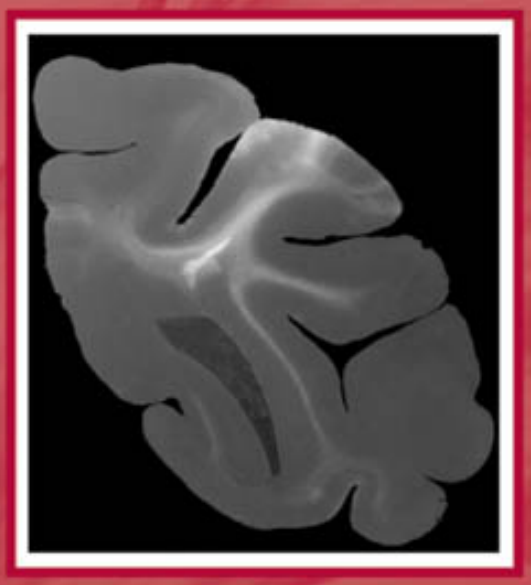

Fiber Pathways of the Brain

JEREMY SCHMAHMANN
DEEPAK PANDYA

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Jeremy D. Schmahmann, MD

Associate Professor of Neurology
Harvard Medical School
Boston, Massachusetts

Director, Ataxia Unit
Cognitive/Behavioral Neurology Unit
Geriatric Neurobehavior Clinic
Department of Neurology
Massachusetts General Hospital
Boston, Massachusetts

Deepak N. Pandya, MD

Professor of Anatomy and Neurobiology
Boston University School of Medicine
Boston, Massachusetts

Harvard Neurological Unit
Beth Israel Deaconess Medical Center
Boston, Massachusetts

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To the memory of Henricus (Hans) G. J. M. Kuypers (1925–1989), whose original ideas concerning corticocortical organization had a fundamental impact on the thinking and career path of D. N. P., and through him to J. D. S. Dr. Kuypers encouraged both of us to study the anatomic basis of behavior and to seek functional relevance in anatomic circuits.

To the memory of Norman Geschwind (1926–1984), mentor and friend to D. N. P., teacher and source of inspiration to both of us in basic as well as clinical neuroscience. Dr. Geschwind revitalized behavioral neurology as an integrated discipline in which innovative clinical ideas are fundamentally dependent upon a detailed understanding of the structure and organization of the nervous system.

To Jinny and Adin, whose love sustains me,
to the memory of my parents, Bella and Oscar,
and to my family, friends, patients, and colleagues.
—J. D. S.

To my dear wife, Bonnie, and children, Jay, Dina, and Sunita,
and to all my colleagues with whom I have had the great opportunity
to navigate through the intricacies of the cerebral cortex.
—D. N. P.

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"To say that the white matter is but a uniform substance like wax in which there is no hidden contrivance, would be too low an opinion of nature's finest masterpiece. We are assured that wherever in the body there are fibers, they everywhere adopt a certain arrangement among themselves, created more or less according to the functions for which they are intended . . . all the diversity of our sensation and our movements depends upon this. We admire the skillful construction . . . where each of these fibers, confined in a small space, functions without confusion and without disorder."

—Nicolaus Steno, 1669

"The work which I have now the honour to present . . . calls the attention of the reader to those laws of Divine order by which the universe is governed and supported; in it we find that the minutest beings share in the protection, and triumph in the bounty of the Sovereign of all things: that the infinitely small, manifest to the astonished eye the same proportion, regularity and design, which are conspicuous to the unassisted sight in the largest parts of creation. By finding all things formed in beauty, and produced for use, the mind is raised from the fleeting and evanescent appearances of matter, to contemplate the permanent principles of truth . . ."

—George Adams, 1798

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Foreword

Nothing defines the function of a neuron better than its connections. Information flows along connections; growth factors are transported along connections; viruses move along connections; epileptic discharges spread through connections. When deprived of connections, neurons pine away and eventually expire through retrograde and transsynaptic degeneration. The neuronal death in amyotrophic lateral sclerosis, neurofibrillary tangles in Alzheimer's disease, atrophy in olivopontocerebellar degeneration progress through neural connections. Once the adult stage of development is reached, connections become more important than even genes or molecules. Despite their vastly different functions, for example, it is quite likely that the genes and proteins of visual and auditory neurons in the cerebral cortex are nearly identical. What ultimately determines the vast differences in their function is not the molecular profile but connectivity.

