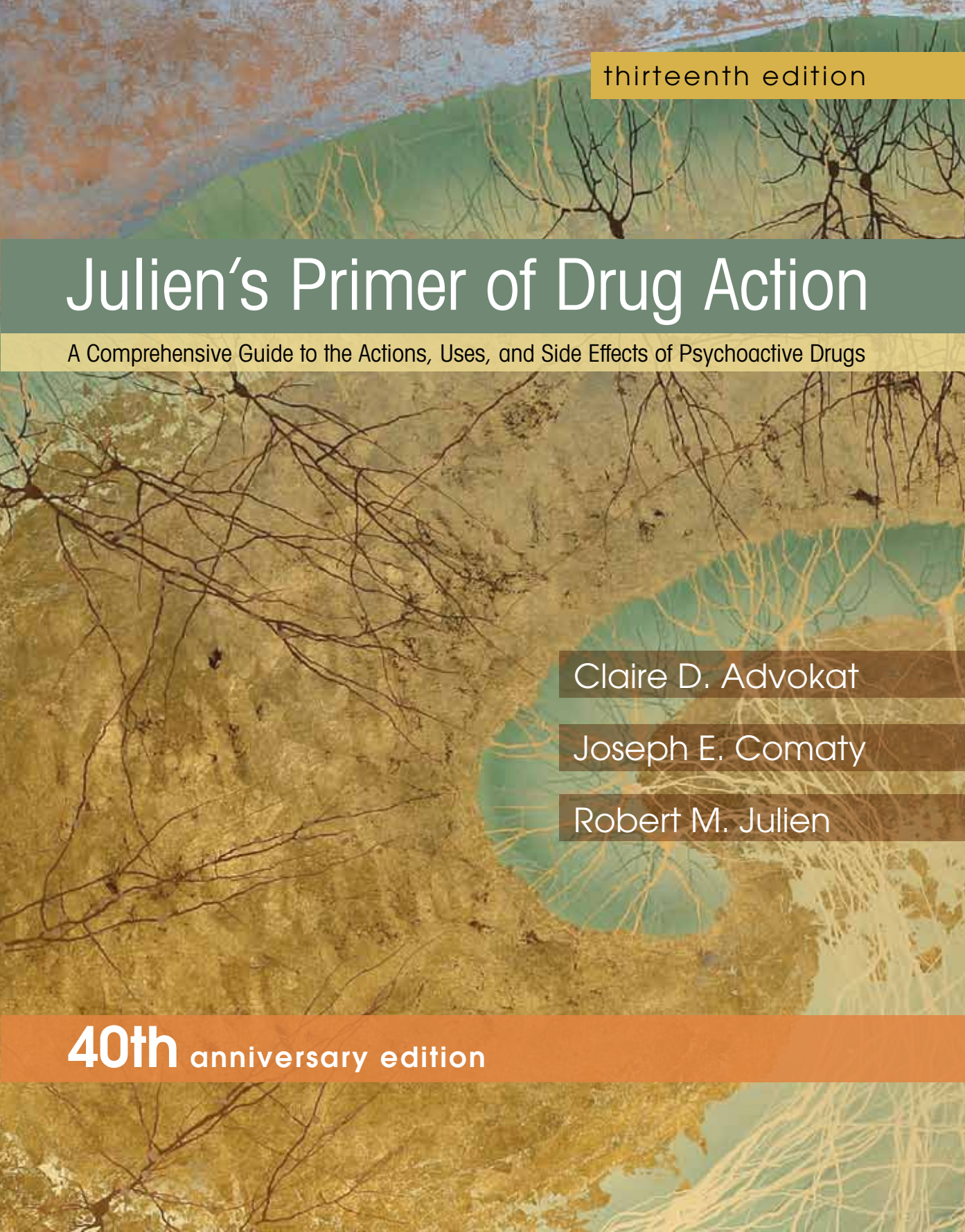
thirteenth edition
Julien's Primer of Drug Action
A Comprehensive Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs
Claire D. Advokat
Joseph E. Comaty
Robert M. Julien
40th anniversary edition

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A Comprehensive Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs

Thirteenth Edition

40th Anniversary Edition

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Claire Advokat received her Ph.D. in physiological psychology from Rutgers University, following which she completed an NIH Postdoctoral Fellowship at the College of Physicians and Surgeons of Columbia University in New York City. She then served on the faculty of the Department of Pharmacology at the University of Illinois Health Sciences Center in Chicago. In 1989 she joined the Department of Psychology at Louisiana State University, where she served as the Faculty Senate President (2004–2005), retiring in 2012 as an emerita professor. Her research area is psychopharmacology, specifically drugs used in the treatment of psychiatric and behavioral disorders. She has published over 80 articles, and received funding for her studies from the National Institute of Drug Abuse (NIDA), the Spencer Foundation, the Board of Regents of Louisiana, the State of Louisiana, and the pharmaceutical firm NPS. She received a university teaching award in 2005, served as an ad hoc reviewer for 20 journals, and serves on the editorial board of *The Journal of Attention Disorders*.

