikes) or local field potentials (LFPs) are recorded by microelectrode arrays inserted into the cortex (or other brain areas). A few representative cortical pyramidal neurons are indicated. (Modified from Wolpaw and Birbaumer, 2006.)*

(chapter 2) provide logical starting points for development of BCI-based control of devices such as robotic arms (chapter 16). On the other hand, the fundamental importance of CNS adaptation for all BCIs, and the evidence that adaptive methods can elicit multiple degrees of freedom even from EEG signals (chapter 13), suggest that the difference between the BCI performance provided by single neurons and by EEG may not be nearly as great as the difference in their topographical resolutions.

Questions about signal selection are empirical issues that can be resolved only by experiment, not by a priori assumptions about the inherent superiority of one signal type or another. For BCIs, the critical issue is which signals can provide the best measure of the user's intent, that is, which signals constitute the best language for communicating to the BCI the output desired by the user. This question can be conclusively answered only by experimental results.

Selection of the best brain areas from which to record the signals is also an empirical question. Studies to date have focused mainly on signals from sensorimotor (and visual) cortical areas. The usefulness of signals from other cortical or subcortical areas is also being explored (e.g., chapter 17). This is an important question, especially because the sensorimotor cortices of many prospective BCI users have been damaged by injury or disease and/or their visual function may be compromised. Different brain areas may well differ in their adaptive capacities and in other factors that may affect their ability to serve as the sources of new CNS outputs.

## RECOGNIZING AND AVOIDING ARTIFACTS

Like most communication and control systems, BCIs face the problems of artifacts that obscure the signals that convey output commands. For BCIs, artifacts may come from the environment (e.g., electromagnetic noise from power lines or appliances), from the body (e.g., muscle (electromyographic [EMG]) activity, eye movement (electrooculographic [EOG]) activity, cardiac (electrocardiographic [EKG]) activity, bodily movements) or from the BCI hardware (e.g., electrode instability, amplifier noise). The different varieties of artifacts and the measures for eliminating them or reducing their impact are addressed in chapters 6 and 7. Particularly for BCIs that record brain signals noninvasively, artifacts present a danger that warrants some discussion even in this introductory chapter.

The first requirement for any BCI study or demonstration is to ensure that it is, in fact, using a BCI (i.e., that *brain signals*, not other types of signals, control its output). Systems that use other kinds of biological signals, such as EMG activity, may be valuable in their own right, but they are not BCIs. Unfortunately, nonbrain signals such as EMG activity may readily masquerade as brain signals. Electrodes placed anywhere on the scalp can record EMG activity from cranial muscles or EOG activity that equals or exceeds EEG activity in amplitude and that overlaps with it in frequency range. Because people can readily control cranial EMG or EOG activity and may not even be aware that they are doing so, such nonbrain activity may contaminate or even dominate the signals recorded by a BCI and may thereby ensure that the BCI outputs are produced in part,

or even entirely, by nonbrain signals. Clearly, effective BCI research and development are not possible in such circumstances. (Indeed, even in the scientific literature there are examples of putative BCI studies in which EMG signals masquerade as EEG signals, so that the results reflect cranial-muscle control rather than brain-signal control.) Commercial devices (e.g., for gaming) that are currently marketed as BCIs often do not differentiate EEG from EMG or other nonbrain signals. Only if it is certain that the control signals arise from brain activity and not from other activity can the results of BCI studies be useful to people whose severe disabilities have eliminated their control of nonbrain signals.

To avoid the danger of contamination by nonbrain signals, EEG-based BCI studies need to incorporate topographical and frequency analyses that are sufficiently comprehensive to distinguish between brain and nonbrain signals. Noninvasive metabolic BCI studies may need to incorporate analogous precautions. EEG studies that simply record from a single site, or that focus on a single narrow frequency band, cannot reliably discriminate between EEG and EMG, and thus, their results may be misleading. These issues are addressed in greater detail in chapters 6 and 7.

## BCI OUTPUT COMMANDS: GOAL SELECTION OR PROCESS CONTROL

A BCI can produce two kinds of output commands: a command that *selects a goal* or a command that *controls a process*. Figure 1.6 illustrates these two options applied to the movement of a motorized wheelchair.

In the *goal-selection* protocol shown at the top, the user and the BCI simply communicate the goal (i.e., the user's intent) to software in the application, and it is the application that then manages the process that accomplishes that intent. For example, the BCI might communicate the goal of moving to a location facing the television. The application device (i.e., the wheelchair) then produces the several concurrent sequences of actions (e.g., movements in $x$ and $y$ directions, turning,