But why should we bother about connectivity in the age of functional imaging, at a time when magnets of ever increasing strength promise to detect the location of even the faintest thought? Isn't it enough to locate cortical areas engaged in deception, wrath, introspection, empathy? Do we really have to worry about their connections? The answer is "yes," principally because the function of a complex system cannot be deduced from an inventory of its components. The relation among components introduces attributes that are not contained in the list of constituent elements. This is why a chemical analysis of the ink does not allow the differentiation of a sublime statement from a ridiculous one. In the case of the nervous system, the unit of relational architecture that allows the whole to exceed the sum of the parts is known as a large-scale network. Its elucidation requires an elaborate understanding of connectivity patterns.

If the cerebral cortex had been organized in the form of an assembly line, where each station adds a new ingredient and hands its product to the next, connections might well have been inferred from judiciously designed functional imaging experiments. But reality is more complex. Connections in association cortex do not follow strict hierarchies. There are feed-forward and feedback connections, reentrant and corollary discharges, nodes of convergence and divergence, and a tremendous capacity for parallel processing whereby two cortical areas can communicate with each other through dozens of alternate pathways, some direct and some through intermediaries that place their own spins on the message that is being transmitted. Through this architecture, the same area can serve as the beginning, the middle and the end of a cognitive process.

The distribution of connections is complex but not chaotic. The choices are many but they obey phylogenetically established constraints. For example, unimodal association areas in different modalities are not interconnected monosynaptically to each other; the hypothalamus establishes its heaviest connections with limbic and paralimbic areas; peristriate areas are connected to visual cortex in parallel rather than serially. Un-

derstanding these patterns of cortical connectivity is absolutely essential for understanding the relational architecture, and therefore function, of large-scale neurocognitive networks.

This book is all about tracing the white matter trajectories of axonal pathways emanating from the cerebral cortex of the monkey brain. It is a splendid volume that reflects a labor of love from a team that combines great experience with great enthusiasm. In my opinion, this is the most important single-volume contribution to primate neuroanatomy since the 1947 publication of Von Bonin and Bailey's *The Neocortex of Macaca Mulatta*. The book has three major components: an erudite historical account of relevant neuroanatomical themes, a comprehensive cytoarchitectonic map, and an unparalleled account of white matter pathways emanating from cortical tracer injection sites in 36 monkeys. In this third and most important component of the book, the connections of the injection sites and their white matter trajectories are beautifully illustrated. Not only does this volume provide a compact compendium of region-specific connections, but it also provides something entirely unique, the ability to determine the disconnections that a focal white matter lesion would cause.

But why should we bother about connections in the monkey when the goal is to understand the functions of the human brain? The reasons are simple and sobering. There is currently no method that can come close to tracing connections in the human brain with the sort of precision described in this book. To be sure, developments based on diffusion tensor imaging and the computational analysis of effective connectivity do appear promising, but they have a long way to go before they can tell us the cells of origin, white matter trajectories, and termination fields of pathways emanating from cortical areas no larger than a few millimeters in size. I have little doubt that breakthroughs will occur and that we will eventually be able to understand human brain connectivity. Until then, however, this book will remain the standard reference source for the connection pathways of the primate cerebral cortex.

M-Marsel Mesulam, MD
Chicago, Illinois

Preface

Fiber Pathways of the Brain was conceived in an attempt to address a fundamental gap in our knowledge of the organization of the brain. The investigation by Joseph Jules Dejerine (1849–1917) in 1895 of the fiber systems of the human brain remains the only comprehensive account of the anatomy of the cerebral white matter pathways. In the material available to him and other early investigators, however, it was not possible to ascertain the origins and terminations of the fiber pathways and thus to determine what information these systems convey. This remains a central problem. Whereas there is a considerable literature on the connections of the cerebral cortical and subcortical regions in the nonhuman primate, there is presently no comprehensive account of the fiber bundles that link them.

In our studies of the cortical and subcortical connections of cerebral association areas, we have been impressed by the ability of the radioisotope technique to delineate not only the projections arising from the cortical areas but also the fiber systems that convey these connections. In this monograph we rely on the technique of radioisotope tract tracing to provide an analysis of the fiber systems in the nonhuman primate brain. Throughout this project, the descriptions and depictions by the early anatomists of the fiber pathways in the human brain have served as a beacon, an invitation to match and update their work with contemporary techniques in the experimental animal.