Joseph E. Comaty received his M.S. in experimental psychology from Villanova University; his Ph.D. in psychology with a specialization in clinical neuropsychology from the Rosalind Franklin University of Medicine and Science, in Illinois; and his postdoctoral Masters Degree in clinical psychopharmacology from Alliant University/CSPP in California. He is a licensed psychologist under the Louisiana State Board of Examiners of Psychologists (LSBEP) and a licensed medical psychologist under the Louisiana State Board of Medical Examiners. He retired from the Louisiana Department of Health and Hospitals, Office of Behavioral Health in 2013 where he was the Chief Psychologist and Medical Psychologist and Director of the Division of Quality Management. He is an adjunct assistant professor in psychology at Louisiana State University (LSU) in Baton Rouge and serves as emeritus faculty of the Southern Louisiana Internship Consortium (SLIC) in psychology at LSU. He has served as a member and chair of the LSBEP; he is a member and current chair of the RxP Designation Committee of APA, and a site reviewer for APA's Committee on Accreditation. He is a member of the Model Act and Regulation Revision Committee for the Association of State and Provincial Psychology Boards (ASPPB). His research is in the areas of behavior therapy, pharmacology, and clinical psychopharmacology. He is the author of over 50 articles, book chapters, and presentations. He has served on federal grant review committees and has been a reviewer for *Psychiatric Services; The Journal of Gerontology: Psychological Sciences*; and the *Journal of Behavioral Health Services and Research*.

Robert M. Julien, M.D., received his M.S. and Ph.D. in pharmacology from the University of Washington and his medical degree from the University of California at Irvine. His many research articles focus on the psychopharmacology of sedative and anti-epileptic drugs. Formerly an associate professor of pharmacology and anesthesiology at the Oregon Health Sciences University, Dr. Julien has retired from the practice of anesthesiology and is currently a psychopharmacology consultant in Portland, Oregon.

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Preface

The thirteenth edition of *A Primer of Drug Action* marks nearly 40 years of continuous publication of this now classic textbook. Through these years, *A Primer of Drug Action* has documented the dramatic advances made in the psychopharmacological treatment of mental illness and substance abuse. The initial discoveries that certain chemical compounds could help people who suffer from psychosis, depression, anxiety, mania, and other neurological and psychological conditions, led to the development of medications that greatly improved our treatment of these devastating disorders. There has been a corresponding explosion in our knowledge of the neurological substrates, the receptors and enzymes that are affected by these drugs, and an appreciation that they can be most effective when integrated with appropriate behavioral therapy. Comparable advances have been made in understanding the neurobiological consequences of substance abuse and dependence, which have opened new avenues for pharmacological approaches to addiction.

Each of the prior twelve editions sought to present these developments in a clear, concise, and timely manner. We have strived to maintain this quality in the thirteenth edition, describing the general principles of each class of psychoactive drug, as well as providing specific information about the individual agents. Each chapter includes an overview of the current models of the disorders, background and mechanisms of action of the drugs, and rationales for drug treatment. Chapters on drugs of abuse provide historical context and epidemiological updates, discussions of the classic agents and thorough descriptions of the most recent drugs of concern, as well as the latest developments in regard to pharmacological treatments of these disorders. Addiction is not only a significant behavioral disorder but, in many cases, the same drugs may have addictive properties as well as therapeutic applications.

Features of the Thirteenth Edition

For nearly 40 years of uninterrupted publication, *A Primer of Drug Action* has been the classic psychopharmacology textbook, thanks to the dedication of its founding author, Robert Julien, M.D., Ph.D. For over three decades, Dr. Julien single-handedly accomplished the herculean tasks of revising each edition and maintaining a succinct yet comprehensive and clear review of the most up-to-date advances in psychopharmacology. The book was the premier text for anyone interested in learning about this expanding and important body of science. To acknowledge this accomplishment, we are pleased to announce that the title of

this classic text has been modified. Starting from this, the thirteenth edition, the book will be titled, *Julien's Primer of Drug Action.* This change recognizes Dr. Julien's unique achievement in providing a text that has served for decades to make the immense amount of information accessible and timely to all those interested in understanding this important area of study. We are proud to have the privilege of collaborating with Bob in this endeavor, and to be chosen as coauthors of this classic text. We are committed to maintaining its stature as a prominent volume in the field of psychopharmacology.

Dr. Advokat is an emerita professor in the Department of Psychology at Louisiana State University in Baton Rouge. Dr. Comaty recently retired from his position as chief psychologist, HIPAA privacy officer, and director of the Division of Quality Management of the Louisiana State Office of Behavioral Health, Department of Health and Hospitals, in Baton Rouge, Louisiana. He currently serves as a consultant to that office, and also holds an adjunct faculty appointment in the Department of Psychology, Louisiana State University. Dr. Comaty is a clinical and medical psychologist, licensed to prescribe psychotherapeutic drugs in the state of Louisiana. Dr. Julien retired as staff anesthesiologist at St. Vincent Hospital and Medical Center in Portland, Oregon. He is an active consultant and lecturer on pharmacology and anesthesiology.

We three authors worked closely on the last two editions, and we are dedicated to maintaining the high standard in this newest volume, namely, concise description and analysis, clarity of writing, and inclusion of the most current information available. As in earlier editions, each chapter of the thirteenth edition has been revised to reflect the latest developments in the field. A broad overview of these changes since the last edition suggests the following prominent themes.

