KAPLAN & SADOCK'S

SYNOPSIS OF PSYCHIATRY

Behavioral Sciences/Clinical Psychiatry

ELEVENTH EDITION

Benjamin James Sadock, M.D.
Virginia Alcott Sadock, M.D.
Pedro Ruiz, M.D.

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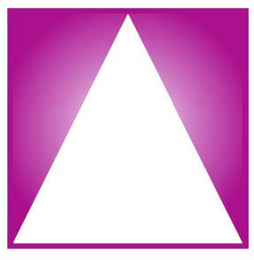
ELEVENTH  EDITION

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To
Our Grandchildren

Preface

This is the eleventh edition of *Kaplan & Sadock's Synopsis of Psychiatry,* which was first published more than 40 years ago. During that time, it has gained the reputation of being an independent, consistent, accurate, objective, and reliable compendium of new events in the field of psychiatry. Since its beginning, the goal of this book has been to foster professional competence and ensure the highest quality care to those with mental illness. An eclectic, multidisciplinary approach has been its hallmark; thus, biological, psychological, and sociological factors are equitably presented as they affect the person in health and disease.

Synopsis serves the needs of diverse professional groups: psychiatrists and nonpsychiatric physicians, medical students, psychologists, social workers, psychiatric nurses, and other mental health professionals, such as occupational and art therapists, among others. *Synopsis* is also used by nonprofessionals as an authoritative guide to help them collaborate in the care of a family member or friend with mental illness. As authors and editors, we have been extremely gratified by the wide acceptance and use *of Synopsis*, both in the United States and around the world.

We are especially pleased that Pedro Ruiz, M.D., who joined us as third editor for the last (Tenth) edition of the *Comprehensive Textbook of Psychiatry,* is continuing his association with us as co-author of *Synopsis.* Dr. Ruiz is not only a close friend but is a distinguished academic psychiatrist, renowned as both an educator and clinician. He is past president of the American Psychiatric Association and serves as the current president of the World Psychiatric Association. Dr. Ruiz is Professor of Psychiatry and Executive Vice-Chair and Director of Clinical Programs at the University of Miami Miller School of Medicine.

HISTORY

This textbook evolved from our experience editing the *Comprehensive Textbook of Psychiatry*. That book is nearly 4,000 double-column pages long, with more than 450 contributions by outstanding psychiatrists and behavioral scientists. It serves the needs of those who require an exhaustive, detailed, and encyclopedic survey of the entire field. In an effort to be as comprehensive as possible, the textbook spans two volumes to cover the material, clearly rendering it unwieldy for some groups, especially medical students, who need a brief and more condensed statement of the field of psychiatry. To accomplish this, sections of the *Comprehensive Textbook of Psychiatry* were deleted or condensed, new subjects were introduced, and all sections were brought up to date, especially certain key areas, such as psychopharmacology. We wish to acknowledge our great and obvious debt to the more than 2,000 contributors to the current and previous editions of the *Comprehensive Textbook of Psychiatry*, all of whom have allowed us to synopsize their work. At the same time, we must accept responsibility for the modifications and changes in the new work.

COMPREHENSIVE TEACHING SYSTEM

This textbook forms one part of a comprehensive system developed by us to facilitate the teaching of psychiatry and the behavioral sciences. At the head of the system is the *Comprehensive Textbook of Psychiatry*, which is global in depth and scope; it is designed for and used by psychiatrists, behavioral scientists, and all workers in the mental health field. *Synopsis of Psychiatry* is a relatively brief, highly modified, and current version useful for medical students, psychiatric residents, practicing psychiatrists, and mental health professionals. Two special editions derived from *Synopsis*, *Concise Textbook of Clinical Psychiatry* and *Concise Textbook of Child and Adolescent Psychiatry*, contain descriptions of all psychiatric disorders, including their diagnosis and treatment in adults and children, respectively. They will be useful for clinical clerks and psychiatric residents who need a succinct overview of the management of clinical problems. Another part of the system, *Study Guide and Self-Examination Review of Psychiatry*, consists of multiple-choice questions and answers; it is designed for students of psychiatry and for clinical psychiatrists who require a review of the behavioral sciences and general psychiatry in preparation for a variety of examinations. The questions are modeled after and consistent with the format used by the American Board of Psychiatry and Neurology (ABPN), the National Board of Medical Examiners (NBME), and the United States Medical Licensing Examination (USMLE). Other parts of the system are the various editions of the pocket handbooks: *Pocket Handbook of Clinical Psychiatry, Pocket Handbook of Psychiatric Drug Treatment, Pocket Handbook of Emergency Psychiatric Medicine,* and *Pocket Handbook of Primary Care Psychiatry*. Those books cover the diagnosis and treatment of psychiatric disorders, psychopharmacology, psychiatric emergencies, and primary care psychiatry, respectively, and are designed and written to be carried by clinical clerks and practicing physicians, whatever their specialty, to provide a quick reference. Finally, *Comprehensive Glossary of Psychiatry and Psychology* provides simply written definitions for psychiatrists and other physicians, psychologists, students, other mental health professionals, and the general public. Together, these books create a multiple approach to the teaching, study, and learning of psychiatry.

CLASSIFICATION OF DISORDERS

DSM-5

A fifth edition of the *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders* was published in 2013 called DSM-5. It contains the official nomenclature used by psychiatrists and other mental health professionals in the United States; the psychiatric disorders discussed in the textbook are consistent with and follow that nosology. Every section dealing with clinical disorders has been updated thoroughly and completely to include the revisions contained in DSM-5. The reader also will find DSM-5 tables for most major mental disorders reprinted in this textbook as it has been in each of our editions.

The DSM is the "law of the land" and, as mentioned previously, is the nomenclature used throughout this textbook; however, some clinicians and researchers have reservations about various aspects of the DSM, which readers will find mentioned in *Synopsis*. As future editions of the DSM appear, this textbook, as always, will allow room for dissent before and especially after every new version appears. It will continue to provide a forum for discussion, evaluation, criticism, and disagreement, while duly acknowledging the official nomenclature.

ICD-10

Readers also should be aware of a parallel classification system developed by the World Health Organization (WHO) called the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10). There are textual differences between DSM and ICD, but according to treaties between the United States and the WHO, the diagnostic code numbers must be identical to ensure uniform reporting of national and international psychiatric statistics. ICD diagnoses and numerical codes are accepted by Medicare, Medicaid, and private insurance companies for reimbursement purposes in the United States.

COVER ART AND ILLUSTRATIONS

Synopsis was one of the first modern psychiatric textbooks to use art and photographs to illustrate psychiatric subjects in order to enrich the learning experience, and we have continued that tradition through each edition.

The cover art is a detail of a painting entitled *Artist Surrounded by Masks* by the Belgian-born artist James Ensor (1860–1949), who was fascinated by masks, which for him represented the hypocrisy of humankind. Masks have played a role throughout human history. They both hide and reveal; they hide what we do not wish to show to others or to ourselves or what we wish to keep secret, and they reveal what we wish others to see. In the rehabilitation of psychiatric patients, making masks has been used by art therapists to help patients explore their feelings and to experience their creativity. The psychiatrist Hervey Cleckley coined the term "mask of sanity" to refer to the psychopath who manipulates others but who is, beneath the façade of normality, profoundly disturbed. Carl Jung wrote of the persona (derived from the Latin word for mask) as the image we wish to present to the world behind which lay other images of the self. We hope that the cover art enriches the learning experience for our readers.

As in all *Kaplan & Sadock* books, color plates of proprietary forms of commonly used psychiatric drugs including their dosage forms are pictured. All new drugs developed since the last edition was published are included. In addition, new illustrations and color plates have been added to many sections.

CASE HISTORIES

Case histories are an integral part of *Synopsis.* They are used extensively throughout the text to add clarity and bring life to the clinical disorders described. Cases come from various sources including the contributors to the current and previous editions of the *Comprehensive Textbook of Psychiatry* and our hospital colleagues, all of whom we thank for their contributions. Some also come from the authors' clinical experience at Bellevue Hospital in New York. Cases appear in tinted type to help the reader find them easily.

NEW AND UPDATED SECTIONS

The introduction of DSM-5 in 2013 reframed psychiatric nosology, and the reader will find every section of *Synopsis* revised and updated to reflect those changes. The chapter on *Classification in Psychiatry* provides a concise overview and definition of every psychiatric disorder listed in DSM-5. In the rest of the book, each of these disorders is discussed in great detail in separate chapters and sections. In addition, almost every major mental disorder is accompanied by its corresponding DSM-5 diagnostic table.

The table of contents was reorganized starting with the chapter called *Neural Sciences,* in which three new sections were added: *Neural Development and Neurogenesis* reflects the important role of the developing nervous system in the causation of mental illness; *Applied Electrophysiology* describes the effects of electrical impulses in the brain and its relation to clinical psychiatry; and *Immune System and Central Nervous System Interactions* describes the complex effects of the immune system on the brain in health and disease.