We were also motivated throughout this endeavor by the clinical mandate set forth by Norman Geschwind, who emphasized the phenomenon of cerebral disconnection as a critical element in the disruption of higher-order behavior. Geschwind's conception presaged the notion that brain function is the result of effective communication between structures geographically distributed around the nervous system. This idea places the means of communication, namely the white matter fiber systems, squarely at the core of the distributed neural circuitry hypothesis. In so doing, it underscores the relevance of this anatomical investigation as much for clinical purposes as for the broader need to explore the neural substrates of behavior.

This work is presented in monograph form in an attempt to provide a single coherent reference that will permit the comparison, analysis, and discussion of brain fiber systems. An overarching view of the cortical and subcortical pathways could not adequately be achieved in a series of papers devoted to each fiber bundle. We wanted to explore the historical evolution of ideas about the white matter, analyze the fibers that subserve each brain region, and develop hypotheses regarding their possible functional roles. The knowledge gained in the past few decades concerning the anatomy, connections, and functional attributes of the cerebral cortex, and the association cortices in particular, has made it possible to speculate on the functions of the white matter bundles by recognizing the cortical and subcortical areas that they link.

Since we began this project in 1994, studies of cerebral white matter have risen to the forefront of contemporary clinical and basic neuroscience research. The development of diffusion tensor and diffusion spectrum magnetic resonance imaging and white matter tractography permits the visualization of the fiber pathways with a precision that had previously been unattainable *in vivo*. These emerging techniques rely on knowledge of anatomical pathways that was derived from methodologies constrained by the limitations inherent in the earlier experimental approaches. In addition, the evolution of the notion that cognitive and behavioral changes, including dementia, may result directly from damage to cerebral white matter has added a clinical urgency to the need to better understand the cerebral white matter and the fiber tracts it contains. The new information stemming from the analysis of the constituents and topography of white matter tracts in the monkey therefore has significance for understanding both brain anatomy and organization, and the clinical disorders that affect white matter. We hope that this work will facilitate a more sophisticated and detailed understanding of the fiber systems, prove useful in future investigations, and contribute to achieving the goal of improving diagnosis and management of brain-based disorders in humans.

The process of learning about the fiber systems of the brain has at times been arduous, but it has been deeply satisfying for us to work in a collaborative manner, rendering the task not only manageable but also thoroughly enjoyable. The many years that we have worked together on this and other projects have been mutually rewarding and beneficial. Our journey through this project has been like the course of the fiber systems through the hemispheres: it had an origin and an intended termination, but the course taken held a wonder of its own. We are pleased now to be able to share the results of these investigations with the larger community.

Acknowledgments

This project could not have been completed without the superb assistance of a number of individuals and institutions whom we acknowledge here with deep gratitude. Together, J. D. S. and D. N. P. generated hand-drawn images of the fiber systems on template images of the brain. J. D. S. then transformed these into the line art seen throughout the monograph. These line drawings, however, had to be scanned and manipulated using contemporary computer graphics. Similarly, the photomicrographs were often photomontages, even using a 0.5× lens and stage, and this too required close attention to detail. This exhaustive work was performed by Charlene DeMong, and we are grateful to Charlene for her commitment to this project. Amy Hurwitz and Lisa Patterson provided much-needed assistance during the earliest phases of the project. The valuable efforts of Jason MacMore have also been indispensable throughout the completion of the final stages of this work.

Historical accounts from medical antiquity until the latter part of the 17th century were derived from secondary sources, including Todd (1845), Neuberger edited by Clarke (1897/1981), Polyak (1957), Garrison/McHenry (1969), Meyer (1971), and Clarke and O'Malley (1996). Large sections of the text dealing with the era of gross dissection forward, commencing with Vicq d'Azyr, consist of primary historical research, except where specifically quoted and referenced from other sources. We gratefully acknowledge the assistance of librarians in the Countway Library of Medicine housing the Boston Medical Library, the library of Harvard Medical School, and the Rare Books and Special Collections Department.