First, there has been continued expansion in the clinical applications of the major therapeutic drug classes. Distinctions among the accepted indications of major psychotropic drugs have become more diffuse. A parallel reconsideration of the diagnostic categories themselves is evident in the new version of the American Psychiatric Association's *Diagnostic and Statistical Manual,* the *DSM-5,* published in May 2013, and discussed in Chapter 17.

Second, there is a realization that newer medications may not represent better medications. Initial optimism for the most recent (and most expensive) drugs has been tempered by findings that they may not be more effective than the older agents, although they may present a different side effect profile. This understanding has revived interest in the classic agents and in comparisons of therapeutic effectiveness not only among psychiatric medications but also between pharmacological and nonpharmacological treatments.

These developments signal a period of maturation and reassessment in the field of psychopharmacology. Recent challenges (discussed in Chapter 17), have questioned whether the pharmacological revolution in psychiatry has made progress against these disorders. Arguments have been proposed that psychiatric medications have not been successful in mitigating mental illness, and may, in some circumstances, even exacerbate the problems. One practical effect of this pessimistic view is a decrease in current pharmaceutical investment into research and development of new psychotropic medications. Perhaps it is to be expected that the rapid discovery of the first psychiatric drugs would be followed by a more measured analysis of the progress and an appreciation of how much is yet to be accomplished.

Although drug development may be undergoing a hiatus, there has been continuing interest in understanding the genetic basis of the disorders, drug effects, and interactions. This has increased scientific research into the genome and how it is altered by chemical and other environmental stimulation. Increased knowledge of how the environment interacts with our genetic substrate is having a profound effect on all aspects of medicine, and, in our context, especially on theories of addiction and how genetic susceptibility is involved in the etiology of substance abuse. In this edition, we added a new section on epigenetics that includes epigenetic influences in addiction (Chapter 4).

At the same time, there has been a dramatic increase in the variety and extent of drug abuse since the last edition of the *Primer.* Reports of new compounds, often synthetic agents, have appeared worldwide in almost every category of addictive substances, including stimulants (Chapter 7), hallucinogens (Chapter 8), cannabis (Chapter 9), and opiates (Chapter 10), producing novel adverse and sometimes dangerous reactions. For example, in this edition, we explore new research that suggests a link between early-onset cannabis use and psychosis and examine the risks associated with herbal marijuana alternatives (HMAs) (Chapter 9). Meanwhile, the increase in opiate prescription abuse has continued, resulting in an extraordinary effort to develop products that are resistant to misuse and diversion. We discuss the Food and Drug Administration's 2013 *Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling,* which lists several possible categories of abuse-deterrent formulations (Chapter 10).

As always, we are optimistic that scientific investigation will result in new insights into the etiology of mental illness and addiction and that the future will bring more effective treatments for these devastating disorders. Future editions of this text will parallel the progress.

Finally, we appreciate that keeping current with medical literature is a daunting task and it is unrealistic to expect practitioners to read and analyze the field critically. Therefore, prescribers rely on sources of information that can be presented in compact formats or review articles that provide an informed, comprehensive summary of the important topics. It may be difficult for anyone to know fully whether to trust any article as unbiased. Unfortunately, there is reason to be concerned about this issue.

But, there are some routine things one can do. Look at the disclaimer statement at the bottom of the article; do the authors have any connection to the pharmaceutical company whose products are being tested in the article? Have they received financial support from the company? Are they part of the company's speaker's bureau? When following a particular drug across multiple studies, does the drug perform the same or are the results variable?

In general, drugs that are new to the market have only been examined in small-scale clinical trials using well-defined patient groups treated for short periods of time. Results from these studies may not reflect the broader population of patients to which the drug is going to be prescribed. And, the studies may be too short in duration to allow for the emergence of side effects that will occur under usual clinical prescribing practices when the drug comes to market. Therefore, approaching the use of newly approved drugs with caution is a good idea until there is aftermarket experience with the drug.

Seek out unbiased sources of information. Such resources include publications such as the *Carlat Psychiatry Report,* which does not accept any ads or drug company money;

studies funded by government agencies such as the National Institute of Mental Health (NIMH); reviews of information by the Agency for Healthcare Research and Quality (AHCRQ); and the Cochran Library reviews.

None of the authors of this book have financial ties with the pharmaceutical industry, and we strive to ensure that the information we provide is as objective and unbiased as possible.

Media and Supplements

A free companion Web site for *Julien's Primer of Drug Action,* Thirteenth Edition, is located at www.worthpublishers.com/Julien13e. This free Web site contains resources for both instructors and students and does not require any special access codes or passwords.

Also available is the *Computerized Test Bank* by Mark Hurd, College of Charleston. The *Test Bank* contains approximately 850 items in multiple-choice and true/false formats, as well as separate multiple-choice Web Quiz questions to be made available on the student's book companion site. Each question is keyed to the page in the book on which the answer is located as well as to the Blooms Taxonomy of Learning Levels and the APA Guidelines for the Undergraduate Psychology Major. If you are an instructor and would like to order the *Test Bank,* contact your Worth Publishers sales representative.