A new section entitled *Normality and Mental Health* provides the reader with a framework within which to understand the boundaries of mental illness. Similarly, another new section, *Positive Psychology,* describes emerging theories and therapeutic approaches that contribute to mental health.

A chapter called *Contributions of the Sociocultural Sciences* contains three new sections entitled *Sociology and Ethology, Transcultural Psychiatry,* and *Culture-Bound Syndromes* that, taken together, reflect the tremendous impact that culture has on both the manifestations and prevalence of mental disorders around the world.

The chapter *End-of-Life Issues* covers death, dying, bereavement, and palliative care to reflect the important role psychiatrists have in the clinical specialty of palliative medicine. This chapter also covers pain control, which is a relatively new but important area in which psychiatrists play a significant role. In the chapter entitled *Gender Dysphoria*—a new diagnostic category included in DSM-5—special attention is given to issues that affect gay, lesbian, bisexual, and transgender persons. The chapter *Psychiatry and Reproductive Medicine* was revised extensively to keep pace with advances in women's health issues. The chapter *Ethics in Psychiatry* was updated to include an extensive discussion of physician-assisted suicide.

This topic is also given special attention in the section entitled *Euthanasia and Physician-Assisted Suicide.* In the last edition, the section on *Posttraumatic Stress Disorder* covered the tragic events of September 11, 2001, involving the World Trade Center in New York and the Pentagon in Washington. Regrettably, other disasters such as Hurricane Sandy and the Newtown killings have occurred since then. The psychological effects of those events are covered, as are the effects of the wars in Iraq and Afghanistan on the mental health of the veterans of those wars. Related to that is new coverage of the effects of terrorism and torture, two areas rarely covered in textbooks of psychiatry, but of extreme importance to psychiatrists who treat its victims.

Two new chapters, *Public Psychiatry* and *World Aspects of Psychiatry,* have been added to this edition, both of which reflect the national and global scope of psychiatry and the need for clinicians to understand disorders that appear around the world. A new section called *Brain Stimulation Methods* describes such new advances as transmagnetic and deep brain stimulation developed to restore health to those patients who have not responded to conventional therapies and who are among the most severely mentally ill.

The chapter on psychotherapy has been expanded to include newer treatments such as *Mentalization* and *Mindfulnes*s, both of which are covered in a newly written section. And, as in previous editions, the chapter *Pharmacological Treatment* covers every drug used by psychiatrists to treat mental illness. It has been completely updated to include all new drugs introduced since the last edition of this book was published.

Finally, every chapter in the behavioral sciences section has been revised and updated to reflect the latest advances in the field.

PSYCHOPHARMACOLOGY

The authors are committed to classifying drugs used to treat mental disorders according to their pharmacological activity and mechanism of action rather than using such categories as antidepressants, antipsychotics, anxiolytics, and mood stabilizers, which are overly broad and do not reflect, scientifically, the clinical use of psychotropic medication. For example, many antidepressant drugs are used to treat anxiety disorders; some anxiolytics are used to treat depression and bipolar disorders; and drugs from all categories are used to treat other clinical problems, such as eating disorders, panic disorders, and impulse-control disorders. Many drugs are also used to treat a variety of mental disorders that do not fit into any broad classification. Information about all pharmacological agents used in psychiatry, including pharmacodynamics, pharmacokinetics, dosages, adverse effects, and drug–drug interactions, was thoroughly updated to reflect recent research.

CHILDHOOD DISORDERS

The chapters covering childhood disorders were extensively revised to include important new material. DSM-5 introduced new childhood diagnostic categories and eliminated others. For example, diagnoses such as *Pervasive Developmental Disorder, Rett's Disorder,* and *Asperger's Disorder* are now subsumed under the rubric of *Autism Spectrum Disorder,* and *Disruptive Mood Dysregulation Disorder* and *Attenuated Psychosis Syndrome* were added as new diagnostic entities. These and other changes are reflected in the expanded coverage of disorders that usually begin in childhood and adolescence. The section dealing with the impact of terrorism has been updated to reflect new information about posttraumatic stress disorders in children, including the latest data on the psychological effects on children exposed to natural and man-made disasters. The section *Anxiety Disorders* was reorganized and updated thoroughly, and *Obsessive-Compulsive Disorder* is now a separate chapter. The section that deals with the use of pharmacological agents in children was updated extensively to reflect the many changes in the use of medications to treat disorders of childhood that have occurred since the last edition this book was published.

GLOSSARY

Unique to this edition is a new and updated comprehensive glossary of psychiatric signs and symptoms. Psychiatry is a descriptive science and the knowledge and accurate usage of the many terms available to the clinician is crucial to successful diagnosis and treatment. We hope readers find this new addition to the textbook of use.

REFERENCES

Each section in *Synopsis* ends with a number of citations that include reviews of the literature and up-to-date references in addition to relevant chapters in our larger textbook, *Comprehensive Textbook of Psychiatry*. References are limited in number; in part this was to conserve space, but more importantly, we are mindful that modern-day readers consult Internet databases such as *PubMed* and *Google Scholar* to stay abreast of the most current literature, and we encourage that trend.

ACKNOWLEDGMENTS

We deeply appreciate the work of our distinguished contributing editors, who gave generously of their time and expertise. Caroly Pataki, M.D., was responsible for updating and revising the section on childhood and adolescent disorders. She has served with distinction as Contributing Editor of child psychiatry in the *Comprehensive Textbook* for many editions, and we thank her for her tremendous help in this area. Norman Sussman, M.D., updated the section on psychopharmacology, enabling us to provide the reader with the current material in this ever-changing and rapidly expanding area. He also served as Contributing Editor for the *Comprehensive Textbook* in the area of psychopharmacology. We thank Dorice Viera, Associate Curator of the Frederick L. Ehrman Medical Library at the New York University School of Medicine, for her valuable assistance in the preparation of this and previous editions in which she participated.

We especially wish to express our deep thanks to our two project editors in New York: Nitza Jones-Sepulveda was with us for over a decade and worked on this and on many other *Kaplan & Sadock* books before moving into the private sector, and her vast knowledge of every aspect of book publishing was indispensable. She will be greatly missed. We also wish to thank Hayley Weinberg, who played a major role in the production of this book. She worked with enthusiasm, intelligence, and alacrity. We also wish to acknowledge and thank Gloria Robles in Miami,

who was of invaluable assistance to all of the authors, especially Dr. Ruiz. Among the many others to thank are Seeba Anam, M.D., René Robinson, M.D., Nora Oberfield, M.D., Marissa Kaminsky, M.D., Caroline Press, M.D., Michael Stanger, M.D., Rajan Bahl, M.D., and Jay K. Kantor, Ph.D., all of whom contributed to various editions of *Synopsis*. Laura Erikson-Schroth, M.D., deserves special thanks for her help in the section on *Gender Dysphoria*. We especially want to thank Samoon Ahmad, M.D., who helped us tremendously as Consulting Editor in the area of psychopharmacology.

We also wish to acknowledge the contributions of James Sadock, M.D., and Victoria Sadock Gregg, M.D., for their help in their areas of expertise: emergency adult and emergency pediatric medicine, respectively.

We thank Alan and Marilyn Zublatt for their generous support of this and other *Kaplan & Sadock* textbooks. Over the years they have been unselfish benefactors to many educational, clinical, and research projects at the NYU Medical Center. We are deeply grateful for their help.

We want to take this opportunity to acknowledge those who have translated this and other *Kaplan & Sadock* books into foreign languages, including Chinese, Croatian, French, German, Greek, Indonesian, Italian, Japanese, Polish, Portuguese, Romanian, Russian, Spanish, and Turkish, in addition to a special Asian and international student edition.

Lippincott Williams & Wilkins has been our publisher for nearly half a century and as always, their staff was most efficient. Jamie Elfrank, Acquisitions Editor at LWW was extremely helpful in many aspects of our work and we value not only her assistance but her friendship as well. We also wish to thank Andrea Vosburgh, Production Editor at LWW who helped immeasurably in the many details involved in putting this book together. She went far beyond her role as production editor serving as part-time copy editor, picture editor, permissions editor and many other roles too numerous to mention. Her optimism and dedication to the project were extraordinarily helpful. Chris Miller at Aptara also deserves our thanks for her work on this and other *Kaplan & Sadock* titles. We especially wish to acknowledge Charley Mitchell, past Executive Editor at LWW, who encouraged and guided us for over 20 years before moving on to a career in academia. We value his friendship now as much as we did throughout the years he was at LWW.

Finally, we want to express our deep thanks to Charles Marmar, M.D., Professor and Chairman of Psychiatry at New York University School of Medicine, who gave us his full support throughout the project. He has guided the department into the 21st century with dedication, skill, and enthusiasm. Under his leadership, NYU has become one of the leading centers of psychiatry and neuroscience both in this country and around the world.