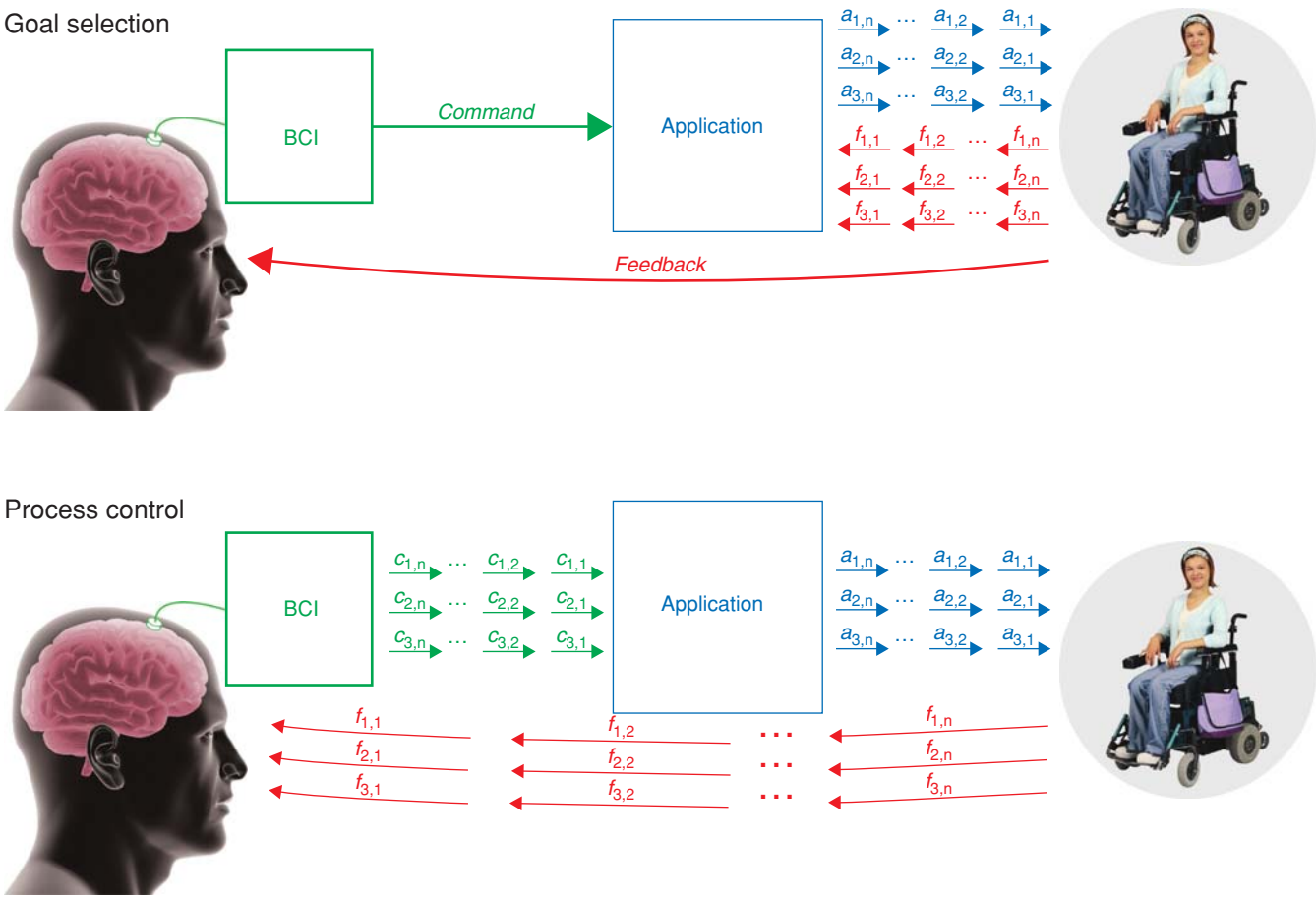


***Figure 1.6*** *BCI outputs: goal selection versus process control. BCI output commands can either select goals or control processes. In goal selection the BCI command specifies only the user's intent; the process that achieves this intent is accomplished by the application (i.e., the motorized wheelchair), which produces several concurrent sequences of actions (e.g., $a_{1,t=1}$, $a_{1,t=2}$, . . . $a_{1,t=n}$; $a_{2,t=1}$, $a_{2,t=2}$, . . . $a_{2,t=n}$; etc.) that control its movement and also manage the ongoing interactions between these actions and the resulting sequences of feedback (e.g., $f_{1,t=1}$, $f_{1,t=2}$, . . . $f_{1,t=n}$; $f_{2,t=1}$, $f_{2,t=2}$, . . . $f_{2,t=n}$; etc.). The feedback to the user is mainly the end result. In process control the brain and the BCI provide several concurrent sequences of commands (e.g., $c_{1,t=1}$, $c_{1,t=2}$, . . . $c_{1,t=n}$; $c_{2,t=1}$, $c_{2,t=2}$, . . . $c_{2,t=n}$; etc.) that correspond to the sequences of actions that the application produces; and the brain and the BCI continue to manage the ongoing interactions between these actions and the resulting feedback. The most successful BCIs are likely to combine goal selection and process control appropriately for each purpose and to thereby emulate the distributed control characteristic of natural muscle-based CNS outputs. (Modified from Wolpaw, 2007.)*

braking) (denoted by *a*'s in fig. 1.6[top]) that move the wheelchair to the desired location at a safe speed. The wheelchair application also receives concurrent detailed feedback (denoted by *f*'s) that allows it to adjust its actions as needed to avoid dangers such as staircases and obstacles such as walls, furniture, and other people. As the figure illustrates, the goal-selection protocol places most of the burden (i.e., for complex high-speed interactive control) on the application. The BCI simply communicates the goal, and the user simply views, and benefits from, the overall result. This example is analogous to using a global positioning system (GPS) to select a destination and then putting your vehicle on automatic pilot (assuming of course that it is equipped with this option!).

In contrast, in the *process-control* protocol shown at the bottom of figure 1.6, the user and the BCI control all the details of the process that accomplishes the user's intent. The user and BCI produce sequences of commands (denoted by *c*'s), which the wheelchair simply converts into actions (e.g., movements in *x* and *y* directions, turning, braking). The user processes the concurrent sequences of feedback to adjust the BCI's commands appropriately. The user and the BCI manage all the details of the process that puts the user in front of the television. The wheelchair simply does exactly what it is told to do. If goal selection is like using a GPS and an automatic pilot, process control is like driving the vehicle yourself and making all the decisions on which way to turn, how fast to go, when to stop, and so forth.

A simple summary of the difference between these two kinds of BCI output commands is that in goal selection the BCI tells the application what to do, whereas in process control it tells it how to do it. As chapters 12–18 illustrate, goal-selection and process-control protocols have both been used in a variety of BCIs, noninvasive as well as invasive.

From the point of view of the CNS and the BCI, goal selection is relatively easy. It requires only that the BCI provide the goal (i.e., the user's intent), which is the one part of the desired action that the application alone cannot provide. Once the goal is communicated, the application software and hardware are expected to achieve the goal rapidly and reliably. Goal selection is generally most appropriate for simpler BCI applications in which the set of possible commands is relatively small and fully defined (e.g., word-processing or wheelchair navigation in a specific environment with limited destinations). For more demanding applications, in which the set of possible goals may be large and not fully defined, or in which unexpected complications can occur (e.g., multidimensional control of a robotic arm or wheelchair navigation in different environments with many possible destinations), it may be necessary to use process control, which generally places greater demands on the CNS and the BCI.

As illustrated in figure 1.4A, natural CNS outputs are the product of the combined activity of many areas from the cortex to the spinal cord. Furthermore, the distribution of control varies appropriately from action to action. For example, a lengthy clinical and experimental literature indicates that the cortex plays a much greater role in fine finger control than it does in gross movements such as hand grasp (Porter and Lemon, 1993). In accord with the terminology used here, the cortex sometimes functions in a process-control manner in which it controls every detail of an action, and at other times it functions in a goal-selection manner in which it delegates the details to subcortical areas.

The most effective and desirable BCIs are likely to be those that imitate to the greatest extent possible the action-appropriate distribution of control that characterizes natural CNS function. To do this, BCIs might combine the two approaches of goal selection and process control. For example, in reaching to and grasping an object with a robotic arm, the cortex and the BCI might command the three-dimensional movement of the hand, the hand orientation, and the grasp while the application device might handle the details of the movements of the individual limb segments and the details of wrist rotation and finger flexion. Such distributed designs, which place fewer demands on the user and the BCI, may also be more realistic in the present state of BCI development. As progress continues, and as BCIs incorporate more elaborate and timely feedback from the evolving action to the CNS, goal selection and process control might be combined so that BCIs can emulate with steadily growing fidelity the speed, reliability, and ease of the brain's natural outputs.

## VALIDATING AND DISSEMINATING USEFUL BCI APPLICATIONS

Because of the complexity and multidisciplinary requirements of BCI development, most research groups focus on a single aspect, such as recording hardware, signal processing, or application design. This focus is both understandable and important for making substantive contributions. At the same time, the continuation and ultimate success of BCI development depend on realizing systems that are useful to the people with severe disabilities who are the principal reason for the existence of the field and for the substantial attention and support it currently receives. Thus, it is essential to develop systems that are clinically useful.

This task is an extremely demanding endeavor. It requires effective interdisciplinary collaborations and management of the complicated clinical and administrative requirements of human research (chapter 20) as well as attention to the more or less unique ethical issues associated with BCI research (chapter 24). Clinically useful BCI systems must function effectively and reliably in complex and often changing environments. They must be usable by nonexperts without excessive technical support and must provide applications that improve the lives of their users. These requirements constitute a hard and unforgiving test for systems first developed in the laboratory. At the same time, satisfying them validates the entire field of BCI research and development.

Even when BCI systems are clinically validated, their wider dissemination to the people who need them most faces several practical challenges. The dissemination of new medical technologies is typically a commercial endeavor and thus requires a reasonable expectation of profitability. However, the number of people who need the relatively modest capabilities of current BCIs, or of the BCIs likely to be available in the near future, is relatively small by typical marketing standards.

Thus, the immediate user population may not be large enough to attract and reward the commercial entities that could manufacture, market, and support current BCIs for those who need them most. Effective approaches to this problem may lie in therapeutic BCI applications (chapter 22) that can serve larger populations (e.g., people who have had strokes) and in well-structured commercial initiatives that target both the core group of people with severe disabilities and the much larger numbers of people in the general population who might use BCIs for other purposes (chapter 23). These difficult issues and their potential solutions are discussed in chapters 21 and 24.

## SUMMARY

The CNS interacts continuously with the outside world and the body through its natural neuromuscular and hormonal outputs. *BCIs measure CNS activity and convert it into artificial outputs that replace, restore, enhance, supplement, or improve the natural CNS outputs.* Thus, BCIs change the interactions between the CNS and its environment. The *new CNS outputs* that the BCI creates are fundamentally different from natural CNS outputs, which come from spinal motoneurons. BCI outputs come from brain signals that reflect activity elsewhere in the CNS (e.g., motor cortex). Effective BCI operation requires that the CNS control that activity nearly as accurately and reliably as it normally controls motoneurons. The achievement of such accuracy and reliability is a major challenge for BCI research.

The adaptations that optimize natural CNS outputs occur mainly in the CNS. In contrast, the adaptations that optimize BCI outputs can also occur in the BCI. Thus, BCI operation relies on the interaction between, and the adaptive capacities of, *two adaptive controllers*: the CNS and the BCI. The design of this additional adaptive controller (i.e., the BCI) and the management of its interactions with the adaptations of the CNS constitute a particularly challenging aspect of BCI research.

BCIs might use any of a variety of *different kinds of brain signals* recorded in a variety of different ways from a variety of different brain areas. Questions of which signals from which brain areas are best for which applications are empirical issues that need to be answered by experiment.

Like other communication and control interfaces, BCIs can encounter *artifacts* that obscure or imitate their critical signals. EEG-based BCIs must exercise particular care to avoid mistaking nonbrain signals recorded from the head (e.g., cranial EMG activity) for brain signals. This entails appropriately comprehensive topographical and spectral analyses.