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PART 1

Introduction to Psychopharmacology: Biological Basis of Drug Action

Pharmacology is the science of how drugs affect the body. *Psychopharmacology*, a subdivision of pharmacology, is the study of how drugs specifically affect the brain and behavior. To understand the actions, behavioral uses, therapeutic uses, and abuse potentials of psychoactive drugs, we need to know how the body responds when we take them. This understanding involves some knowledge of brain anatomy, the basic principles of drug absorption, distribution, metabolism, and excretion (collectively termed *pharmacokinetics*) as well as the interactions of a drug with its "receptor," or the structure with which the drug interacts to produce its effects (the area of study termed *pharmacodynamics*).

This book specifically concerns drugs that affect the brain and behavior. It is an introduction to psychopharmacology, presenting not only drugs useful in treating psychological disorders but also drugs prone to compulsive use and abuse. The book begins with three chapters devoted to the fundamentals of drug action. For readers without a background in neuroscience, Chapter 1 introduces the structure and function of the nervous system and the neuron, because this is where psychoactive drugs produce their effects. We focus on the connection between two different neurons, the *synapse*, and the chemical substances through which neurons communicate, the *neurotransmitters*. By studying the process of synaptic transmission we begin to understand the mode of action of psychoactive drugs. Furthermore, the phenomenon of synaptic transmission is not static; rather, neurons have the ability to remodel themselves continually, a process called *synaptic plasticity*, which mediates learning and memory as well as such disorders as anxiety, depression, and addiction. A healthy, functioning brain is one that through this process of synaptic plasticity is continually remodeling itself in response to the environment. Healthy neurons continually form new synaptic contacts, maintaining the beautiful architecture that exists through normal interactions with millions of other neurons.

Chapter 2 explores the area of *pharmacokinetics*, the movement of drug molecules into, through, and out of the body. It addresses such questions as: What are the ways

by which drugs get into the body, and how does that relate to their actions? Once in the body, how do drugs get to the sites at which they produce their effects? Once a drug exerts its effect, how is that action terminated? Finally, how does the body eventually get rid of the drug?

Chapter 3 explores the area of *pharmacodynamics*. It examines the interaction between drugs and the receptors to which the drugs attach, and through which they produce their effects. Receptors are described both structurally and functionally, and how drugs alter receptor structure and function is discussed. Finally, we summarize the ways in which such actions underlie the therapeutic effects and the side effects of drugs. These three chapters provide the basic foundation for understanding more specific information in subsequent chapters.

Chapter 1

The Neuron, Synaptic Transmission, and Neurotransmitters

All our thoughts, actions, memories, and behaviors result from biochemical interactions that take place in and between *neurons*. Drugs that affect these processes are called *psychoactive drugs*. In essence, psychoactive drugs are chemicals that alter (mimic, potentiate, disrupt, or inhibit) the normal processes associated with neuronal function or communication between neurons. Therefore, to understand the actions of psychoactive drugs, it is necessary to have some idea of how the brain is organized, what a neuron is, and how neurons interact with each other.

Overall Organization of the Brain

The human nervous system consists of two divisions, the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and the spinal cord; the PNS includes the nerves that originate in the spinal cord and that connect the spinal cord to the organs of the body. The drugs discussed in this book exert their primary actions and some of their side effects by acting in the brain. However, many of their side effects are produced by their actions in the PNS, that is, at various organ systems, such as the digestive system and the cardiovascular system, as described in subsequent chapters.

The human brain consists of perhaps 90 billion individual neurons located in the skull and the spinal cord. Figure 1.1A shows the organization of the brain, with the major divisions indicated. There are three primary divisions: the *hindbrain*, the *midbrain*, and the *forebrain*. The hindbrain and the forebrain are further divided, each into two subdivisions, which results in five major sections. Figure 1.1B shows the anatomical arrangement of these structures.

The *spinal cord* is essentially the "information highway of the body," through which messages are sent back and forth between the brain and the rest of the body. This information includes touch, temperature, pain, joint position, and signals telling muscles to move.