Contents

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Benjamin James Sadock, M.D., is the Menas S. Gregory Professor of Psychiatry in the Department of Psychiatry at the New York University (NYU) School of Medicine. He is a graduate of Union College, received his M.D. degree from New York Medical College, and completed his internship at Albany Hospital. He completed his residency at Bellevue Psychiatric Hospital and then entered military service as Captain US Air force, where he served as Acting Chief of Neuropsychiatry at Sheppard Air Force Base in Texas. He has held faculty and teaching appointments at Southwestern Medical School and Parkland Hospital in Dallas and at New York Medical College, St. Luke's Hospital, the New York State Psychiatric Institute, and Metropolitan Hospital in New York City. Dr. Sadock joined the faculty of the NYU School of Medicine in 1980 and served in various positions: Director of Medical Student Education in Psychiatry, Co-Director of the Residency Training Program in Psychiatry, and Director of Graduate Medical Education. Currently, Dr. Sadock is Co-Director of Student Mental Health Services, Psychiatric Consultant to the Admissions Committee, and Co-Director of Continuing Education in Psychiatry at the NYU School of Medicine. He is on the staff of Bellevue Hospital and Tisch Hospital and is a Consulting Psychiatrist at Lenox Hill Hospital. Dr. Sadock is a Diplomate of the American Board of Psychiatry and Neurology and served as an Associate Examiner for the Board for more than a decade. He is a Distinguished Life Fellow of the American Psychiatric Association, a Fellow of the American College of Physicians, a Fellow of the New York Academy of Medicine, and a member of Alpha Omega Alpha Honor Society. He is active in numerous psychiatric organizations and was president and founder of the NYU-Bellevue Psychiatric Society. Dr. Sadock was a member of the National Committee in Continuing Education in Psychiatry of the American Psychiatric Association, served on the Ad Hoc Committee on Sex Therapy Clinics of the American Medical Association, was a Delegate to the Conference on Recertification of the American Board of Medical Specialists, and was a representative of the American Psychiatric Association Task Force on the National Board of Medical Examiners and the American Board of Psychiatry and Neurology. In 1985, he received the Academic Achievement Award from New York Medical College and was appointed Faculty Scholar at NYU School of Medicine in 2000. He is the author or editor of more than 100 publications (including 49 books), a reviewer for psychiatric journals, and lectures on a broad range of topics in general psychiatry. Dr. Sadock maintains a private practice for diagnostic consultations and psychiatric treatment. He has been married to Virginia Alcott Sadock, M.D., Professor of Psychiatry at NYU School of Medicine, since completing his residency. Dr. Sadock enjoys opera, golf, skiing, traveling, and is an enthusiastic fly fisherman.

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Virginia Alcott Sadock, M.D., joined the faculty of the New York University (NYU) School of Medicine in 1980, where she is currently Professor of Psychiatry and Attending Psychiatrist at the Tisch Hospital and Bellevue Hospital. She is Director of the Program in Human Sexuality at the NYU Langone Medical Center, one of the largest treatment and training programs of its kind in the United States. She is the author of more than 50 articles and chapters on sexual behavior and was the developmental editor of *The Sexual Experience*, one of the first major textbooks on human sexuality, published by Williams & Wilkins. She serves as a referee and book reviewer for several medical journals, including the *American Journal of Psychiatry* and the *Journal of the American Medical Association*. She has long been interested in the role of women in medicine and psychiatry and was a founder of the Committee on Women in Psychiatry of the New York County District Branch of the American Psychiatric Association. She is active in academic matters, served as an Assistant and Associate Examiner for the American Board of Psychiatry and Neurology for more than 20 years, and was also a member of the Test Committee in Psychiatry for both the American Board of Psychiatry and the Psychiatric Knowledge and Self-Assessment Program (PKSAP) of the American Psychiatric Association. She has chaired the Committee on Public Relations of the New York County District Branch of the American Psychiatric Association, has been a regional council member of the American Association of Sex Education Counselors and Therapists, a founding member of The Society of Sex Therapy and Research, and is President of the NYU Alumni Association of Sex Therapists. She has participated in the National Medical Television Network series *Women in Medicine* and the Emmy Award–winning PBS television documentary *Women and Depression* and currently hosts the radio program *Sexual Health and Well-being* (Sirius-XM) at NYU Langone Medical Center. She lectures extensively both in this country and abroad on sexual dysfunction, relational problems, and depression and anxiety disorders. She is a Distinguished Fellow of the American Psychiatric Association, a Fellow of the New York Academy of Medicine, and a Diplomate of the American Board of Psychiatry and Neurology. Dr. Sadock is a graduate of Bennington College, received her M.D. degree from

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1 Neural Sciences

▲ 1.1 Introduction

The human brain is responsible for our cognitive processes, emotions, and behaviors—that is, everything we think, feel, and do. Although the early development and adult function of the brain are shaped by multiple factors (e.g., epigenetic, environmental, and psychosocial experiences), the brain is the final integrator of these influences. Despite the many advances in neural sciences over the last several decades, including the "decade of the brain" in the 1990s, and the wide acceptance of the brain as the biological substrate for normal and abnormal mental functions, there has not been a true transformational advance in the treatment of mental disorders for more than half a century. The most obvious reason for the absence of more progress is the profound complexity of the human brain. A perhaps less obvious reason is the current practice of psychiatric diagnosis, which, for most clinicians, is based on syndrome-based classification systems.

The purpose of this chapter is to introduce the neural sciences sections, which describe the anatomy and function of the human brain, and then to discuss how an evolution of thinking toward a brain-based or biologically based diagnostic system for mental illness might facilitate our efforts to advance brain research, to develop better treatments, and to improve patient care.

In other fields of medicine, diagnosis is based on physical signs and symptoms, a medical history, and results of laboratory and radiological tests. In psychiatry, a diagnosis is based primarily on the clinician's impression of the patient's interpretation of his or her thoughts and feelings. The patient's symptoms are then cross-referenced to a diagnostic or classification manual (e.g., *Diagnostic and Statistical Manual of Mental Disorders* [DSM-5], *International Statistical Classification of Diseases and Related Health Problems* [ICD]) containing hundreds of potential syndromes, and one or more diagnoses are applied to the particular patient. These standard classification systems represent significant improvements in reliability over previous diagnostic systems, but there is little reason to believe that these diagnostic categories are valid, in the sense that they represent discrete, biologically distinct entities. Although a patient with no symptoms or complaints can be diagnosed as having diabetes, cancer, or hypertension on the basis of blood tests, X-rays, or vital signs, a patient with no symptoms cannot be diagnosed with schizophrenia, for example, because there are no currently recognized objective, independent assessments.

The goals of clinicians and researchers are to reduce human suffering by increasing our understanding of diseases, developing new treatments to prevent or cure diseases, and caring for patients in an optimal manner. If the brain is the organ of focus for mental illnesses, then it may be time to be more ambitious in building the classification of patients with mental illnesses directly from our understanding of biology, rather than only from the assessment of a patient's symptoms.

THE HUMAN BRAIN

The following neural sciences sections each address a field of brain biology. Each of these fields could be relevant to the pathophysiology and treatment of mental illnesses. Although the complexity of the human brain is daunting compared with other organs of the body, progress can only be made if one approaches this complexity consistently, methodically, and bravely.

The neuronal and glial cells of the human brain are organized in a characteristic manner, which has been increasingly clarified through modern neuroanatomical techniques. In addition, our knowledge of normal human brain development has become more robust in the last decade. The human brain clearly evolved from the brain of lower animal species, allowing inferences to be made about the human brain from animal studies. Neurons communicate with one another through chemical and electrical neurotransmission. The major neurotransmitters are the monoamines, amino acids, and neuropeptides. Other chemical messengers include neurotrophic factors and an array of other molecules, such as nitric oxide. Electrical neurotransmission occurs through a wide range of ion channels. Chemical and electrical signals received by a neuron subsequently initiate various molecular pathways within other neurons that regulate the biology and function of individual neurons, including the expression of individual genes and the production of proteins.

In addition to the central nervous system (CNS), the human body contains two other systems that have complex, internal communicative networks: the endocrine system and the immune system. The recognition that these three systems communicate with each other has given birth to the fields of psychoneuroendocrinology and psychoneuroimmunology. Another property shared by the CNS, the endocrine system, and the immune system is the regular changes they undergo with the passage of time (e.g., daily, monthly), which is the basis of the field of chronobiology.

PSYCHIATRY AND THE HUMAN BRAIN

In the first half of the 20th century, the advances in psychodynamic psychiatry, as well as in social and epidemiological psychiatry, led to a separation of psychiatric research from the

study of the human brain. Since the 1950s, the appreciation of the effectiveness of medications in treating mental disorders and the mental effects of illicit drugs, have reestablished a biological view of mental illness, which had already been seeded by the introduction of electroconvulsive therapy (ECT) and James Papez's description of the limbic circuit in the 1930s. This biological view has been reinforced further by the development of brain imaging techniques that have helped reveal how the brain performs in normal and abnormal conditions. During this period, countless discoveries have been made in basic neural science research using experimental techniques to assess the development, structure, biology, and function of the CNS of humans and animals.