BCI outputs can either *select a goal* or *control a process*. Ultimately, BCIs are likely to be most successful by combining goal selection and process control, that is, by distributing control between the BCI and the application in a manner appropriate to the current action. By such distribution, they could most closely emulate natural CNS function.

The continuation and ultimate success of BCI development depend on realizing systems that are useful to people with severe disabilities. The *clinical evaluation and validation* of BCIs are demanding endeavors requiring interdisciplinary collaboration and satisfaction of the complicated requirements of clinical research.

BCI research, which occupied only a handful of laboratories 15 years ago, is now an explosively growing field involving hundreds of research groups throughout the world. Its excitement and potential are drawing many young scientists and engineers into a vibrant research community that is engaging the numerous issues and pursuing the great promise of BCI technology. The intent of this book is to contribute to the further growth and success of this community by providing a solid grounding in fundamental principles and methods, by summarizing the current state of the art, and by raising and discussing critical issues.

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# PART II. | BRAIN SIGNALS FOR BCIs

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# 2 | NEURONAL ACTIVITY IN MOTOR CORTEX AND RELATED AREAS

LEE E. MILLER AND NICHOLAS HATSOPOULOS

In 1870, Eduard Hitzig and Gustav Fritsch applied electrical stimuli to a region on the surface of a dog's brain that caused the limb on the opposite side of its body to move. This observation was critical in a number of respects. It demonstrated that, like muscles, the brain is electrically excitable. By finding limb movement represented in a particular area, it also addressed the larger issue of whether different parts of the brain, and of the cerebral cortex in particular, were devoted to different functions. In the middle of the 19th century opinions on this point ranged from that of the minute cortical specialization held by the phrenologists (Gall and Spurzheim 1809), to that of Pierre Flourens, who held that the cerebral cortex was largely unspecialized (Flourens 1824). Based on their experiments, Hitzig and Fritsch ultimately described the area of the brain that we now know as the *primary motor cortex* (Fritsch and Hitzig 1870). Also in the 1870s, David Ferrier conducted experiments similar to those of Hitzig and Fritsch using monkeys as subjects (Ferrier 1873).

Today, neurosurgeons routinely use electrical stimulation to map the brains of awake human patients undergoing surgical procedures for treatment of severe epilepsy or tumor resection. The goal is to identify *eloquent cortex*, (i.e., areas where damage will result in paralysis or in loss of sensation or linguistic ability). These methods were pioneered by the Canadian neurosurgeon Wilder Penfield, whose work led to the now familiar map of the *motor homunculus* that is reproduced in different versions in nearly every textbook dealing with neuroscience (Penfield and Boldrey 1937; Penfield 1958) (fig. 2.1). This map depicts the areas of motor cortex associated with distinct motor functions. It is a distorted image of the body in which parts that require more finely graded control (e.g., the hand) have disproportionately large representations.

Beyond the primary motor cortex, Penfield identified the areas that we now refer to as the premotor cortex and the supplementary motor area (Penfield and Welch 1951). These names (and the names of several other premotor areas) reflect their connections into primary motor cortex and their relatively sparse projections into the spinal cord. Other investigators working in the same period included Woolsey and colleagues (Woolsey et al. 1952), who used a variety of techniques in experimental animals to map not only the motor cortex but also the sensory areas of cortex that are part of a larger network of sensory, association, and motor areas that function together to produce normal movement.

At about the time of Woolsey's experiments, the first recordings of electrical activity from single neurons in the brains of either awake or lightly anesthetized animals were conducted in the laboratories of Vernon Mountcastle, David Hubel, Herbert Jasper, and Edward Evarts (Mountcastle 1957; Hubel 1957; Jasper et al. 1958; Evarts 1966). By inserting microelectrodes into the cortex so that their exposed tips were close to individual cortical neurons, they were able to record single *action potentials,* or *spikes*, from these neurons.

An *action potential* is a brief (about 1 msec) and highly stereotyped fluctuation in neuronal membrane potential that occurs when excitatory synaptic input to the neuron triggers an abrupt, transient opening of channels in the cell's membrane, through which specific ions can flow. These action potentials are actively regenerated as they travel down a neuron's axon to provide synaptic input to other neurons. Action potentials are

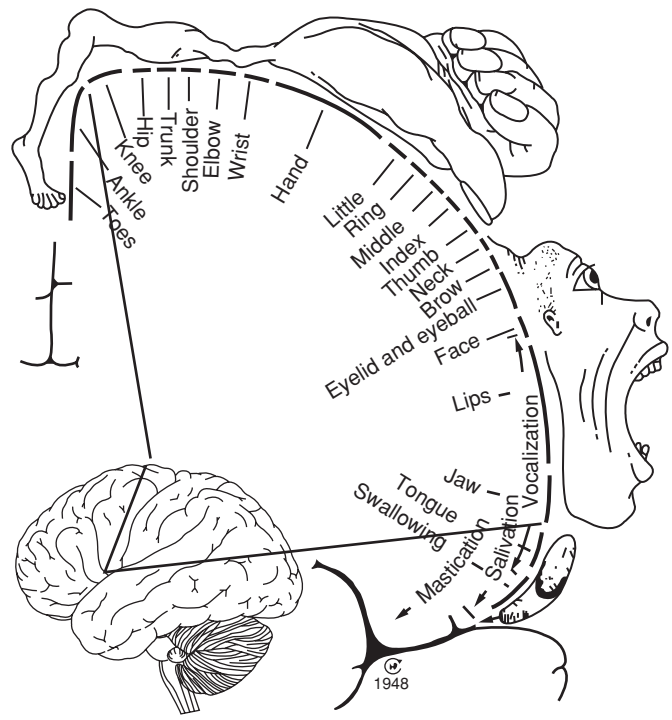


***Figure 2.1*** *The motor homunculus derived by Wilder Penfield illustrating the effects of electrical stimulation of the cortex of human neurosurgical patients. Adapted from Nolte (2002).*

viewed as the basic units of interneuronal communication and information transfer in the nervous system. A detailed description of this fundamental phenomenon may be found in any basic neurophysiology textbook.

These seminal neuronal-recording experiments began to reveal the relationships between neuronal discharge (i.e., spikes) in motor and sensory areas of cortex and movements or external sensory events. In the decades since these first studies, tremendous improvements have been made in microelectrode and electronics technology so that it is now possible to record the activity of many tens or hundreds of neurons simultaneously. This new technology has helped give rise to the brain-computer interface (BCI), whereby such recordings can be interpreted by a computer and used as a source of control signals, ultimately to provide movement or communication to a paralyzed person.

This chapter has six sections. The first four discuss the anatomy and functional roles of the brain areas that are most relevant to the development of BCI technology. This coverage is intended to provide a basic background for those readers who are not familiar with these topics and a succinct review for those readers who are. The final two sections discuss the information content of neuronal discharge recorded from these areas and review current methods for recording and analyzing spikes from many cortical neurons simultaneously (these two topics are discussed further in chapters 5 and 16).

## OVERVIEW OF BRAIN ANATOMY

In humans, most of the brain consists of the two paired *cerebral hemispheres* (fig. 2.2). Each hemisphere is covered with *cortex*, a structure that varies in thickness in different regions from about 1.5 to 4.0 mm. The cortex is known colloquially as *gray matter* because of the color imparted by its large number of neurons. Beneath the cortex are a number of other deeper gray-matter structures, the *subcortical* areas including the basal ganglia, cerebellum, brainstem, and thalamus. The brain's *white matter* (so-called because of its lighter color) consists of the many nerve fibers that interconnect the various cortical areas and that connect the cortex to subcortical areas (and visa versa).

The left panel of figure 2.3 shows the trajectory of a single corticospinal fiber (i.e., one that extends from the cortex to the spinal cord). This fiber starts in motor cortex, goes through the cerebral peduncle, the pons, and into the medulla, where it crosses to the other side of the body and enters the spinal cord. It ultimately projects to interneurons and motoneurons in the ventral horn of the spinal cord on that side. Thus, in general, corticospinal fibers from neurons on one side of the brain activate muscles on the other side of the body.

Because the cerebral cortex is responsible for movement planning and because it is relatively accessible experimentally, it is the brain area of primary focus in most BCI research. Accordingly, this section of the chapter will focus mainly on the cortex, with brief additional discussion of the subcortical areas with which it is interconnected and that affect and modulate its activity.