The translation of papers by earlier investigators made it possible to understand the contributions of pioneers in this field and helped resolve the confusion that has abounded in the discussion of many of the white matter pathways. We are indebted to Jan Drappatz, who during his neurology residency at Massachusetts General Hospital engaged enthusiastically in this project, translating with us the German texts of Reil, Burdach, Onufrowicz, Kaufmann, Muratoff, Obersteiner and Redlich, Sachs, and others. It was a pleasure working with Jan to interpret the sometimes-arcane linguistic style of the early writers in order to develop a readable text true to the original intention of the authors. Similarly, Jean-Jacques Soghomonian, Associate Professor of Anatomy and Neurobiology at Boston University School of Medicine (BUSM), worked with us to translate relevant sections of the work by Dejerine that proved invaluable in our analysis. We were mindful of Macdonald Critchley's cautionary note (1979, p. 35) about "the exceeding difficulty, if not impossibility, of rendering a faithful translation from one language to another . . . (and that) every language has its little stock of subtle words which baffle an interpreter." The translations of Drs. Drappatz and Soghomonian made it possible for us to listen to the scholarly deliberations that characterized the early liter-

ature. Many of the seminal observations from these pioneers are presented in unabridged form in footnotes to the text, as they are either not available at all or can be found only in précis form or as limited direct quotes in a small number of other sources devoted to the history of neuroscience. To our knowledge no comprehensive compilation of these historical accounts of the anatomy of the white matter systems in the words of the original investigators is currently available in the English language.

J. D. S. takes this opportunity to gratefully acknowledge the deep clinical grounding imparted at the University of Cape Town Medical School by my teachers, including Francis Ames, Solly Benatar, Ralph Kirsch, Stuart Saunders, and J. C. de Villiers, and the mentoring and inspiration of my teachers in the Neurological Unit of Boston City Hospital, including Thomas D. Sabin, Simeon Locke, H. Royden Jones, Jr., and Thomas Kemper. Alan Peters gave me the opportunity to train in his department of anatomy and neurobiology at BUSM, and this made it possible to embark on the journey with my mentor, friend, and co-author D. N. P. Joseph P. Martin and Allan Ropper invited me to join the Massachusetts General Hospital (MGH) and Harvard Medical School, which have been my intellectual home and source of inspiration since 1989. I am grateful to Anne B. Young, chair of the Department of Neurology at the MGH, for fostering and encouraging an atmosphere of independent scholarship. This has allowed me to explore these questions of neuroanatomy while pursuing active clinical and teaching interests. The Department of Anatomy and Neurobiology at BUSM has continued to be a supportive and scientific home for D. N. P. and a gracious host to me. I would also like to express my gratitude to my other teachers and colleagues at the Boston City Hospital (Milton Jay, Harold Schiff, Fereydoun Sharokhi, and Nagagopal Venna); Lahey Clinic Medical Center (Paul T. Gross, José Gutrecht, Steven Kott, Simmons Lessell, Irma Lessell, and Prather Palmer); New England Deaconess Medical Center (Roy Freeman and Daniel Tarsy); and the BUSM Department of Anatomy and Neurobiology (Mark Moss and Douglas Rosene). I have also learned from my clinical interactions with many colleagues at the Massachusetts General Hospital, including Raymond D. Adams, Marilyn Albert, Bob Brown, Ferdy Buonanno, David Caplan, Verne Caviness, Bill Falk, C. Miller Fisher, Tessa Hedley-Whyte, Phil Kistler, Walter Koroshetz, Neil Kowall, Nikos Makris, Bruce Price, the late E.P. Richardson, Martin Samuels, Janet Sherman, and Mark Tramo.

D. N. P. would like to express deep gratitude to the late Walle J. Nauta, who inspired me to enter the field of neuroanatomy and provided continued encouragement and friendship for many years. I am indebted to the late Hans Kuypers, under whom I received training in neuroanatomy in the mid-1960s. Dr. Kuypers was a perfect teacher to many of us. I have tried to follow his thinking in my approach to neurological investigation. I am grateful also to the late Dr. Friedrich Sanides for introducing me to the intricacies of cortical architecture. My research was greatly supported by the late Norman Geschwind, who was always ready to accommodate my needs and who provided much-needed mentoring during my early career in Boston. I am grateful to Alan Peters and Mark Moss for providing me with generous support and inspiration. Most of my research studies were conducted in the department of anatomy and neurobiology at BUSM. In the 1970s, while working as a full-time internist at the Bedford Veterans Administration Hospital, I was able to continue my research and teaching through the kind generosity of the department of medicine. Many of our concepts regarding corti-