Psychopharmacology

The effectiveness of drugs in the treatment of mental illness has been a major feature of the last half-century of psychiatric practice. The first five editions of this textbook divided psychopharmacological treatment into four chapters on antipsychotic, antidepressant, antianxiety, and mood-stabilizing drugs. The prior division of psychiatric drugs into four classes is less valid now than it was in the past for the following reasons: (1) Many drugs of one class are used to treat disorders previously assigned to another class; (2) drugs from all four categories are used to treat disorders not previously treatable by drugs (for example, eating disorders, panic disorders, and impulse control disorders); and (3) drugs such as clonidine (Catapres), propranolol (Inderal), and verapamil (Isoptin) can effectively treat a variety of psychiatric disorders and do not fit easily into the aforementioned classification of drugs.

The primary motivation for this change was that the variety and application of the drug treatments no longer clearly fit a division of disorders into psychosis, depression, anxiety, and mania. In other words, the clinical applications of biologically based treatments did not neatly align with our syndrome-based diagnostic system. An implication of this observation could be that drug response might be a better indicator of underlying biological brain dysfunction than any particular group of symptoms. For example, although the DSM-5 distinguishes major depressive disorder from generalized anxiety disorder, most clinicians are aware that these are often overlapping symptoms and conditions in clinical practice. Moreover, the same drugs are used to treat both conditions.

The animal models that are used to identify new drug treatments may also have affected our ability to advance research and treatment. Many major classes of psychiatric drugs were discovered serendipitously. Specifically, the drugs were developed originally for nonpsychiatric indications, but observant clinicians and researchers noted that psychiatric symptoms improved in some patients, which led to focused study of these drugs in psychiatric patients. The availability of these effective drugs, including monoaminergic antidepressants and antipsychotics, led to the development of animal models that could detect the effects of these drugs (e.g., tricyclic antidepressants increase the time mice spend trying to find a submerged platform in a "forced swim" test). These animal models were then used to screen new compounds in an attempt to identify drugs that were active in the same animal models. The potential risk of this overall strategy is that these animal models are merely a method for detecting a particular molecular mechanism of action (e.g., increasing serotonin concentrations), rather than a model for a true behavioral analog of a human mental illness (e.g., behavioral despair in a depressed patient).

Endophenotypes

A possible diagnosis-related parallel to how this textbook separated the four classes of psychotropic drugs into approximately 30 different categories is the topic of *endophenotypes* in psychiatric patients. An endophenotype is an internal phenotype, which is a set of objective characteristics of an individual that are not visible to the unaided eye. Because there are so many steps and variables that separate a particular set of genes from the final functioning of a whole human brain, it may be more tractable to consider intermediate assessments such as endophenotypes. This hypothesis is based on the assumption that the number of genes that are involved in an endophenotype might be fewer than the number of genes involved in causing what we would conceptualize as a disease. The nature of an endophenotype, as considered in psychiatry, is biologically defined on the basis of neuropsychological, cognitive, neurophysiological, neuroanatomical, biochemical, and brain imaging data. Such an endophenotype, for example, might include specific cognitive impairments as just one of its objectively measured features. This endophenotype would not be limited to patients with a diagnosis of schizophrenia because it might also be found in some patients with depression or bipolar disorder.

The potential role of an endophenotype can be further clarified by stating what it is not. An endophenotype is not a symptom, and it is not a diagnostic marker. A classification based on the presence or absence of one or more endophenotypes would be based on objective biological and neuropsychological measures with specific relationships to genes and brain function. A classification based on endophenotypes might also be a productive approach toward the development of more relevant animal models of mental illnesses, and thus the development of novel treatments.

PSYCHIATRY AND THE HUMAN GENOME

Perhaps 70 to 80 percent of the 25,000 human genes are expressed in the brain, and because most genes code for more than one protein, there may be 100,000 different proteins in the brain. Perhaps 10,000 of these are known proteins with somewhat identified functions, and no more than 100 of these are the targets for existing psychotherapeutic drugs.

The study of families with the use of population genetic methods over the last 50 years has consistently supported a genetic, heritable component to mental disorders. More recent techniques in molecular biology have revealed that specific chromosomal regions and genes are associated with particular diagnoses. A potentially very powerful application of these techniques has been to study transgenic models of behavior in animals. These transgenic models can help us understand the effects of individual genes as well as discover completely novel molecular targets for drug development.

It may be a natural response to resist "simple" genetic explanations for human features. Nonetheless, research on humans

generally has found that approximately 40 to 70 percent of aspects of cognition, temperament, and personality are attributable to genetic factors. Because these are the very domains that are affected in mentally ill patients, it would not be surprising to discover a similar level of genetic influence on mental illness, especially if we were able to assess this impact at a more discrete level, such as with endophenotypes.

Individual Genes and Mental Disorders

Several types of data and observations suggest that any single gene is likely to have only a modest effect on the development of a mental disorder, and that when a mental disorder is present in an individual, it represents the effects of multiple genes, speculatively on the order of five to ten genes. This hypothesis is also supported by our failure to find single genes with major effects in mental illnesses. Some researchers, however, still consider it a possibility that genes with major effects will be identified.

"Nature" and "Nurture" within the CNS

In 1977, George Engel, at the University of Rochester, published a paper that articulated the biopsychosocial model of disease, which stressed an integrated approach to human behavior and disease. The biological system refers to the anatomical, structural, and molecular substrates of disease; the psychological system refers to the effects of psychodynamic factors; and the social system examines cultural, environmental, and familial influences. Engel postulated that each system affects and is affected by the others.

The observation that a significant percentage of identical twins are discordant for schizophrenia is one example of the type of data that support the understanding that there are many significant interactions between the genome and the environment (i.e., the biological basis of the biopsychosocial concept). Studies in animals have also demonstrated that many factors—including activity, stress, drug exposure, and environmental toxins—can regulate the expression of genes and the development and functioning of the brain.

Mental Disorders Reflect Abnormalities in Neuroanatomical Circuits and Synaptic Regulation

Although genes lead to the production of proteins, the actual functioning of the brain needs to be understood at the level of regulation of complex pathways of neurotransmission and intraneuronal signaling, and of networks of neurons within and between brain regions. In other words, the downstream effects of abnormal genes are modifications in discrete attributes such as axonal projections, synaptic integrity, and specific steps in intraneuronal molecular signaling.

Why Not a Genetic-Based Diagnostic System?

Some researchers have proposed moving psychiatry toward a completely genetic-based diagnostic system. This proposal, however, seems premature based on the complexity of the genetic factors presumably involved in psychiatric disorders, the current absence of sufficient data to make these genetic connections, and the importance of epigenetic and environmental influences on the final behavioral outcomes resulting from an individual's genetic information.

LESSONS FROM NEUROLOGY

Clinical and research neurologists seem to have been able to think more clearly than psychiatrists about their diseases of interest and their causes, perhaps because the symptoms are generally nonbehavioral. Neurologists have biologically grounded differential diagnoses and treatment choices. This clarity of approach has helped lead to significant advances in neurology in the last two decades, for example, clarification of the amyloid precursor protein abnormalities in some patients with Alzheimer's disease, the presence of trinucleotide repeat mutations in Huntington's disease and spinocerebellar ataxia, and the appreciation of alpha-synucleinopathies, such as Parkinson's disease and Lewy body dementia.

The continued separation of psychiatry from neurology is in itself a potential impediment to good patient care and research. Many neurological disorders have psychiatric symptoms (e.g., depression in patients following a stroke or with multiple sclerosis or Parkinson's disease), and several of the most severe psychiatric disorders have been associated with neurological symptoms (e.g., movement disorders in schizophrenia). This is not surprising given that the brain is the organ shared by psychiatric and neurological diseases, and the division between these two disease areas is arbitrary. For example, patients with Huntington's disease are at much greater risk for a wide range of psychiatric symptoms and syndromes, and thus many different DSM-5 diagnoses. Because we know that Huntington's disease is an autosomal dominant genetic disorder, the observation that it can manifest with so many different DSM-5 diagnoses does not speak to a very strong biological distinction among the existing DSM-5 categories.

EXAMPLES OF COMPLEX HUMAN BEHAVIORS

The goal to understand the human brain and its normal and abnormal functioning is truly one of the last frontiers for humans to explore. Trying to explain why a particular individual is the way he or she is, or what causes schizophrenia, for example, will remain too large a challenge for some decades. It is more approachable to consider more discrete aspects of human behavior.