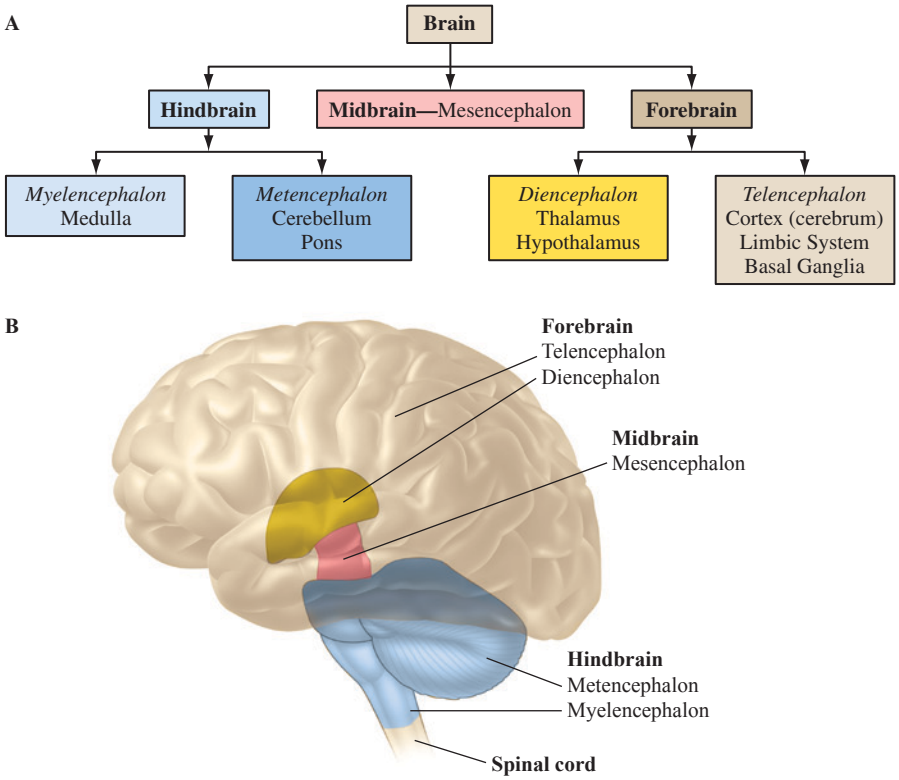

FIGURE 1.1 **A.** Flowchart of the brain and its major divisions. **B.** Outline of the human brain and its primary divisions.

Extending from the bottom of the brain (the medulla), to the sacrum (the bone in the lower part of the spine that forms the back of the pelvis), the spinal cord is made up of neurons and fiber tracts which:

- Carry sensory information from the skin, muscles, joints, and internal body organs to the brain
- Modulate sensory input (including pain impulses)
- Organize and modulate the motor outflow to the muscles (to produce coordinated movement)
- Provide autonomic (involuntary) control of vital body functions

The part of the brain that is attached to the top of the spinal cord is the *brain stem* (Figure 1.2). It is divided into three parts: the *medulla* (its full name is the *medulla oblongata*), the *pons,* and the *midbrain.* All impulses that are conducted in either direction between the spinal cord and the brain pass through the brain stem, which is also important in the regulation of vital body functions, such as respiration, blood pressure, heart rate, gastrointestinal functioning, and the states of sleep and wakefulness. The brain stem is also involved in behavioral alerting, attention, and arousal responses. Depressant

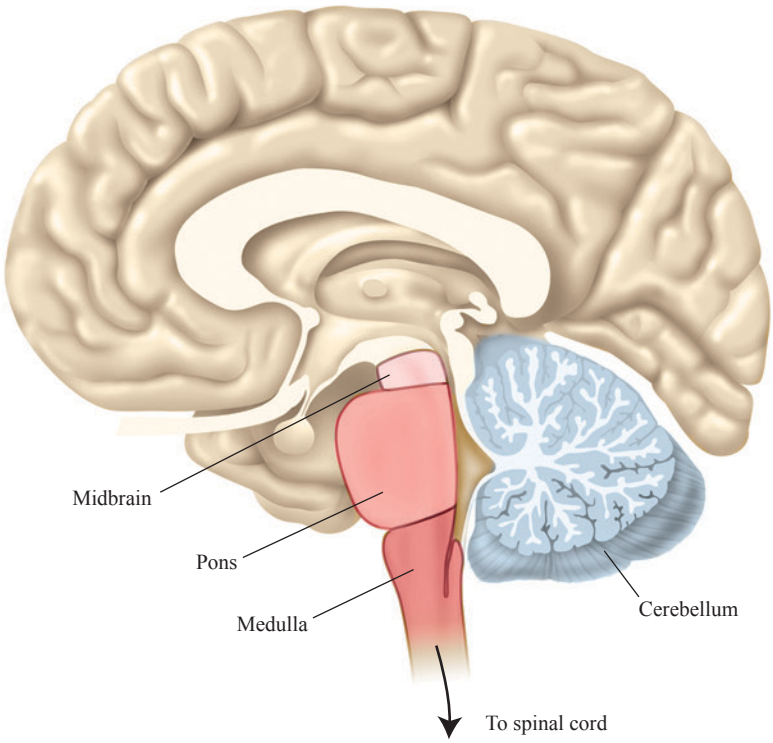

FIGURE 1.2 The brain stem is the portion of the brain consisting of the medulla, pons, and midbrain, which connects the spinal cord to the forebrain.

drugs, such as the barbiturates (see Chapter 5), depress the brain-stem activating system, which probably underlies much of their hypnotic action.

Behind the brain stem is a large, bulbous structure—the *cerebellum.* A highly convoluted structure, the cerebellum is connected to the brain stem by large nerve tracts. The cerebellum is necessary for the proper integration of movement and posture. The staggering gait that is associated with drunkenness, termed ataxia (loss of coordination and balance), is caused largely by an alcohol-induced depression of cerebellar function.

An important part of the brain stem, even though it is only about 2 centimeters long, is the midbrain, which sits between the forebrain and the hindbrain. The upper half (*tectum*, or "roof") contains pathways that carry sensory information, while the bottom half (*tegmentum*, or "floor") contains two important nuclei, which are connected, respectively, to two other systems, whose primary structures are located in the forebrain. The first of these nuclei, the *substantia nigra,* is associated with the neuroanatomical system called the basal ganglia (discussed below, see Figure 1.4), which is responsible for coordination of movement and integration of motor control. Next to the substantia nigra is a more diffuse group of neurons called the *ventral tegmental area* (*VTA*), which is part of the neuroanatomical system called the *reward circuit*, located in the limbic system (discussed below; see Figure 1.5). As shown in Figure 1.13, on page 21, most of the neurons that make up these two nuclei contain the neurotransmitter dopamine.