### TERMINOLOGY FOR DIRECTIONS IN THE CNS

Several different coordinate axes are used to describe directions within the body in general and the CNS in particular (fig. 2.2). The *mediolateral axis is perpendicular to the midline,* and the body is bilaterally symmetrical along this axis. That is, the zero point of the mediolateral axis is at the midline, and the value rises as distance to the left or right increases. The *rostral* (or *cranial*) to *caudal* axis (also called the *rostrocaudal* axis) goes from the head (or more precisely, the face or mouth) to the tail. Thus, the most rostral part of the CNS is the front of the frontal lobe, and the most caudal is the end of the spinal cord. The third axis is the *dorsoventral* axis; it is perpendicular to both the mediolateral and rostrocaudal axes, and goes from the back (or *dorsum*) to the front (or *ventrum*). In a quadruped, these definitions remain consistent for the spinal cord and brain. In a biped, the rostrocaudal and dorsoventral axes rotate forward, such that the dorsoventral axis becomes parallel to the gravity vector (fig. 2.2, lower).

Axis terminology is further complicated by the anterior-posterior axis. In general, *anterior* refers to the direction toward the front of the head or body (i.e., the face or abdomen), and *posterior* refers to the opposite direction. However, when applied to the brain, the anterior-posterior axis is the same as the rostrocaudal axis. Thus, the front edge of the frontal lobe is the most rostral, or anterior part, of the cerebrum, and the tip of the occipital lobe is the most caudal or posterior. In contrast, when applied to the spinal cord, the anterior-posterior axis is the same as the dorsoventral axis. Finally, the terms used for specifying location along the main axis of a limb are *proximal* and *distal*: *proximal* means close to the body, whereas *distal* means far from the body (e.g., the hand or foot).

### THE CEREBRAL CORTEX

The cerebral cortex has four major parts, or *lobes*:

- *frontal*
- *parietal*
- *occipital*
- *temporal*

Whereas the cerebral cortex of lower mammals (e.g., rodents, rabbits, and some primates) is a relatively smooth sheet, the cerebral cortex of higher mammals is highly convoluted by a set of gyri (ridges) and sulci (grooves) that divide the cortex into distinct anatomical regions. The convolutions have presumably evolved to increase cortical volume while maintaining an unchanged thickness. The sulci and gyri define the four main lobes of the cerebral cortex, as well as other cortical subdivisions (fig. 2.2). The *frontal and parietal lobes* are separated by the *central sulcus (CS)*, which is a deep groove between the cortical folds (called *gyri*) (fig. 2.2). The *frontal lobe* lies on the anterior side of the CS and the *parietal lobe* lies on its posterior side. The gyrus on the anterior side of the CS is the *precentral gyrus*, that on the posterior side is the

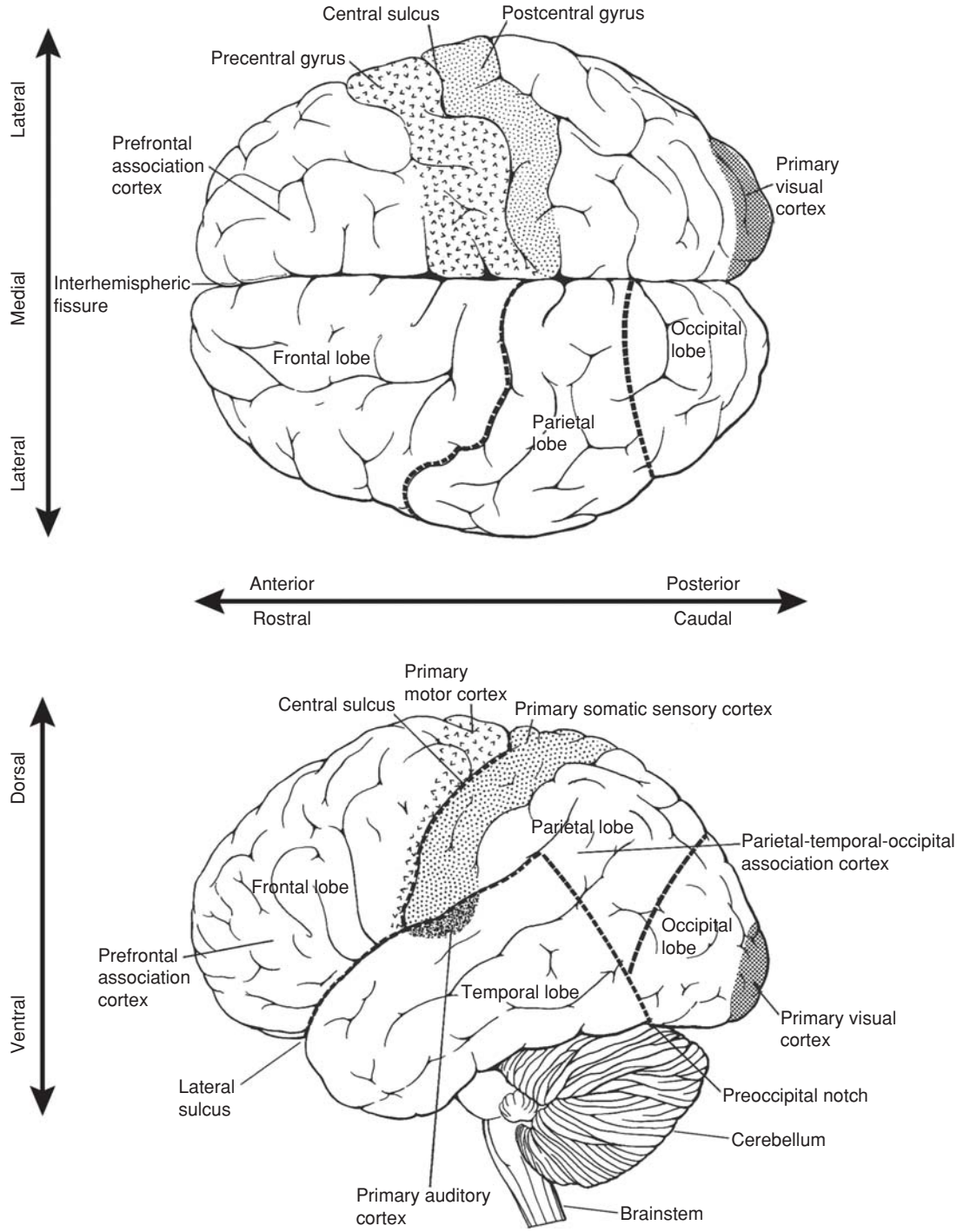


***Figure 2.2*** *Major divisions of the human cerebral cortex in dorsal (from above) and lateral views. The four major lobes (frontal, parietal, occipital, and temporal) are indicated, as well as several of the functionally defined cortical areas. Adapted from Kandel et al. (1991).*

*postcentral gyrus*. Primary motor cortex (M1) lies along the anterior wall of CS and continues into the precentral gyrus. Primary somatosensory cortex (S1) lies along the posterior wall of the CS and continues into the postcentral gyrus.

The frontal lobe is dramatically expanded in humans, even compared to our closest primate relatives. Much of this expansion is within the most anterior, *prefrontal area* (fig. 2.2), which is involved in higher-order executive function, including complex cognitive behaviors, personality, and decision making.

Posterior (or caudal) to the CS are the *parietal lobe* and then the *occipital lobe*. Primary somatosensory cortex (S1) is within the most anterior part of the parietal lobe. Farther posterior, in what is referred to as the *posterior parietal cortex* (PPC), is a region of *multimodal association cortex*, that receives input from the somatosensory, visual, and auditory sensory areas that surround it.