It is not the role of textbooks to set policies or to write diagnostic manuals, but rather to share knowledge, generate ideas, and encourage innovation. The authors believe, however, that it is time to reap the insights of decades of neural science and clinical brain research and to build the classification of mental illnesses on fundamental principles of biology and medicine. Regardless of official diagnostic systems, however, clinicians and researchers should fully understand the biological component of the biopsychosocial model, and not let research or patient care suffer because of a diagnostic system that is not founded on biological principles.

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▲ 1.2 Functional Neuroanatomy

The sensory, behavioral, affective, and cognitive phenomena and attributes experienced by humans are mediated through the brain. It is the organ that perceives and affects the environment and integrates past and present. The brain is the organ of the mind that enables persons to sense, do, feel, and think.

Sensory systems create an internal representation of the external world by processing external stimuli into neuronal impulses. A separate map is formed for each sensory modality. *Motor systems* enable persons to manipulate their environment and to influence the behavior of others through communication. In the brain, sensory input, representing the external world, is integrated with internal drivers, memories, and emotional stimuli in *association units,* which in turn drive the actions of motor units. Although psychiatry is concerned primarily with the brain's association function, an appreciation of information processing of the sensory and motor systems is essential for sorting logical thought from the distortions introduced by psychopathology.

BRAIN ORGANIZATION

The human brain contains approximately 10^{11} *neurons* (nerve cells) and approximately 10^{12} *glial cells.* Neurons most classically consist of a *soma,* or cell body, which contains the nucleus; usually multiple *dendrites,* which are processes that extend from the cell body and receive signals from other neurons; and a single *axon,* which extends from the cell body and transmits signals to other neurons. Connections between neurons are made at *axon terminals;* there the axons of one neuron generally contact the dendrite or cell body of another neuron. Neurotransmitter release occurs within axon terminals and is one of the major mechanisms for intraneuronal communications, and also for the effects of psychotropic drugs.

There are three types of glial cells, and although they have often been thought of as having only a supportive role for neuronal functioning, glia have been increasingly appreciated as potentially involved in brain functions that may contribute more directly to both normal and disease mental conditions. The most common type of glial cell are the *astrocytes,* which have a number of functions, including nutrition of neurons, deactivation of some neurotransmitters, and integration with the blood–brain barrier. The *oligodendrocytes* in the central nervous system and the *Schwann cells* in the peripheral nervous system wrap their processes around neuronal axons, resulting in *myelin sheaths* that facilitate the conduction of electrical signals. The third type of glial cells, the *microglia,* which are derived from macrophages, are involved in removing cellular debris following neuronal death.

The neurons and glial cells are arranged in regionally distinct patterns within the brain. Neurons and their processes form groupings in many different ways, and these patterns of organization, or architecture, can be evaluated by several approaches. The pattern of distribution of nerve cell bodies, called *cytoarchitecture,* is revealed by aniline dyes called Nissl stains that stain ribonucleotides in the nuclei and the cytoplasm of neuronal cell bodies. The Nissl stains show the relative size and packing density of the neurons and, consequently, reveal the organization of the neurons into the different layers of the cerebral cortex.

SENSORY SYSTEMS

The external world offers an infinite amount of potentially relevant information. In this overwhelming volume of sensory information in the environment, the sensory systems must both detect and discriminate stimuli; they winnow relevant information from the mass of confounding input by applying filtration at all levels. Sensory systems first transform external stimuli into neural impulses and then filter out irrelevant information to create an internal image of the environment, which serves as a basis for reasoned thought. Feature extraction is the quintessential role of sensory systems, which achieve this goal with their hierarchical organizations, first by transforming physical stimuli into neural activity in the primary sense organs and then by refining and narrowing the neural activity in a series of higher cortical processing areas. This neural processing eliminates irrelevant data from higher representations and reinforces crucial features. At the highest levels of sensory processing, neural images are transmitted to the association areas to be acted on in the light of emotions, memories, and drives.

Somatosensory System

The *somatosensory system,* an intricate array of parallel point-to-point connections from the body surface to the brain, was the first sensory system to be understood in anatomical detail. The six somatosensory modalities are light touch, pressure, pain, temperature, vibration, and proprioception (position sense). The organization of nerve bundles and synaptic connections in the somatosensory system encodes spatial relationships at all levels, so that the organization is strictly *somatotopic* (Fig. 1.2-1).

Within a given patch of skin, various receptor nerve terminals act in concert to mediate distinct modalities. The mechanical properties of the skin's mechanoreceptors and thermoreceptors generate neural impulses in response to dynamic variations in the environment while they suppress static input. Nerve endings are either fast or slow responders; their depth in the skin also determines their sensitivity to sharp or blunt stimuli. Thus the representation of the external world is significantly refined at the level of the primary sensory organs.

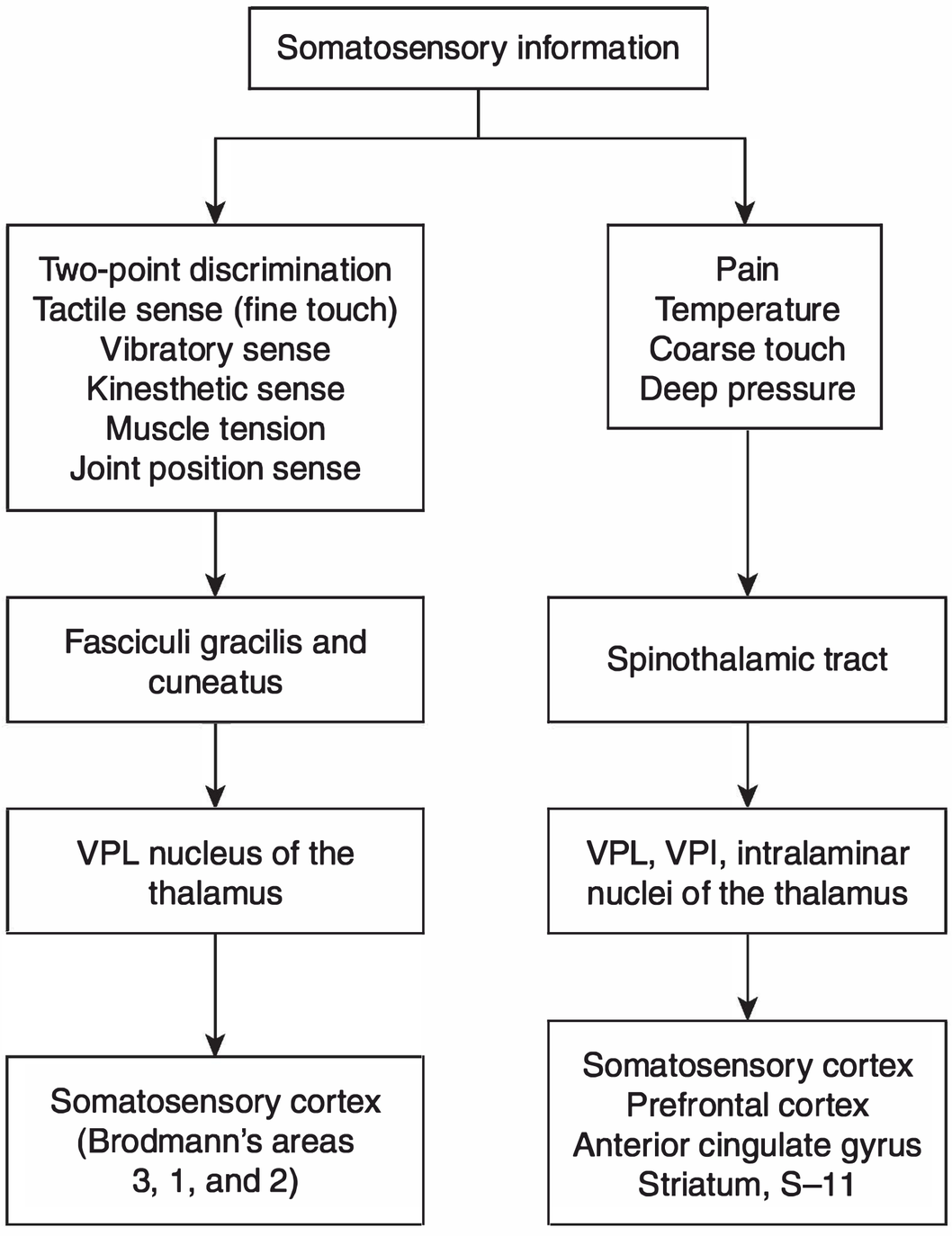

FIGURE 1.2-1
Pathway of somatosensory information processing. (Adapted from Patestas MA, Gartner LP. *A Textbook of Neuroanatomy*. Malden, MA: Blackwell; 2006:149.)

The receptor organs generate coded neural impulses that travel proximally along the sensory nerve axons to the spinal cord. These far-flung routes are susceptible to varying systemic medical conditions and to pressure palsies. Pain, tingling, and numbness are the typical presenting symptoms of peripheral neuropathies.