cal connections and pathways have evolved over the course of several years. I would therefore like to express my sincere thanks to all our colleagues with whom I have had the opportunity to work: Helen Barbas, Clifford Barnes, Gene Blatt, Nelson Butters, Doug Chavis, Ben Cipolloni, Patricia Dye, Barbara Fullerton, Albert Galaburda, Mark Hallett, David Heilbronn, Ken Heilman, Eduardo Karol, Pat Lele, Nikos Makris, Marsel Mesulam, Robert Morecraft, Elliot Mufson, Sanat Mukherjee, Michael Petrides, Kathy Rockland, Doug Rosene, Monalisa Schultz, Benjamin Seltzer, Don Siwek, Gary Van Hoesen, Luigi Vignolo, Brent Vogt, and Edward Yeterian.

The case material that we have analyzed here has been generated over a number of years. Many individuals have been involved in preparing these materials with great dedication and enthusiasm. We therefore would like to acknowledge their valuable technical assistance: Deborah Burke, Brian Butler, Mary Chiavarras, Andrew Doolittle, Valerie Killgreen, John C. Klick, Valerie Knowlton, Ann Mahoney, David Moser, Tim Murphy, and Michael Schorr. Without the efforts of these individuals, many of whom have gone on to their own careers in neuroscience, this work would not have been possible. The meticulous artist's renditions of the fiber tracts depicted in chapters 13 through 19 were prepared by Marcia Williams.

For both of us, our colleagues, students, residents, and fellows teach us constantly and remind us of the wonder and humility inherent in this field. Our patients, who exemplify courage and the human spirit in the face of adversity, are our driving force to increase knowledge of the brain so that we may more effectively answer their call. It would have been inconceivable to have completed this project without the support of our families, and we would like particularly to thank our wives Jinny (J. D. S.) and Bonnie (D. N. P.) for their nurturing and patience. The untiring assistance of Marygrace Neal over the years has been of inestimable value in facilitating the completion of this project.

Oxford University Press, personified for us first by Jeffrey House and then by Fiona Stevens, has been patient beyond measure. Expecting a completed work in 1998, Fiona stayed with us as the project stretched from 4 years to 12, and the encouragement, support, and editorial counsel offered by her and other members of the Oxford University Press staff have been valued and crucial.

Financial support that has helped this work come to fruition was provided in part by the National Institutes of Health, the Veterans Administration, and the Boston University School of Medicine Alzheimer's Disease Center (J. D. S. and D. N. P.) and by the McDonnell-Pew Program in Cognitive Neuroscience and the Birmingham Foundation (J. D. S.).

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Contents

Relevance of the Cerebral White Matter Fiber Pathways

PART I

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Introduction

1

The cerebral cortex has long been recognized as the essential neural correlate of human experience. Its approximately 20 billion neurons (Pakkenberg and Gundersen, 1997) are arranged in multiple distinct areas that have been characterized extensively with respect to their morphological and cellular specialization. The architecture of each of these cortical areas subserves functionally distinct domains of sensorimotor perception and action, emotional experience, and complex reasoning. The cerebral cortex does not support nervous system function in isolation, however. It has become apparent that all behaviors are subserved by distributed neural systems that comprise anatomic regions, or nodes, each displaying unique architectural properties, distributed geographically throughout cortical and subcortical areas of the nervous system, and linked anatomically and functionally in a precise and unique manner (Geschwind 1965a,b; Goldman-Rakic, 1988; Goldman-Rakic and Selemon, 1990; Jones and Powell, 1970; Luria, 1966; Mesulam, 1981, 1990, 1998, 2000; Nauta, 1964; Pandya and Kuypers, 1969; Pandya and Yeterian, 1985; Ungerleider and Mishkin, 1982).