The area immediately above the brain stem and covered by the cerebral hemispheres (cerebrum or cortex) is the *diencephalon* (Figure 1.3) consisting primarily of the thalamus and hypothalamus. The *hypothalamus* is a collection of neuronal structures near the junction of the midbrain and the thalamus just above the pituitary gland (whose function it modulates). There are 11 major nuclei that make up the hypothalamus and are responsible for the integration of our entire autonomic (involuntary or vegetative) nervous system. Thus, the hypothalamus controls such vegetative functions as eating and drinking, sleeping, regulation of body temperature, and sexual behavior, in large part by controlling the hormonal output of the pituitary gland. Neurons in the hypothalamus produce substances called *releasing factors,* which travel to the nearby pituitary gland, inducing the secretion of hormones that regulate such processes as the menstrual cycle in females and sperm formation in males. The hypothalamus is a site of action for many psychoactive drugs, either for the primary effect or for the side effects produced by the drug.

The thalamus, located above the hypothalamus, consists of two symmetrical lobes on either side of the midbrain. It is often viewed as a way station, or relay, between multiple subcortical areas and the cerebral cortex. That is because every sensory system (except the olfactory system) passes through a thalamic nucleus, consisting of a group of neurons that receives sensory signals from specific organs (such as the eyes and ears) which sends the information to the appropriate primary cortical area for processing.

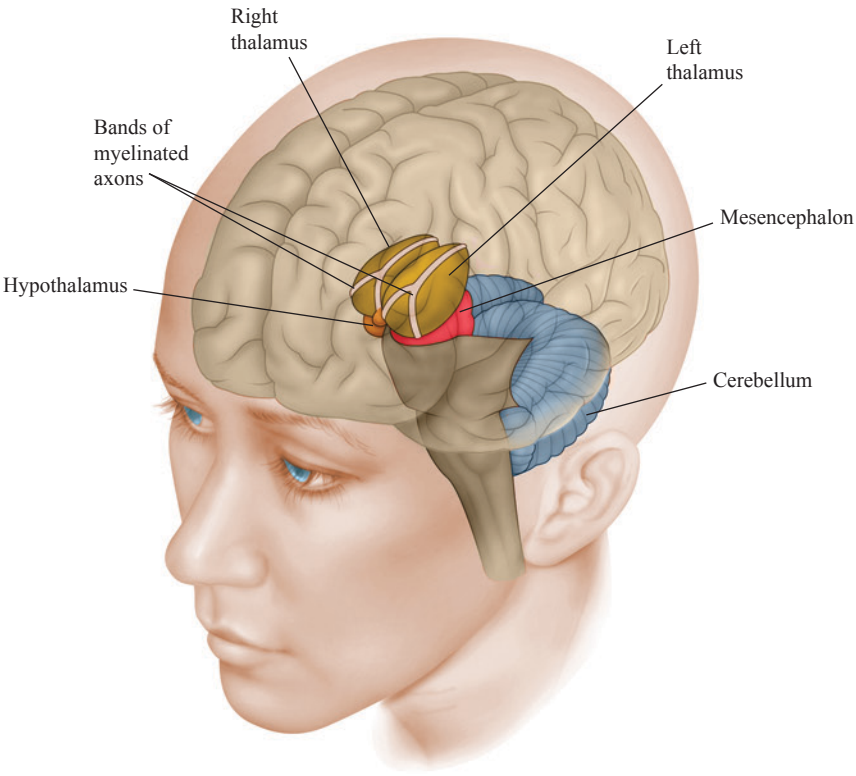

FIGURE 1.3 The diencephalon. [After Pinel (2007), p. 53, Figure 2.23.]

The last major division of the brain, the telencephalon, includes two important subdivisions, the *basal ganglia* and the *limbic system*. The major structures of the basal ganglia (Figure 1.4A and B) are the caudate nucleus and putamen (together, often referred to as the striatum) and the globus pallidus, which consists of two parts, the lateral (or external) and the medial (or internal) (see Figure 1.4B). Sometimes all three structures are referred to as the corpus striatum, because of their striated (striped) appearance when the tissue is stained so that it can be studied microscopically. In addition to these primary nuclei the basal ganglia are associated with two additional structures, the subthalamic nucleus and the substantia nigra (see Figure 1.4B; located in the midbrain as noted above).

One major function of the basal ganglia is the integration of movement. Depending on which part of the system is impaired, disorders of the basal ganglia can cause the gradual loss of the ability to initiate movement, such as in Parkinson's disease, or, conversely, an inability to prevent parts of the body from moving unintentionally, as in Huntington's disease.