The *occipital lobe,* at the posterior pole of the brain, consists primarily of visual areas. The *temporal lobes* are located ventrally

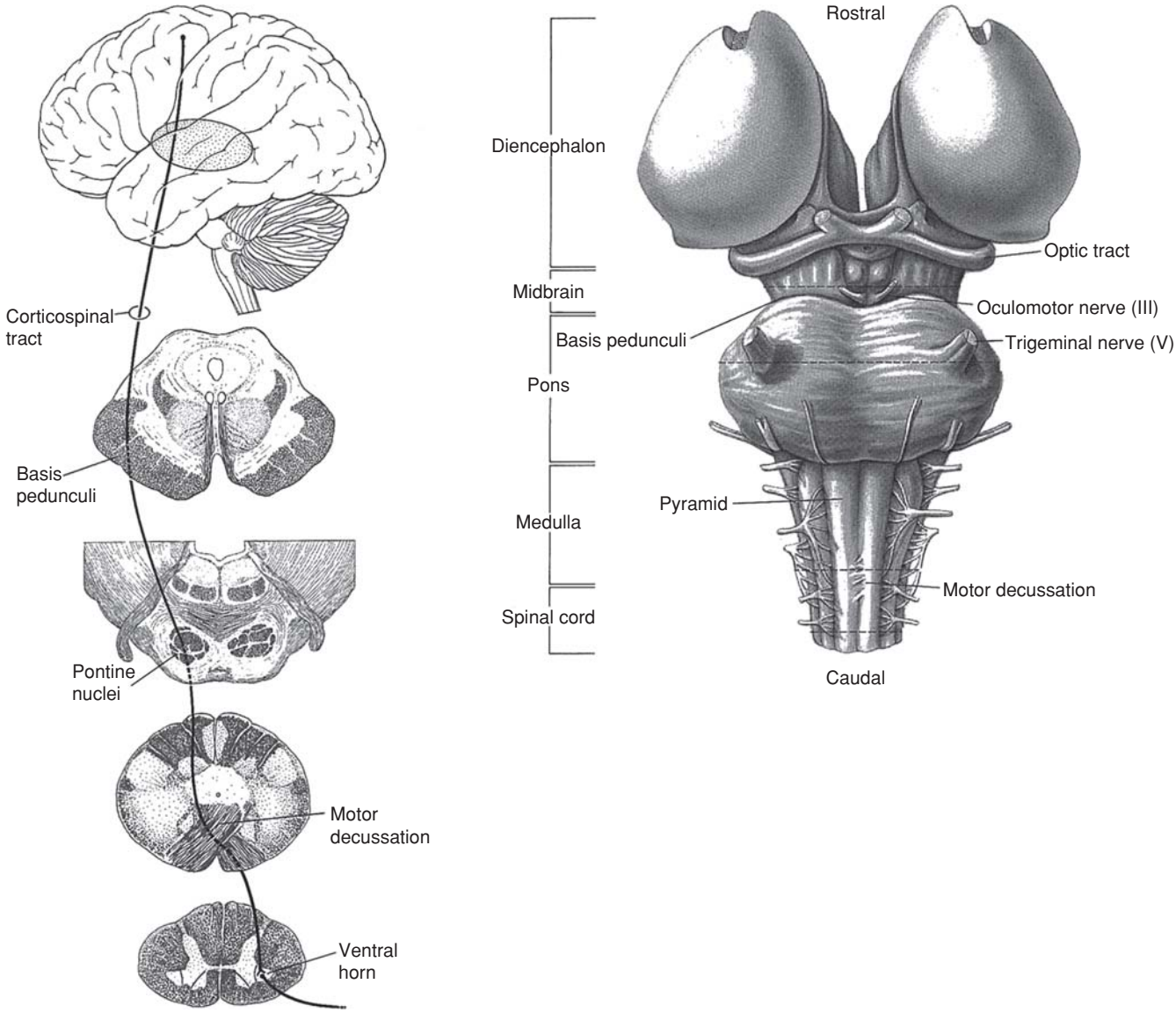


***Figure 2.3*** *(Left) The corticospinal tract as it descends from the cerebrum through the brainstem to the spinal cord. (Right) Ventral view of the midbrain, pons, medulla, and spinal cord; the cerebellum (not shown) is behind (i.e., dorsal to) the pons and medulla. Adapted from Kandel et al. (1991).*

along the sides of the brain. They are critical for auditory signal processing, higher-level visual processing, and memory.

The cerebral cortex has three histologically distinguishable parts: the neocortex; the paleocortex; and the archicortex. The *neocortex* comprises most of the cortex in mammals and is discussed in detail in this chapter. The paleocortex and archicortex are evolutionarily older forms of cortex. The paleocortex comprises a region at the bottom (i.e., the ventral side) of the cerebrum that includes, but is not limited to, the olfactory cortex. The archicortex (largely synonymous with the *hippocampus*) is a structure located deep within the temporal lobes that plays a critical role in the formation of new memories and in spatial navigation.

In the early 1900s, Korbinian Brodmann differentiated approximately 50 areas within the cerebral cortex, based largely on the distribution, density, and types of cells within each area (Brodmann 1909). His published cytoarchitectonic map provided the framework for many subsequent investigations into the functional differentiation of the cerebral cortex. This map is shown in figure 2.4, and some of the important areas are noted in table 2.1. With the advent of modern anatomical and physiological techniques, many of the Brodmann areas have been further subdivided. The overlap between the anatomically defined maps and functional maps determined later by physiological methods is rather remarkable.

## THE SIX LAYERS OF NEOCORTEX

Neocortex is composed of six morphologically distinct layers (labeled I–VI), distinguishable mainly by the types of cells they contain. *Pyramidal cells* (named for their pyramidal shape) are projection neurons (i.e., their axons extend to other cortical regions and/or to subcortical regions as far away as the spinal cord). Of the nonpyramidal neurons, *stellate* cells (also called *granule* cells) are the most numerous; stellate cells have extensive

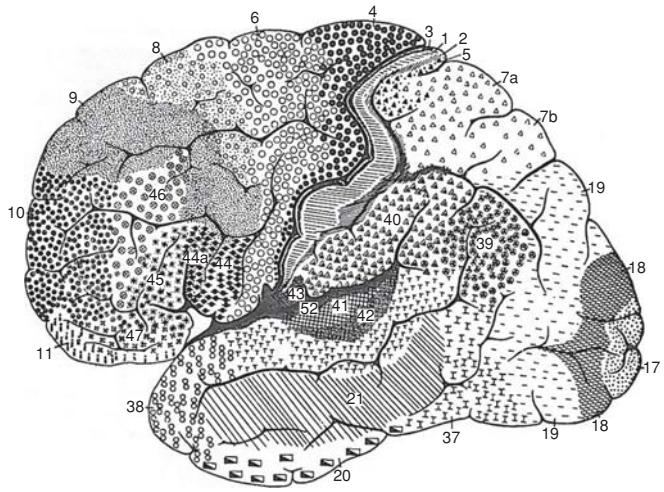


***Figure 2.4*** *Lateral view of the cerebral cortex from the work of Korbinian Brodmann. Each of the different symbols represents an area Brodmann considered to be anatomically distinct. He identified and numbered a total of more than 50 such areas. His numbering is best understood in terms of his sectioning methodology. Unlike modern brain sectioning, which usually proceeds along the rostrocaudal axis, Brodmann sectioned along the dorsoventral axis, so that his areal numbering begins at the top of the brain (i.e., the central sulcus) and often alternates anteriorly and posteriorly as it proceeds ventrally. From Nolte (2002).*

dendrites that arise from the cell body and that terminate, along with the axon, within a restricted region of the cortex. Stellate cells are primarily involved in processing information locally.

Layer I, the outermost layer of the neocortex, is called the molecular layer. It contains very few neurons and is composed mostly of the dendrites arising from pyramidal neurons in deeper layers and horizontally running axons. Layer II is called the external granular layer and contains mostly stellate cells and small pyramidal cells. Layer III is called the external pyramidal layer and contains both small and medium-sized pyramidal cells. It is the primary source of fibers that interconnect the different areas of cortex. Layer IV is the internal granular layer. It contains many nonpyramidal neurons and receives much of the input coming to the cortex. These fibers that come *to* the cortex (and are therefore called *afferent* fibers) originate in the thalamus and carry signals from each of the primary senses. Layer V is the internal pyramidal layer. It contains the largest pyramidal cells, the source of the long axons that project *out* of the cerebrum (and are therefore called *efferent* fibers). The largest of these Layer V pyramidal cells are located in the primary motor cortex and are referred to as Betz cells (Betz 1874). Finally, Layer VI, called the multiform layer, contains the greatest variety of cell types. It is the source of most fibers from the cortex (i.e., efferent fibers) to the thalamus.

In different cortical regions, the amount of cortex devoted to a given layer varies depending on the function of the area. For example, the primary visual and somatic sensory cortices have an input layer IV that is much thicker than that in the primary motor cortex; in contrast, the output layer V predominates in primary motor cortex. In sensory regions of cortex, layer IV contains a large number of granule cells. These regions are therefore often referred to as *granular cortex*. In contrast, motor areas of cortex lack a prominent layer IV and are termed *agranular*.