All somatosensory fibers project to, and synapse in, the thalamus. The thalamic neurons preserve the somatotopic representation by projecting fibers to the somatosensory cortex, located immediately posterior to the sylvian fissure in the parietal lobe. Despite considerable overlap, several bands of cortex roughly parallel to the sylvian fissure are segregated by a somatosensory modality. Within each band is the sensory "homunculus," the culmination of the careful somatotopic segregation of the sensory fibers at the lower levels. The clinical syndrome of *tactile agnosia* (*astereognosis*) is defined by the inability to recognize objects based on touch, although the primary somatosensory modalities—light touch, pressure, pain, temperature, vibration, and proprioception—are intact. This syndrome, localized at the border of the somatosensory and association areas in the posterior parietal lobe, appears to represent an isolated failure of only the highest order of feature extraction, with preservation of the more basic levels of the somatosensory pathway.

Reciprocal connections are a key anatomical feature of crucial importance to conscious perception—as many fibers project down from the cortex to the thalamus as project up from the thalamus to the cortex. These reciprocal fibers play a critical role in filtering sensory input. In normal states, they facilitate the sharpening of internal representations, but in pathological states, they can generate false signals or inappropriately suppress sensation. Such cortical interference with sensory perception is thought to underlie many psychosomatic syndromes, such as the hemisensory loss that characterizes conversion disorder.

The prenatal development of the strict point-to-point pattern that characterizes the somatosensory system remains an area of active study. Patterns of sensory innervation result from a combination of axonal guidance by particular molecular cues and pruning of exuberant synaptogenesis on the basis of an organism's experience. Leading hypotheses weigh contributions from a genetically determined molecular map—in which the arrangement of fiber projections is organized by fixed and diffusible chemical cues—against contributions from the modeling and remodeling of projections on the basis of coordinated neural activity. Thumbnail calculations suggest that the 30,000 to 40,000 genes in human deoxyribonucleic acid (DNA) are far too few to encode completely the position of all the trillions of synapses in the brain. In fact, genetically determined positional cues probably steer growing fibers toward the general target, and the pattern of projections is fine-tuned by activity-dependent mechanisms. Recent data suggest that well-established adult thalamocortical sensory projections can be gradually remodeled as a result of a reorientation of coordinated sensory input or in response to loss of part of the somatosensory cortex, for instance, in stroke.

Development of the Somatosensory System

A strict somatotopic representation exists at each level of the somatosensory system. During development, neurons extend axons to connect to distant brain regions; after arriving at the destination, a set of axons must therefore sort itself to preserve the somatotopic organization. A classic experimental paradigm for this developmental process is the representation of a mouse's whiskers in the somatosensory cortex. The murine somatosensory cortex contains a barrel field of cortical columns, each of which corresponds to one whisker. When mice are inbred to produce fewer whiskers, fewer somatosensory cortex barrels appear. Each barrel is expanded in area, and the entire barrel field covers the same area of the somatosensory cortex as it does in normal animals. This experiment demonstrates that certain higher cortical structures can form in response to peripheral input and that different input complexities determine different patterns of synaptic connectivity. Although the mechanisms by which peripheral input molds cortical architecture are largely unknown, animal model paradigms are beginning to yield clues. For example, in a mutant mouse that lacks monoamine oxidase A and, thus, has extremely high cortical levels of serotonin, barrels fail to form in the somatosensory cortex. This result indirectly implicates serotonin in the mechanism of barrel field development.

In adults, the classic mapping studies of Wilder Penfield suggested the existence of a homunculus, an immutable cortical representation of the body surface. More recent experimental evidence from primate studies and from stroke patients, however, has promoted a more plastic conception than that of Penfield. Minor variations exist in the cortical pattern of normal individuals, yet dramatic shifts in the map can occur in response to loss of cortex from stroke or injury. When a stroke ablates a significant fraction of the somatosensory homunculus, the homuncular representation begins to contract and shift proportionately to fill the remaining intact cortex.

Moreover, the cortical map can be rearranged solely in response to a change in the pattern of tactile stimulation of the fingers. The somatotopic representation of the proximal and distal segments of each finger normally forms a contiguous map, presumably because both segments contact surfaces simultaneously. However, under experimental conditions in which the distal segments of all fingers are simultaneously stimulated while contact of the distal and proximal parts of each finger is separated, the cortical map gradually shifts 90 degrees to reflect the new sensory experience. In the revised map, the cortical representation of the proximal segment of each finger is no longer contiguous with that of the distal segment.

These data support the notion that the internal representation of the external world, although static in gross structure, can be continuously modified at the level of synaptic connectivity to reflect relevant sensory experiences. The cortical representation also tends to shift to fit entirely into the available amount of cortex.

These results also support the notion that cortical representations of sensory input, or of memories, may be holographic rather than spatially fixed: The pattern of activity, rather than the physical structure, may encode information. In sensory systems, this plasticity of cortical representation allows recovery from brain lesions; the phenomenon may also underlie learning.

Visual System

Visual images are transduced into neural activity within the retina and are processed through a series of brain cells, which respond to increasingly complex features, from the eye to the higher visual cortex. The neurobiological basis of feature extraction is best understood in finest detail in the visual system. Beginning with classic work in the 1960s, research in the visual pathway has produced two main paradigms for all sensory systems. The first paradigm, mentioned earlier with respect to the somatosensory system, evaluates the contributions of genetics and experience—or nature and nurture—in the formation of the final synaptic arrangement. Transplantation experiments, resulting in an accurate point-to-point pattern of connectivity, even when the eye was surgically inverted, have suggested an innate, genetically determined mechanism of synaptic pattern formation. The crucial role of early visual experience in establishing the adult pattern of visual connections, on the other hand, crystallized the hypothesis of activity-dependent formation of synaptic connectivity. The final adult pattern is the result of both factors.

The second main paradigm, most clearly revealed in the visual system, is that of highly specialized brain cells that respond exclusively to extremely specific stimuli. Recent work, for example, has identified cells in the inferior temporal cortex that respond only to faces viewed at a specific angle. An individual's response to a particular face requires the activity of large neural networks and may not be limited to a single neuron. Nevertheless, the cellular localization of specific feature extraction is of critical importance in defining the boundary between sensory and association systems, but only in the visual system has this significant question been posed experimentally.

In the primary visual cortex, columns of cells respond specifically to lines of a specific orientation. The cells of the primary visual cortex project to the secondary visual cortex, where cells respond specifically to particular movements of lines and to angles. In turn, these cells project to two association areas, where additional features are extracted and conscious awareness of images forms.

The inferior temporal lobe detects the shape, form, and color of the object—the *what* questions; the posterior parietal lobe tracks the location, motion, and distance—the *where* questions. The posterior parietal lobe contains distinct sets of neurons that signal the intention either to look into a certain part of visual space or to reach for a particular object. In the inferior temporal cortices (ITCs), adjacent cortical columns respond to complex forms. Responses to facial features tend to occur in the left ITC, and responses to complex shapes tend to occur in the right ITC. The brain devotes specific cells to the recognition of facial expressions and to the aspect and position of faces of others with respect to the individual.

The crucial connections between the feature-specific cells and the association areas involved in memory and conscious thought remain to be delineated. Much elucidation of feature recognition is based on invasive animal studies. In humans, the clinical syndrome of *prosopagnosia* describes the inability to recognize faces, in the presence of preserved recognition of other environmental objects. On the basis of pathological and radiological examination of individual patients, prosopagnosia is thought to result from disconnection of the left ITC from the visual association area in the left parietal lobe. Such lesional studies are useful in identifying necessary components of a mental pathway, but they may be inadequate to define the entire pathway. One noninvasive technique that is still being perfected and is beginning to reveal the full anatomical relation of the human visual system to conscious thought and memory is functional neuroimaging.

As is true for language, there appears to be a hemispheric asymmetry for certain components of visuospatial orientation. Although both hemispheres cooperate in perceiving and drawing complex images, the right hemisphere, especially the parietal lobe, contributes the overall contour, perspective, and right-left orientation, and the left hemisphere adds internal detail, embellishment, and complexity. The brain can be fooled in optical illusions.

Neurological conditions such as strokes and other focal lesions have permitted the definition of several disorders of visual perception. *Apperceptive visual agnosia* is the inability to identify and draw items using visual cues, with preservation of other sensory modalities. It represents a failure of transmission of information from the higher visual sensory pathway to the association areas and is caused by bilateral lesions in the visual association areas. *Associative visual agnosia* is the inability to name or use objects despite the ability to draw them. It is caused by bilateral medial occipitotemporal lesions and can occur along with other visual impairments. Color perception may be ablated in lesions of the dominant occipital lobe that include the splenium of the corpus callosum. *Color agnosia* is the inability to recognize a color despite being able to match it. *Color anomia* is the inability to name a color despite being able to point to it. *Central achromatopsia* is a complete inability to perceive color. *Anton's syndrome* is a failure to acknowledge blindness, possibly owing to interruption of fibers involved in self-assessment. It is seen with bilateral occipital lobe lesions. The most common causes are hypoxic injury, stroke, metabolic encephalopathy, migraine, herniation resulting from mass lesions, trauma, and leukodystrophy. *Balint's syndrome* consists of a triad of optic ataxia (the inability to direct optically guided movements), *oculomotor apraxia* (inability to direct gaze rapidly), and *simultanagnosia* (inability to integrate a visual scene to perceive it as a whole). Balint's syndrome is seen in bilateral parietooccipital lesions. *Gerstmann's syndrome* includes agraphia, calculation

difficulties (acalculia), right–left disorientation, and finger agnosia. It has been attributed to lesions of the dominant parietal lobe.