The second major subdivision of the telencephalon is the *limbic system* (Figure 1.5), the major components of which are the *amygdala* and the *hippocampus*. These structures are involved in memory (hippocampus) and emotion (amygdala). Because the limbic system and the hypothalamus interact to regulate emotion and emotional expression, these structures are the site of action for many psychoactive drugs that alter mood, affect, emotion, or responses to emotional experiences. As discussed in subsequent chapters, this includes drugs used in the treatment of schizophrenia, depression, and Alzheimer's disease. Many side effects of therapeutic drugs also result from actions on the structures in this system. In addition, the limbic system includes the brain structures that make up the *reward circuit* (discussed in Chapter 4). This circuit is believed to be responsible for the feelings of pleasure that we experience in response to activities that we enjoy, such as eating and drinking. Because such activity includes the recreational use of abused drugs, the reward circuit is considered to be the substrate for drug addiction as well as for the more typical sources of pleasurable stimulation.

Almost completely covering the brain stem and the diencephalon is the *cerebrum* (Figure 1.6). In humans the cerebrum is the largest part of the brain. It is separated into two distinct hemispheres, left and right, with numerous fiber tracts connecting the two.

Because skull size is limited and the cerebrum is so large, the outer layer of the cerebrum, the *cerebral cortex,* is deeply convoluted and fissured. Like other parts of the brain, the cerebral cortex is subdivided; it consists of four major lobes, each of which having areas that are responsible for specific functions, such as vision (occipital lobe), hearing (temporal lobe), sensory perception (parietal lobe), and higher-level cognitive functions (frontal lobe).

Did You Know?

Obama's BRAIN Initiative

In April 2013 President Obama announced the BRAIN Initiative to map activity and connections within the brain. Obama's 2014 budget proposal will include $100 million to jumpstart this "big science" initiative, which builds on researchers' interest in understanding the neural circuits that are activated when we perceive, think, and act. The acronym BRAIN stands for Brain Research through Advancing Innovative Neurotechnologies. In his announcement, Obama compared the neuroscience initiative to the Human Genome Project that finished sequencing the entire human genome over a decade ago.