In contrast to the detailed understanding of the cerebral cortex, there is a dearth of information on the fiber pathways that link the different components of the distributed neural system. Descriptive terms such as centrum semiovale and corona radiata were initially applied to the cerebral white matter because of its seemingly amorphous appearance on naked eye inspection. Investigators in the 1800s used gross dissection and, later, myelin-stained material to evaluate the fiber bundles, and degeneration techniques were used in clinical cases to examine connectivity among cortical areas. These studies identified and named some of the major association tracts, including the cingulum bundle and uncinate fasciculus. Descriptions of other systems, including the arcuate fasciculus/superior longitudinal fasciculus and the inferior longitudinal fasciculus, have remained in use despite unresolved controversies in the literature. Some information concerning the fibers leading from the cerebral cortex to subcortical structures (the projection systems) was also available from earlier studies. It was not known, however, how the subcortical fibers differentiate from the association systems as they emanate from the cerebral cortex, and details regarding the trajectories of the fibers within the internal capsule and sagittal stratum remained to be established. The limitations of the techniques used by the early investigators also made it impossible to determine the precise organization of these pathways, or their origins and terminations.

There is a considerable literature on the biology and pathology of myelinated axons, but little is known about the way these axons form the connecting links of the distributed neural systems or the kind of information that these fiber bundles convey. Understanding the white matter tracts is a pivotal step in the further elaboration of knowledge of brain structure and function, particularly with regard to the anatomic substrates of

higher-order behavior. Fundamental questions concerning their organization remain unresolved, however. Which fiber pathways do the different cortical areas use to convey information to the other cortical and subcortical nodes? Are fiber bundles specific to certain cortical areas? Is there intrabundle topography of axons arising from adjacent cortical areas?

A deeper understanding of the white matter pathways is relevant also for clinical purposes. A number of diseases are characterized predominantly by affliction of the white matter, such as multiple sclerosis, and in other conditions white matter abnormalities exist but have been underappreciated, such as in Alzheimer's disease and normal aging. Selected disconnection syndromes have received prominent attention through the clinical efforts of such investigators as Dejerine, Geschwind, and Gazzaniga, but the cognitive failure that accompanies white matter destruction following ischemia, radiation damage, and human immunodeficiency virus infection, among many others, underscores the recognition that these classic syndromes represent examples of a substantially larger clinical problem. Information about damaged pathways in clinical studies would be enhanced by knowledge of the entire trajectory of the affected pathways derived from experimental investigations in the non-human primate.

The recent development of diffusion tensor magnetic resonance imaging (DTI) has made it possible to identify *in vivo* some details of organization within the major white matter pathways (Basser et al., 1994; LeBihan et al., 2001; Pierpaoli et al., 1996), both in normal brains and in clinical situations in which the pathways are damaged (Cellerini et al., 1997; Jones et al., 1999; Makris et al., 1997). This promising technology was initially limited by the visualization only of the major tributaries of the pathways and the inability to determine their origins or terminations or the nature of the information they convey. The imaging techniques and mathematical models have become increasingly sophisticated with the development of MR tractography (e.g., Bammer et al., 2003; Catani et al., 2002) and diffusion spectrum imaging (Lin et al., 2003), and it is likely that the field of *in vivo* white matter tractography in humans will acquire a greater degree of technical precision, useful for understanding normal brain anatomy and relevant for clinical studies as well.

There are some important constraints upon tractography, however. The calculated trajectory of the fiber tract may fail to follow the true fiber tract trajectory because of the ability of trajectories to jump to adjacent structures via noisy or partially volumed voxels (Basser et al., 2000), and because tractography is particularly prone to noise due to cumulative error along the length of the trajectory path (Tench et al., 2002). Tractography therefore has the potential to introduce fiber continuity where there is none, producing anatomically plausible but erroneous trajectories and false connections (Basser et al., 2000), and the reliability of this technique is receiving active scrutiny (e.g., Ciccarelli et al., 2003). These new imaging techniques also rely on *a priori* hypotheses derived from earlier anatomical conclusions regarding the course of the fiber bundles (Basser et al., 2000; Catani et al., 2003), particularly for the association fiber pathways. Misinterpretations of postmortem histologic and gross dissection preparations, as well as the terminological confusion that developed as a consequence of early uncertainty, have become traditional teaching in anatomical texts, and these erroneous conclusions are now being replicated in the DTI literature. These include descriptions of probably nonexistent bundles such as an "inferior fronto-occipital fasciculus," the

conflation of the actual fronto-occipital fasciculus with the subcallosal fasciculus of Muratoff, and the bundling together of all three components of the superior longitudinal fasciculus and their merger with the anatomically separate and functionally distinct arcuate fasciculus, among others.