**TABLE 2.1** Common names and abbreviations of the major cortical motor areas together with their Brodmann and Matelli designations*

| COMMON NAME | COMMON ABBREVIATION | BRODMANN (Vogt 1919) | MATELLI |
|---|---|---|---|
| Primary motor cortex | M1 | 4 | F1 |
| Premotor cortex (Dorsal, rostral division) | PMdr | 6 (6aβ) | F7 |
| Premotor cortex (Dorsal, caudal division) | PMdc | 6 (6aα) | F2 |
| Premotor cortex (Ventral, rostral division) | PMvr | 6 (6aα) | F5 |
| Premotor cortex (Ventral, caudal division) | PMvc | 6 (4c) | F4 |
| Supplementary motor area | SMA | 6 (6aα) | F3 |
| Presupplementary motor area | pre-SMA | 6 (6aβ) | F6 |
| Cingulate motor area (rostal division) | CMAr | 24 | 24c |
| Cingulate motor area (caudal division) | CMAc | 23 | 24d |
| Anterior intraparietal area | AIP | 7 | |
| Ventral intraparietal area | VIP | 5/7 | |
| Medial intraparietal area | MIP | 5 | |
| Parietal reach region | PRR | 5 | |
| Primary somatosensory cortex | S1 | 1, 2, 3 | |
| Prefrontal cortex | PFC | 9 | |

*Matelli et al. (1985, 1991).

Intracortical efferents arising in layer III project ipsilaterally within a given gyrus and interconnect cortical regions in different lobes of the ipsilateral side. The longest fibers travel in association bundles. For example, the superior longitudinal fasciculus contains the fibers that interconnect the frontal and parietal lobes. Fibers projecting between the hemispheres travel primarily through the corpus callosum, which contains some 300 million fibers.

## SUBCORTICAL AREAS

The major subcortical areas of the brain that interact with cortex and are intimately involved in motor and sensory function include the:

- *thalamus*
- *brainstem*

- *basal ganglia*
- *cerebellum*

The *thalamus* is located below the cortex and deep within the cerebrum. It serves as the main gateway to the cerebral cortex for sensory inputs from the spinal cord and from other subcortical structures including the basal ganglia and cerebellum. It also receives input from the cerebral cortex, which suggests that the thalamus plays a complex regulatory function.

The *brainstem* is at the base of brain (just visible in fig. 2.2, lower panel). The brainstem, consisting of the *midbrain*, *pons,* and *medulla oblongata*, can be seen in greater detail in figure 2.3. The medulla oblongata connects to the spinal cord. The brainstem contains nerve fibers descending to and ascending from the spinal cord; it also contains a number of motor and sensory nuclei, collections of neurons that further process these signals. The most numerous of these are within the pons (and are known collectively as the *pontine nuclei*).

The *basal ganglia* are a collection of interconnected nuclei located deep within the cerebrum. They are strongly connected with the cerebral cortex and play a critical role in movement. Both Parkinson's disease and Huntington's chorea are associated with pathology in the basal ganglia.

The *cerebellum* (derived from the Latin for *little brain*) is nestled under the posterior part of the cerebral hemispheres (see fig. 2.2, lower panel). The cerebellum is involved in the production of smooth, coordinated movements as well as in motor learning and adaptation. Although it has no direct connections to the spinal cord, it influences movement indirectly by way of its connections to the cerebrum and brainstem. People with disorders of the cerebellum are still able to move, but their movements lack normal coordination; these characteristic deficits are known collectively as *ataxia*.

### CORTICAL EFFERENT PROJECTIONS

Nerve fibers that leave the cortex are called *cortical efferent fibers*; fibers that enter the cortex are called *cortical afferent fibers*. The cortical efferent fibers converge to pass through the *internal capsule*, a very dense collection of cortical afferent and efferent fibers located just lateral to the thalamus. From the internal capsule, these and other descending fibers form the paired *cerebral peduncles* (*basis pedunculi* in fig. 2.3) each of which contains roughly 20 million fibers. Between 85% and 95% of these fibers terminate within the brainstem, the largest proportion within the pontine nuclei. This *corticopontine pathway* also provides a massive projection from many regions of the cerebral cortex to the cerebellum. Other efferent fibers from the cortex end in the caudate and putamen (collectively known as the *striatum*), the input nuclei of the basal ganglia (see below). Other cortical efferents, known collectively as *corticobulbar fibers*, terminate in the lower brainstem area and include projections to both motor and sensory brainstem nuclei.

The remaining one million cortical fibers form the *medullary pyramids* (which give the *pyramidal tract* its name) and continue to the spinal cord as the *corticospinal* (CST) tract. Eighty to ninety percent of these CST fibers cross the midline at the *pyramidal decussation* (as shown in fig. 2.3) within the caudal medulla and run in the lateral columns of the spinal cord in primates and cats. (In rats, the CST is at the base of the dorsal columns of the spinal cord.) The remaining fibers remain uncrossed until they terminate bilaterally in the spinal cord, and constitute the *ventromedial CST*. In primates particularly, some corticospinal fibers synapse directly on motoneurons within the ventral (or anterior) horn of the spinal gray matter, especially motoneurons supplying the distal extremities. Some CST fibers (those arising from S1) project into the dorsal (or posterior) horn of the spinal gray matter, which receives sensory afferents coming in from the peripheral nerves. However, the majority of CST fibers project to the intermediate zone and influence motoneurons (which are located in the ventral [anterior] horn of the spinal gray matter) indirectly, through spinal interneurons.

## MOTOR AND SENSORY AREAS OF THE CEREBRAL CORTEX

The cerebral cortex is the area of greatest interest in BCI research because it is most accessible to electrode probes (as well as to scalp recording) and because it is highly involved in the executive function of motor and communication behaviors.

The cortical surface features provide convenient landmarks for the identification of particular regions of the brain. In monkeys, the small spur extending posteriorly from the arcuate sulcus (see fig. 2.5), is a useful mediolateral landmark approximating the region of the cortex that controls proximal arm movements (Georgopoulos et al. 1982). In humans, a distinctive portion of the precental gyrus known as the "hand knob" marks the region controlling hand movements (Yousry et al. 1997). These landmarks are often used to guide implantation of intracortical electrodes. However, although they are useful for localization during surgery to place electrodes, the deep sulci make experimental access to the cortex with multielectrode recording techniques more difficult.

Table 2.1 lists the main motor areas of the brain that have been identified by a number of different classification systems. The most widely used are shown in the table and include the common names (column 1); their common abbreviations (column 2); the cytoarchitectonic areas described for the monkey by Brodmann (1909) and by Vogt (1919) (column 3); and a later system based on cytochrome-oxidase staining in the monkey (column 4) (Matelli et al. 1985; Matelli et al. 1991). In this chapter, we use primarily the common names and abbreviations shown in columns 1 and 2 of table 2.1.

### CORTICAL SPECIALIZATION

#### *PRIMARY MOTOR CORTEX*

*Primary motor cortex* (M1), located in the frontal lobe, is a brain region of great importance in BCI research because of its close relation to movement control. Fritsch and Hitzig (1870) and Ferrier (1873) were able to activate muscles with relatively weak electrical stimulation in this area because of the relatively