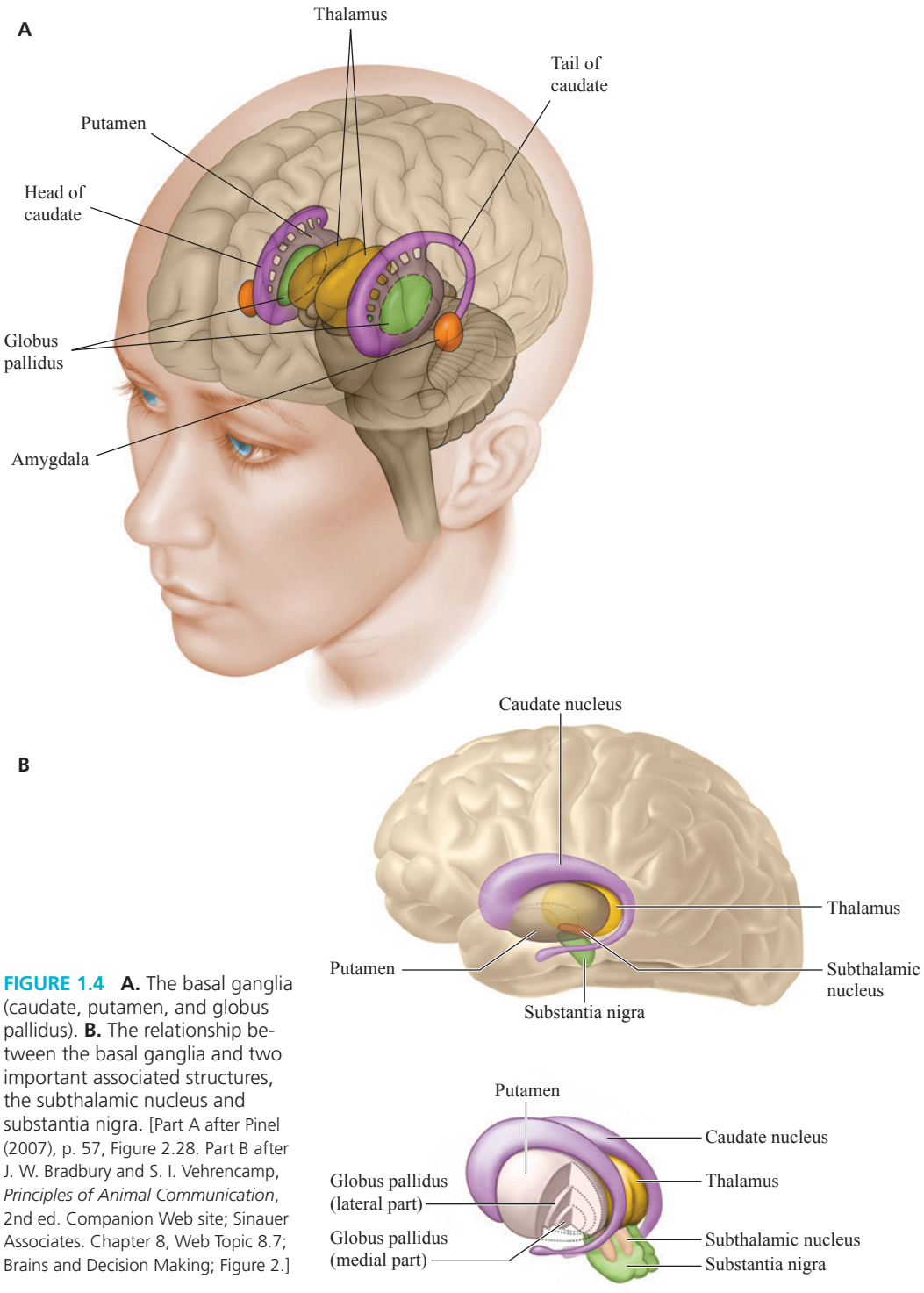

FIGURE 1.4 **A.** The basal ganglia (caudate, putamen, and globus pallidus). **B.** The relationship between the basal ganglia and two important associated structures, the subthalamic nucleus and substantia nigra. [Part A after Pinel (2007), p. 57, Figure 2.28. Part B after J. W. Bradbury and S. I. Vehrencamp, *Principles of Animal Communication*, 2nd ed. Companion Web site; Sinauer Associates. Chapter 8, Web Topic 8.7; Brains and Decision Making; Figure 2.]

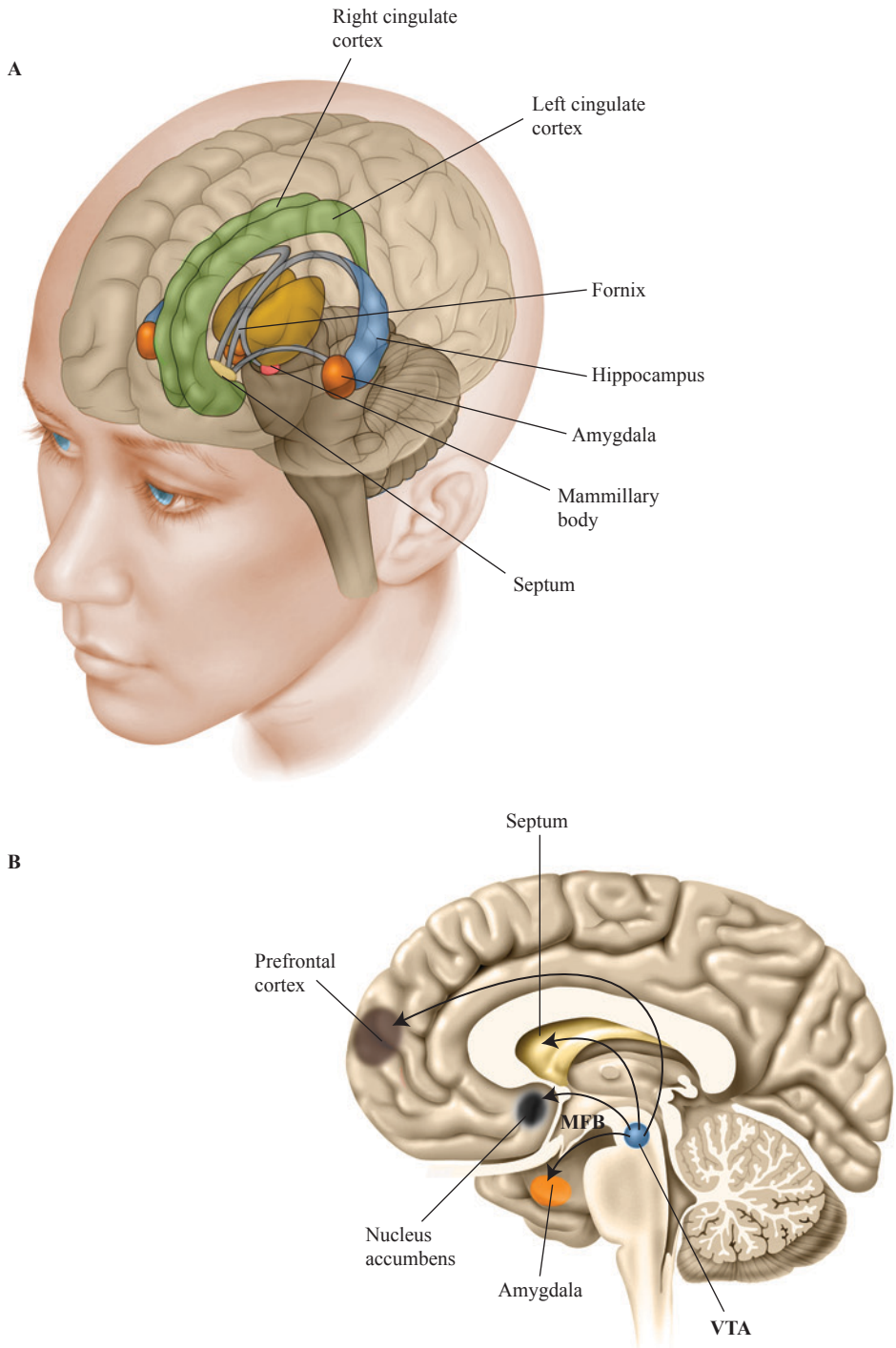

FIGURE 1.5 The limbic system. [After Pinel (2007), p. 57, Figure 2.27.]