The central problem is that there has been no "gold standard" for *in vivo* fiber tractography (Basser et al., 2000; Crick and Jones, 1993), and postmortem dissection, sometimes regarded as the "definitive standard" (e.g., Catani et al., 2003), is anything but definitive, as a century of anatomical and terminological confusion will attest. It should be possible to identify fibers more precisely using MRI once it is known from tract-tracing studies in the experimental animal where they are situated, and what brain regions they link. Whereas the monkey and human brains display considerable differences in detail, the overall structural similarities down to the level of architectonic differentiation are well established (Brodmann, 1909; Macchi and Jones, 1997; Pandya and Barnes, 1987; Petrides and Pandya, 1999; Rajkowska and Goldman-Rakic, 1995a,b). Extrapolation of data concerning white matter pathways from monkey to human has a number of limitations but may be permissible with the understanding that areas in the human brain that are greatly expanded are likely to have more elaborate and complex connections and functions. The analysis of the origins and terminations of the white matter fibers in the experimental animal may thus be useful in the development of a more comprehensive understanding of the data obtained from these imaging studies in humans.

There is a considerable body of literature dealing with corticocortical and corticosubcortical connections in the nonhuman primate, and there are selected studies of white matter pathways using contemporary anatomical techniques. There has been no comprehensive attempt, however, to delineate all the white matter pathways arising from the different areas of the cerebral cortex, together with the termination patterns of projections conveyed by these pathways. In our earlier analyses of corticocortical and corticosubcortical connections in the rhesus monkey we were impressed by the ability of the autoradiographic tract-tracing technique that uses isotope-labeled amino acids to demonstrate the high degree of organization of axons in the white matter. This technique reveals the origins, terminations, and trajectories of the association fibers, as well as of the callosal, striatal, thalamic, pontine, and other subcortical fiber systems. We therefore embarked upon this study to outline the different white matter pathways of the cerebral hemispheres using the autoradiographic technique in the animal model, in order to understand the organization of the fibers that emanate from the cerebral cortex, the "parent" node in the distributed system. Along with the trajectories of the pathways, we documented their termination patterns, enabling the simultaneous determination of the cortical and subcortical relations of each cerebral cortical architectonic region and the fiber bundles that link them. We hope that this anatomical investigation of the fiber pathways in the nonhuman primate will provide the exposition necessary for the more accurate analysis and interpretation of major white matter tracts in the human brain and the further delineation of the distributed systems subserving brain function.

The monograph begins with an historical account of the evolution of ideas about the structure and organization of white matter. This synthesis provides a framework for understanding early notions about the organization of cerebral white matter, it underscores the realization by early neuroscientists of the importance of fiber pathways for a

variety of neurological disorders, and it describes the limitations encountered in these earlier studies. As a result of our analysis, we have presented revised notions of some of the fiber bundles described and discussed in the literature over almost two centuries. In this historical review, we pay homage to the investigations of the pioneers in this field. The technical details of our experimental approach are presented in the methods section, including a description of the isotope technique, our novel approach of identifying the fibers in Nissl-stained sections, and the use of computer technology to permit *de novo* charting of fiber systems from all regions of the cerebral cortex onto a single template brain. This is followed by photomicrographs of the representative sections from the template brain used in this work, with architectonic designations identified. The fiber bundles emanating from all cortical areas share certain features, and these are outlined in the section on organizing principles. A case-by-case description of the results follows in the section on organization of cerebral white matter by region of origin. The chapters in this section present detailed descriptions, illustrations, summary diagrams, and synthesis of the cortical and subcortical fiber pathways emerging from the parietal, superior temporal, inferior temporal, occipital, precentral motor, prefrontal, and cingulate areas. In the next section anatomical details of individual fiber bundles are presented, followed by discussion of their putative functional attributes. The composite summary of cerebral white matter fiber pathways is a series of composite summary diagrams in the coronal plane that depicts the location and constituents of the various white matter tracts. Neurobehavioral manifestations in patients with white matter lesions are addressed in the section on clinical relevance to emphasize the importance of these pathways in the human brain. In the conclusion, we draw upon the anatomy of the cerebral hemisphere fiber pathways to develop hypotheses about their putative functional properties and their roles in a more general view of brain organization. The final chapter, Notes, contains comments and discussion relevant to the text and includes translations of the work of some of the early investigators.