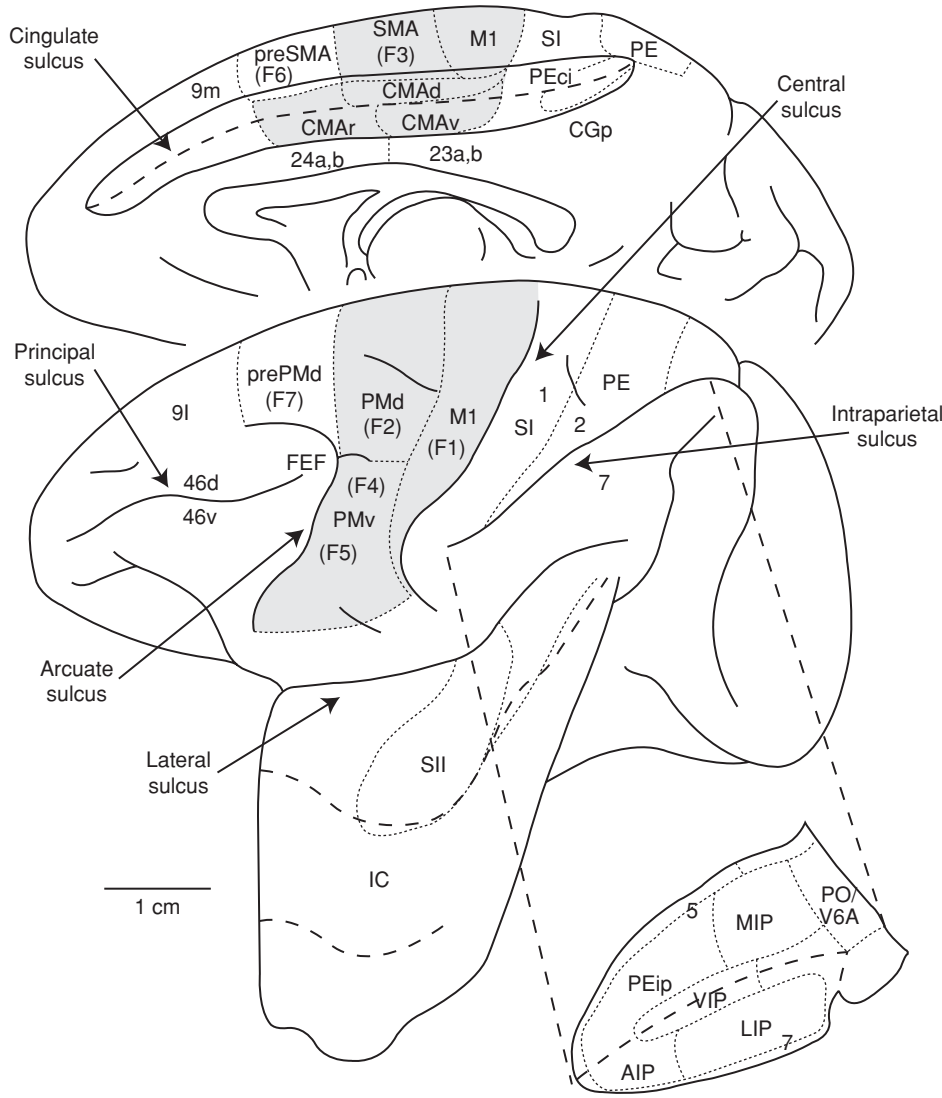


***Figure 2.5*** *Identification of cortical areas in the macaque monkey. Anterior is to the left and posterior is to the right. The cingulate and lateral sulci are unfolded, and each fundus (i.e., the deepest part of the sulcus) is indicated by a bold dashed line. The intraparietal sulcus is unfolded similarly and shown as an inset. The borders between cytoarchitectonic areas are delineated with dotted lines. M1 and the premotor areas are shaded. Abbreviations: AIP, LIP, MIP, VIP are anterior, lateral, medial, and ventral intraparietal areas, respectively; CMAd, CMAv, CMAr are dorsal, ventral, and rostral cingulate motor areas, respectively; F1 to F7 are cytoarchitectonic areas in the frontal lobe according to Matelli et al. (1985, 1991); IC is insular cortex; M1 is primary motor cortex; PMd is dorsal premotor area; PMv is ventral premotor area; prePMd is predorsal premotor area; preSMA is presupplementary motor area; SI is primary somatosensory cortex; SII is secondary somatosensory cortex; SMA is the supplementary motor area; PE and PEip are parietal areas (Pandya and Seltzer 1982); PO is the parietooccipital area or V6A (Wise et al. 1997); 9m, 9l, 46d, 46v are prefrontal areas (Walker 1940; Barbas and Pandya 1989). Adapted from Dum and Strick (2005).*

large density here of giant Betz cells whose axons form the CST. In primates particularly, these cells frequently project directly to spinal motoneurons, which probably contributes to their ability to activate small sets of muscles (Lemon 2008).

The primary motor cortex is organized somatotopically. That is, particular regions of M1 are devoted primarily to the control of particular body areas. This organization is reflected in Penfield's homunculus (fig. 2.1), in which an oddly shaped body is drawn along the central sulcus. Representations of the legs and feet are found within the medial wall of the cerebrum; the trunk, upper arm, and hand representations occur progressively more laterally in the hemisphere; and the face is most lateral. Although neighboring body parts are typically represented within neighboring areas of cortex, these body parts are spatially distorted because control of some body parts is more complex than that of others. For example, control of the many facial or hand muscles is much more complex than is control of the much larger biceps muscle that flexes the elbow. Consequently, a greater amount of cortical area is devoted to the control of the face or the hand than to the upper arm. These general principles of somatotopic organization apply to sensory as well as motor areas of cortex.

Despite the basic appeal of this textbook caricature of cerebral cortex motor representation, a true motor map probably bears a good bit less resemblance to the body (Schieber 2001). Figure 2.6, taken from work in Cheney's laboratory, contains a map that is analogous to Penfield's in that it shows the spatial distribution of motor areas that represent various body areas

(Park et al. 2001). The solid line in this figure represents the lip of the anterior bank of the precentral gyrus. The parallel dashed line indicates the fundus of the central sulcus and the posterior limit of M1. This study achieved much higher spatial resolution than those of Penfield, because it used *intracortical*, rather than surface stimulation and because the stimulating currents were almost 1000-fold smaller. Although the gross features of figure 2.6 are similar to those in figure 2.1 (i.e., the face most lateral, the legs most medial, and the hand and arms in between; see also Sessle and Wiesendanger 1982), it lacks the individual digits and simple linear mapping along the sulcus of the familiar homunculus.

Since Penfield and Woolsey identified the primary and premotor cortices, many additional motor cortical areas have been identified. Although not shown in figure 2.5, M1 can be subdivided into two regions: caudal M1 (M1c) (essentially that lying within the sulcus); and rostral M1 (M1r) (the portion on the cortical surface and extending rostrally—or anteriorly—nearly to the arcuate sulcus [ArS in fig. 2.5]). Neurons in M1c, nearest to the somatosensory cortex, are more strongly influenced by somatosensory inputs than are neurons in M1r (Strick and Preston 1978a; Strick and Preston 1978b). A variety of other motor areas have been identified that have projections into M1.

### PREMOTOR CORTEX

*Premotor cortex* (PM), also located in the frontal lobe, is the area anterior (rostral) to the primary motor cortex (fig. 2.5). In monkeys, the border between the M1 and PM falls roughly midway between the central sulcus (CS) and the arcuate sulcus (ArS) (see fig. 2.5). As noted in the figure, the PM is divided into dorsal (PMd) and ventral (PMv) areas. Each of these is sometimes further divided into rostral (PMdr and PMvr) and caudal (PMdc and PMvc) areas. These subdivisions are distinguished by differences in their parietal and prefrontal inputs, by their outputs to M1, and by whether or not they project to the spinal cord (Ghosh and Gattera 1995; Matelli et al. 1998; Fujii et al. 2000).

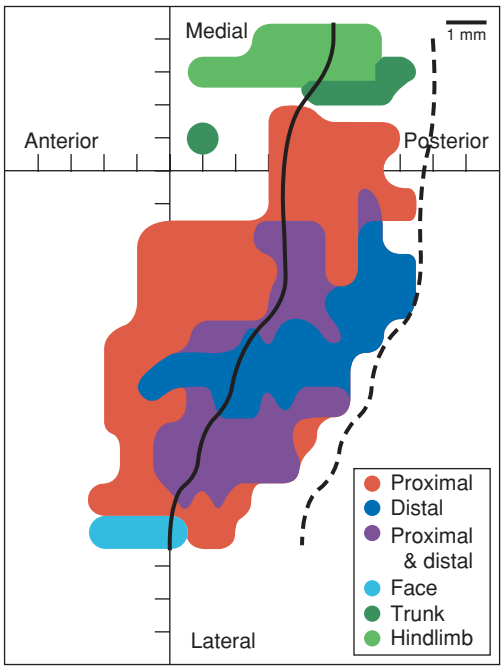


***Figure 2.6*** *Map of the effects of intracortical microstimulation within primary motor cortex of a monkey. The map indicates the body parts that were activated by stimulation at each point in cortex. The central sulcus has been unfolded. The dashed line indicates the fundus (i.e., bottom) of the central sulcus. The solid line is the crown of the precentral gyrus. Adapted from Park et al. (2001).*

In addition to these premotor areas, there are several other limb-related premotor areas that have been identified within the frontal lobe of the monkey. These can be seen in the upper drawing in figure 2.5: the supplementary motor area (SMA) and the cingulate motor area (CMA). SMA is located medial to PMdc, and is primarily within the interhemispheric fissure. It extends slightly onto the exposed surface of the cortex. CMA is located entirely on the medial wall within the cingulate sulcus. As seen in figure 2.5, the CMA has been further subdivided into rostral (CMAr), dorsal (CMAd) and ventral (CMAv) areas.