Development of the Visual System

In humans, the initial projections from both eyes intermingle in the cortex. During the development of visual connections in the early postnatal period, there is a window of time during which binocular visual input is required for development of ocular dominance columns in the primary visual cortex. Ocular dominance columns are stripes of cortex that receive input from only one eye, separated by stripes innervated only by fibers from the other eye. Occlusion of one eye during this critical period completely eliminates the persistence of its fibers in the cortex and allows the fibers of the active eye to innervate the entire visual cortex. In contrast, when normal binocular vision is allowed during the critical development window, the usual dominance columns form; occluding one eye after the completion of innervation of the cortex produces no subsequent alteration of the ocular dominance columns. This paradigm crystallizes the importance of early childhood experience on the formation of adult brain circuitry.

Auditory System

Sounds are instantaneous, incremental changes in ambient air pressure. The pressure changes cause the ear's tympanic membrane to vibrate; the vibration is then transmitted to the ossicles (malleus, incus, and stapes) and thereby to the endolymph or fluid of the cochlear spiral. Vibrations of the endolymph move cilia on hair cells, which generate neural impulses. The hair cells respond to sounds of different frequency in a tonotopic manner within the cochlea, like a long, spiral piano keyboard. Neural impulses from the hair cells travel in a tonotopic arrangement to the brain in the fibers of the cochlear nerve. They enter the brainstem cochlear nuclei, are relayed through the lateral lemniscus to the inferior colliculi, and then to the medial geniculate nucleus (MGN) of the thalamus. MGN neurons project to the primary auditory cortex in the posterior temporal lobe. Dichotic listening tests, in which different stimuli are presented to each ear simultaneously, demonstrate that most of the input from one ear activates the contralateral auditory cortex and that the left hemisphere tends to be dominant for auditory processing.

Sonic features are extracted through a combination of mechanical and neural filters. The representation of sound is roughly tonotopic in the primary auditory cortex, whereas *lexical processing* (i.e., the extraction of vowels, consonants, and words from the auditory input) occurs in higher language association areas, especially in the left temporal lobe. The syndrome of *word deafness,* characterized by intact hearing for voices but an inability to recognize speech, may reflect damage to the left parietal cortex. This syndrome is thought to result from disconnection of the auditory cortex from Wernicke's area. A rare, complementary syndrome, *auditory sound agnosia,* is defined as the inability to recognize nonverbal sounds, such as a horn or a cat's meow, in the presence of intact hearing and speech recognition. Researchers consider this syndrome the right hemisphere correlate of pure word deafness.

Development of the Auditory System

Certain children are unable to process auditory input clearly and therefore have impaired speech and comprehension of spoken language. Studies on some of these children have determined that, in fact, they can discriminate speech if the consonants and vowels—the phonemes—are slowed twofold to fivefold by a computer. Based on this observation, a tutorial computer program was designed that initially asked questions in a slowed voice and, as subjects answered questions correctly, gradually increased the rate of phoneme presentation to approximate normal rates of speech. Subjects gained some ability to discriminate routine speech over a period of 2 to 6 weeks and appeared to retain these skills after the tutoring period was completed. This finding probably has therapeutic applicability to 5 to 8 percent of children with speech delay, but ongoing studies may expand the eligible group of students. This finding, moreover, suggests that neuronal circuits required for auditory processing can be recruited and be made more efficient long after language is normally learned, provided that the circuits are allowed to finish their task properly, even if this requires slowing the rate of input. Circuits thus functioning with high fidelity can then be trained to speed their processing.

A recent report has extended the age at which language acquisition may be acquired for the first time.

A boy who had intractable epilepsy of one hemisphere was mute because the uncontrolled seizure activity precluded the development of organized language functions. At the age of 9 years he had the abnormal hemisphere removed to cure the epilepsy. Although up to that point in his life he had not spoken, he initiated an accelerated acquisition of language milestones beginning at that age and ultimately gained language abilities only a few years delayed relative to his chronological age.

Researchers cannot place an absolute upper limit on the age at which language abilities can be learned, although acquisition at ages beyond the usual childhood period is usually incomplete. Anecdotal reports document acquisition of reading skills after the age of 80 years.

Olfaction

Odorants, or volatile chemical cues, enter the nose, are solubilized in the nasal mucus, and bind to odorant receptors displayed on the surface of the sensory neurons of the olfactory epithelium. Each neuron in the epithelium displays a unique odorant receptor, and cells displaying a given receptor are arranged randomly within the olfactory epithelium. Humans possess several hundred distinct receptor molecules that bind the huge variety of environmental odorants; researchers estimate that humans can discriminate 10,000 different odors. Odorant binding generates neural impulses, which travel along the axons of the sensory nerves through the cribriform plate to the olfactory bulb. Within the bulb, all axons corresponding to a given receptor converge onto only 1 or 2 of 3,000 processing units called *glomeruli.* Because each odorant activates several receptors that activate a characteristic pattern of glomeruli, the identity of external chemical molecules is represented internally by a spatial pattern of neural activity in the olfactory bulb.

Each glomerulus projects to a unique set of 20 to 50 separate columns in the olfactory cortex. In turn, each olfactory cortical column receives projections from a unique combination of glomeruli. The connectivity of the olfactory system is genetically determined. Because each odorant activates a unique set of several receptors and thus a unique set of olfactory bulb glomeruli, each olfactory cortical column is tuned to detect a different odorant of some evolutionary significance to the species. Unlike the signals of the somatosensory, visual, and auditory systems, olfactory signals do not pass through the thalamus but project directly to the frontal lobe and the limbic system, especially the pyriform cortex. The connections to the limbic system (amygdala, hippocampus, and pyriform cortex) are significant. Olfactory cues stimulate strong emotional responses and can evoke powerful memories.

Olfaction, the most ancient sense in evolutionary terms, is tightly associated with sexual and reproductive responses. A related chemosensory structure, the vomeronasal organ, is thought to detect *pheromones,* chemical cues that trigger unconscious, stereotyped responses. In some animals, ablation of the vomeronasal organ in early life may prevent the onset of puberty. Recent studies have suggested that humans also respond to pheromones in a manner that varies according to the menstrual cycle. The structures of higher olfactory processing in phylogenetically more primitive animals have evolved in humans into the limbic system, the center of the emotional brain and the gate through which experience is admitted into memory according to emotional significance. The elusive basic animal drives with which clinical psychiatry constantly grapples may therefore, in fact, originate from the ancient centers of higher olfactory processing.

Development of the Olfactory System

During normal development, axons from the nasal olfactory epithelium project to the olfactory bulb and segregate into about 3,000 equivalent glomeruli. If an animal is exposed to a single dominant scent in the early postnatal period, then one glomerulus expands massively within the bulb at the expense of the surrounding glomeruli. Thus, as discussed earlier with reference to the barrel fields of the somatosensory cortex, the size of brain structures may reflect the environmental input.

Taste

Soluble chemical cues in the mouth bind to receptors in the tongue and stimulate the gustatory nerves, which project to the nucleus solitarius in the brainstem. The sense of taste is believed to discriminate only broad classes of stimuli: sweet, sour, bitter, and salty. Each modality is mediated through a unique set of cellular receptors and channels, of which several may be expressed in each taste neuron. The detection and the discrimination of foods, for example, involve a combination of the senses of taste, olfaction, touch, vision, and hearing. Taste fibers activate the medial temporal lobe, but the higher cortical localization of taste is only poorly understood.

Autonomic Sensory System

The autonomic nervous system (ANS) monitors the basic functions necessary for life. The activity of visceral organs, blood pressure, cardiac output, blood glucose levels, and body temperature are all transmitted to the brain by autonomic fibers. Most autonomic sensory information remains unconscious; if such information rises to conscious levels, it is only as a vague sensation, in contrast to the capacity of the primary senses to transmit sensations rapidly and exactly.