Electrical stimulation applied to the premotor cortices can elicit movement as in M1. However, somewhat higher currents are required here than for M1, and the movements tend not to be isolated to individual parts of the hand or limbs as they are for M1. All of these premotor areas (except for PMdr) are characterized by fairly extensive spinal projections in parallel with those from M1 (Hutchins et al. 1988; Dum and Strick 1991).

### SOMATOSENSORY CORTEX

The *primary somatosensory cortex* (S1), located in the parietal lobe, is important in movement because it conveys the sensations of touch, temperature, pain, and limb position that are important in guiding movement. S1 lies in the most anterior part of the parietal lobe. It starts along the posterior (caudal) wall of the CS and extends into the postcentral gyrus. It receives both tactile and proprioceptive (see below) input from the spinal cord by way of the thalamus.

The sense of touch originates from a combination of mechanoreceptors located either superficially or deep in the skin. Both the depth and the spacing of the receptors determine the spatial resolution of the signals they convey, from the exquisite sensitivity of the tips of the fingers, to the much less sensitive skin on the trunk. In addition, some of these receptors remain sensitive to maintained contact (slowly adapting receptors), whereas others are optimized to sense changes (rapidly adapting receptors).

S1 also conveys *proprioception*, the sense of both limb position and movement. Although less a part of our conscious awareness than either vision or somatosensory modalities, proprioception is, nevertheless, quite important for planning and guiding movement. Proprioceptive input is derived primarily from two types of receptors within the muscles: muscle spindles that are sensitive both to muscle length and to rate of stretch, and Golgi tendon organs that sense muscle force.

As is true of other senses, somatosensory input is relayed to the cerebral cortex by the *thalamus*. The thalamus is located deep within the brain and is subdivided into a number of regions, each of which processes input from a different sensory modality. Thalamic somatosensory inputs converge on several cerebral cortical areas, which together comprise S1. These include

Brodmann areas 3a, 3b, 1, and 2 (fig. 2.7). Area 3a receives primarily proprioceptive input, whereas 3b receives tactile input. The border between 3a and 3b lies within the central sulcus, but its location varies considerably among individuals (Krubitzer et al. 2004). Area 1 is similar to area 3b in that it responds mostly to tactile stimuli, receiving a combination of inputs from the thalamus and area 3b. On the other hand, area 2 is similar in many respects to 3a in that it is predominantly proprioceptive, receiving input both from the thalamus and from area 3a.

Perhaps unexpectedly, S1 also sends many axons to the spinal cord, but the axons terminate mainly in the dorsal part (i.e., the dorsal horn) of the spinal gray matter and are thought to regulate spinal reflexes and afferent input to the cerebrum (Liu and Chambers 1964; Coulter and Jones 1977; Yezierski et al. 1983; Ralston and Ralston 1985).

### POSTERIOR PARIETAL CORTEX

The PPC (i.e., areas 5 and 7, including the regions within the intraparietal sulcus in fig. 2.5) is also involved in sensory function. It is an example of a multimodal *association cortex*, in that many of these neurons receive a combination of visual, auditory, and somatosensory inputs (Blatt et al. 1990; Andersen et al. 1997; Breveglieri et al. 2006). The PPC probably combines this sensory input to form an internal map of the limbs and their relation to the external world that is used to guide movement planning. Lesions within this part of the brain can cause a disorder called *hemispatial neglect*, in which a person becomes unable to recognize the limbs on the opposite side of the body.

Vision and proprioception are undoubtedly the most important of the sensory input modalities that guide movements. Visual signals from the occipital lobe follow two divergent paths, one extending into the PPC and the other into the temporal lobe. These have been referred to, respectively, as the *dorsal and ventral visual streams* (Ungerleider and Mishkin 1982), and the function of these two streams has traditionally been divided into object-*location* (the "where" or dorsal stream), and object-*recognition* (the "what" or ventral stream). Another view is that these two streams might more properly be viewed as vision-for-action and vision-for-perception, respectively (Goodale and Milner 1992), a view that reflects the anatomy of the dorsal action stream, which passes from visual cortex into the PPC and then into the motor areas of the frontal lobe.

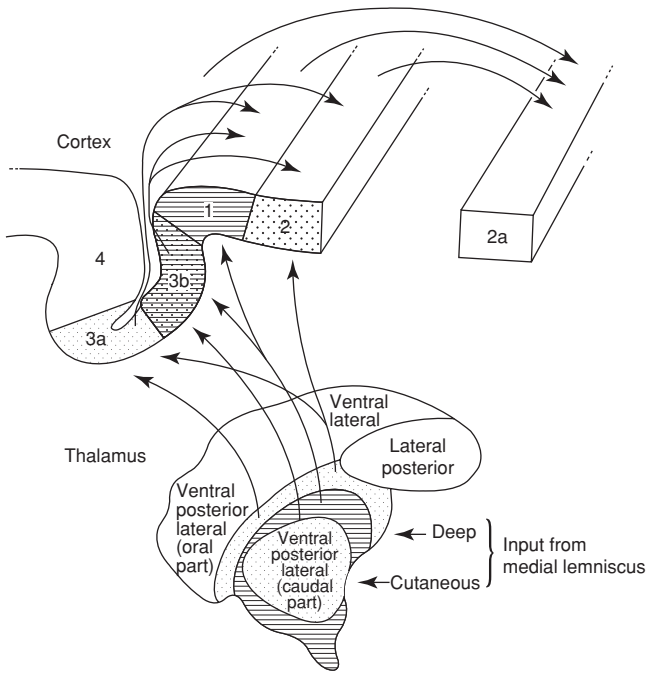


*Figure 2.7* *Projections from the somatosensory portions of the thalamus to the primary somatosensory cortex. Adapted from Kandel et al. (1991).*

As with the visual system's division into object-recognition for perception and object-location for action, the somatosensory system may be similarly divided into representations for perception and action. The ventral stream (perception) analog projects from the secondary somatosensory cortex (SII in figure 2.5) to the insula and is thought to be involved in tactile learning and memory (Mishkin 1979; Friedman et al. 1986). The dorsal stream analog (action) enters the PPC together with visual input and then projects to the frontal lobe.

Within the PPC are several areas that play important roles in the control of movement. These lie near the intraparietal sulcus (IPS) (fig. 2.5). The lateral intraparietal area (LIP) (see fig. 2.5, inset showing detail of the IPS) is primarily involved in the control of saccadic (i.e., rapid) eye movements (Robinson et al. 1978). The ventral intraparietal area (VIP) (fig. 2.5, inset) is located in the groove at the bottom of the IPS and contains neurons with complex tactile/visual receptive fields. VIP is thought to be involved in the coding of space in egocentric, head-centered coordinates (Duhamel et al. 1997, 1998), a function that may be important for both head and limb movements.

The anterior and medial intraparietal areas (AIP and MIP) (fig. 2.5, inset) are both involved in arm and hand movements: MIP is devoted primarily to reaching movements; AIP is devoted to the control of grasping (Mountcastle et al. 1975; Taira et al. 1990; Cohen and Andersen 2002).

An area that has received considerable attention recently is the parietal reach region (PRR) which includes MIP as well as the dorsal aspect of the parietooccipital area (PO; also known as visual area, V6A). Many neurons in PRR encode the endpoint of limb movements in a gaze-centered coordinate system (Batista et al. 1999). These regions project to the PM area PMd, while the ventral and lateral areas (VIP, AIP) project to PMv (Wise et al. 1997; Dum and Strick 2005; Chang et al. 2008). VIP and AIP may specifically target PMvc and PMvr, respectively (Luppino et al. 1999).

### PREFRONTAL CORTEX

The prefrontal cortex (PFC), located in the frontal lobe, surrounds the principal sulcus and includes Brodmann areas 9 and 46 (seen in fig. 2.5). It is usually not grouped with other cortical areas involved in motor control in the primate brain because of its differing anatomical connections and lack of stimulation-evoked movements. The PFC does not contribute to the CST as do primary motor and premotor cortices and parts of the parietal cortex (Lemon 2008); and, unlike premotor and PPC areas, the PFC does not directly project to or receive inputs from M1 (Picard and Strick 2001). The dorsal