Alteration of Conscious Sensory Perception through Hypnosis

Hypnosis is a state of heightened suggestibility attainable by a certain proportion of the population. Under a state of hypnosis, gross distortions of perception in any sensory modality and changes in the ANS can be achieved instantaneously. The anatomy of the sensory system does not change, yet the same specific stimuli may be perceived with diametrically opposed emotional value before and after induction of the hypnotic state. For example, under hypnosis a person may savor an onion as if it were a luscious chocolate truffle, only to reject the onion as abhorrently pungent seconds later, when the hypnotic suggestion is reversed. The localization of the hypnotic switch has not been determined, but it presumably involves both sensory and association areas of the brain. Experiments tracing neural pathways in human volunteers via functional neuroimaging have demonstrated that shifts in attention in an environmental setting determine changes in the regions of the brain that are activated, on an instantaneous time scale. Thus the organizing centers of the brain may route conscious and unconscious thoughts through different sequences of neural processing centers, depending on a person's ultimate goals and emotional state. These attention-mediated variations in synaptic utilization can occur instantaneously, much like the alteration in the routing of associational processing that may occur in hypnotic states.

MOTOR SYSTEMS

Body muscle movements are controlled by the lower motor neurons, which extend axons—some as long as 1 meter—to the muscle fibers. Lower motor neuron firing is regulated by the summation of upper motor neuron activity. In the brainstem, primitive systems produce gross coordinated movements of the entire body. Activation of the rubrospinal tract stimulates flexion of all limbs, whereas activation of the vestibulospinal tract causes all limbs to extend. Newborn infants, for example, have all limbs tightly flexed, presumably through the dominance of the rubrospinal system. In fact, the movements of an anencephalic infant, who completely lacks a cerebral cortex, may be indistinguishable from the movements of a normal newborn. In the first few months of life, the flexor spasticity is gradually mitigated by the opposite actions of the vestibulospinal fibers, and more limb mobility occurs.

At the top of the motor hierarchy is the corticospinal tract, which controls fine movements and which eventually dominates the brainstem system during the first years of life. The upper motor neurons of the corticospinal tract reside in the posterior frontal lobe, in a section of cortex known as the *motor strip*. Planned movements are conceived in the association areas of the brain, and in consultation with the basal ganglia and cerebellum, the motor cortex directs their smooth execution. The importance of the corticospinal system becomes immediately evident in strokes, in which spasticity returns as the cortical influence is ablated and the actions of the brainstem motor systems are released from cortical modulation.

Basal Ganglia

The *basal ganglia,* a subcortical group of gray matter nuclei, appear to mediate postural tone. The four functionally distinct ganglia are the striatum, the pallidum, the substantia nigra,

and the subthalamic nucleus. Collectively known as the corpus striatum, the caudate and putamen harbor components of both motor and association systems. The caudate nucleus plays an important role in the modulation of motor acts. Anatomical and functional neuroimaging studies have correlated decreased activation of the caudate with obsessive-compulsive behavior. When functioning properly, the caudate nucleus acts as a gatekeeper to allow the motor system to perform only those acts that are goal directed. When it fails to perform its gatekeeper function, extraneous acts are performed, as in obsessive-compulsive disorder or in the tic disorders, such as Tourette's disorder. Overactivity of the striatum owing to lack of dopaminergic inhibition (e.g., in parkinsonian conditions) results in *bradykinesia,* an inability to initiate movements. The caudate, in particular, shrinks dramatically in Huntington's disease. This disorder is characterized by rigidity, on which is gradually superimposed choreiform, or "dancing," movements. Psychosis may be a prominent feature of Huntington's disease, and suicide is not uncommon. The caudate is also thought to influence associative, or cognitive, processes.

The globus pallidus contains two parts linked in series. In a cross section of the brain, the internal and external parts of the globus pallidus are nested within the concavity of the putamen. The globus pallidus receives input from the corpus striatum and projects fibers to the thalamus. This structure may be severely damaged in Wilson's disease and in carbon monoxide poisoning, which are characterized by dystonic posturing and flapping movements of the arms and legs.

The substantia nigra is named the black substance because the presence of melanin pigment causes it to appear black to the naked eye. It has two parts, one of which is functionally equivalent to the globus pallidus interna. The other part degenerates in Parkinson's disease. Parkinsonism is characterized by rigidity and tremor and is associated with depression in more than 30 percent of cases.

Finally, lesions in the subthalamic nucleus yield ballistic movements, sudden limb jerks of such velocity that they are compared to projectile movement.

Together, the nuclei of the basal ganglia appear capable of initiating and maintaining the full range of useful movements. Investigators have speculated that the nuclei serve to configure the activity of the overlying motor cortex to fit the purpose of the association areas. In addition, they appear to integrate proprioceptive feedback to maintain an intended movement.

Cerebellum

The cerebellum consists of a simple six-cell pattern of circuitry that is replicated roughly 10 million times. Simultaneous recordings of the cerebral cortex and the cerebellum have shown that the cerebellum is activated several milliseconds before a planned movement. Moreover, ablation of the cerebellum renders intentional movements coarse and tremulous. These data suggest that the cerebellum carefully modulates the tone of agonistic and antagonistic muscles by predicting the relative contraction needed for smooth motion. This prepared motor plan is used to ensure that exactly the right amount of flexor and extensor stimuli is sent to the muscles. Recent functional imaging data have shown that the cerebellum is active, even during the mere imagination of motor acts when no movements ultimately result from its calculations. The cerebellum harbors two, and possibly more, distinct "homunculi" or cortical representations of the body plan.

Motor Cortex

Penfield's groundbreaking work defined a motor homunculus in the precentral gyrus, Brodmann's area 4 (Fig. 1.2-2), where a somatotopic map of the motor neurons is found. Individual cells within the motor strip cause contraction of single muscles. The brain region immediately anterior to the motor strip is called the *supplementary motor area,* Brodmann's area 6. This region contains cells that when individually stimulated can trigger more complex movements by influencing a firing sequence of motor strip cells. Recent studies have demonstrated wide representation of motor movements in the brain.

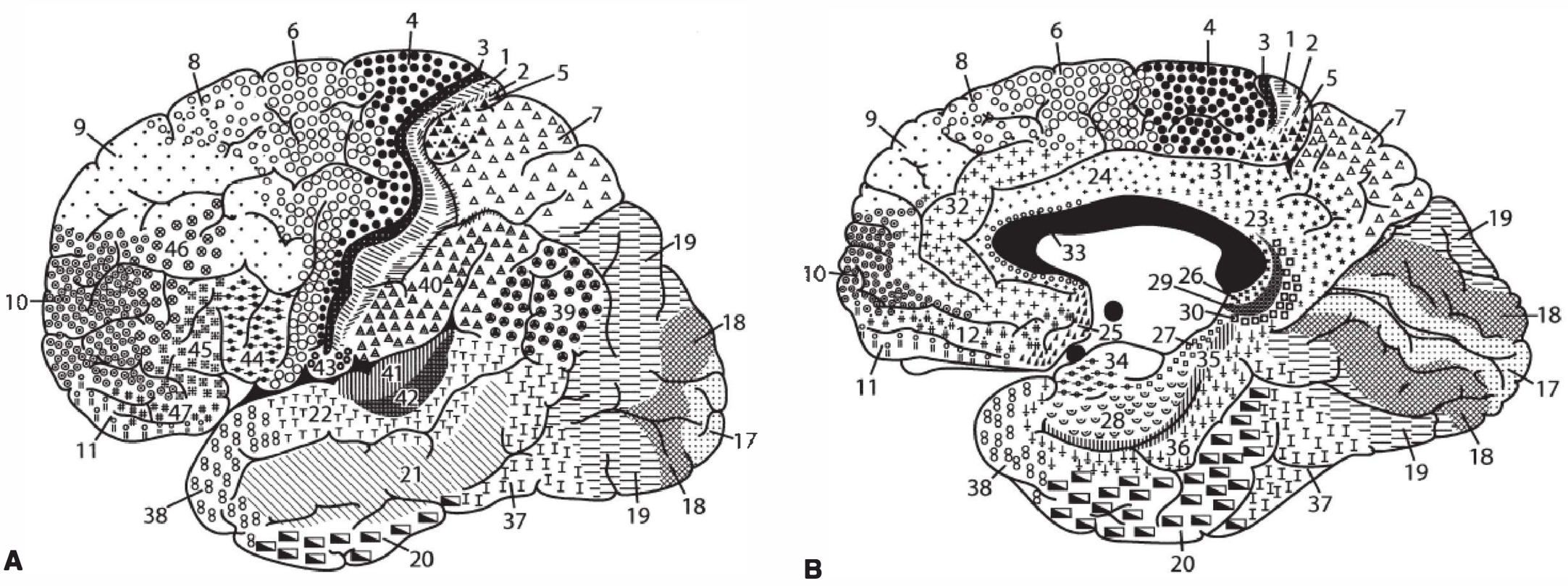

FIGURE 1.2-2

Drawing of the lateral view (**A**) and medial view (**B**) of the cytoarchitectonic subdivisions of the human brain as determined by Brodmann. (From Sadock BJ, Sadock VA, Ruiz P. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009.)