White Matter Pathways in Early Neuroscience

2

Our study of the fiber tracts of the rhesus monkey brain using the anterograde autoradiographic tract-tracing technique follows a long and honored tradition of using contemporary methods to investigate the cerebral white matter. We begin with a comprehensive historical review of the evolution of ideas and observations about the structure and function of the white matter to the present. We undertake this historical review in the light of historian Max Neuburger's (1868–1955) statement that understanding the achievements of modern science "is inconceivable without a knowledge of the history of its development and growth, its origins and sources" (Neuburger/Clarke, 1897/1981, p. 4). In Neuberger's words, "truth is no longer sought in the yellowing pages of old manuscripts, [but] ignorance of the past necessarily leads to an overestimation of the heights achieved by present knowledge" (ibid., pp. 2–4). Like the Italian anatomist Caecilius Folius (1615–1650), we "know quite well that knowledge is acquired by adding one piece of it to another, and that all of us, like children sitting on the shoulders of giants, can see far more than our predecessors could" (ibid., p. 285).

Medical Antiquity

Neurological science traces its recorded origins to the Edwin Smith papyrus of the 17th century BC, a hieroglyphic copy of a manuscript from the Egyptian Pyramid Age composed around 3000 to 2500 BC. In this document, the "brain" is named, its most overt features, including the convolutions and the presence of cerebrospinal fluid, are recognized, and individuals with neurological disorders are described. Conceptual approaches to brain organization and function during classical Greek antiquity were as systematic and detailed as the techniques and known facts would allow, and they were heavily influenced by spiritual and theological notions and by the attempt to identify a locus in the body for the *hegemonikon*, or the ruling soul. The art and science of medicine flourished in antiquity also in the Indian and Chinese subcontinents, similarly influenced by prevailing philosophical and spiritual notions. Detailed accounts of the Ayurvedic approach of Indian medicine (see, for example, Bagchi, 1979; Narayana, 1995) and traditional Chinese notions (as embodied in "The Yellow Emperor's Classic of Internal Medicine," Yellow Emperor, Huang Dynasty [2697–2595 BC], and Shen Nong's "Canon of Herbs" [2700 BC]) are beyond the scope of the present monograph; suffice it to say that the evolution of medical knowledge was not confined to Western medicine, and there appears to have been mutual exchange of ideas in the medical sciences between these ancient societies.

Pythagoras (c. 572–c. 490 BC) is credited with introducing the notion that the brain is concerned with reasoning. The precedent for the influence of teachers on their stu-

dents and the course of subsequent scientific inquiry was established early, in that Pythagoras' student, the physician Alcmaeon (Alkmaion) of Athens, performed human dissections and recognized the role of the brain in sensation, movement, and thinking. Brain dissection was first undertaken systematically by Anaxagoras of Klazomenai (c. 500 BC), who considered the brain to be the organ of the mind, the origin of the nerves, and the seat of the soul. In Hellenized southern Italy, Philolaos of Croton or Tarent (c. 400 BC) also regarded the brain as the seat of intelligence, but he introduced the debate, which would persist for 2,000 years, that the heart, not the brain, was the seat of *hegemonikon*, a fallacy that would receive later support from Aristotle and the ideologists of early Christianity. The Hippocratic school (460 BC–370 BC) recognized the brain as the substrate of nervous action, ascribing to it intelligence, dreams, and thoughts. They introduced the notion of the brain as a gland, secreting phlegm or *pituita,* and acting as a cooling device, a notion that would also persist for two millennia. Vigorous scientific inquiry occurred during the Alexandrine period, when Greek culture was implanted in Egypt (323 BC–212 BC). This included human dissection by Herophilus of Chalcedon (335 BC–280 BC), who described the cerebral ventricles and noted the convoluted character of the cerebrum, and Erasistratus of Chios (c. 310 BC–250 BC), who concluded that cerebral convolutions are related to intelligence because they are more numerous in man than in animals. Other conceptual advances were introduced by Asclepiades of Bithynia (c. 124 BC), who described mania, delirium, and absence of mind (psychosis), and by Rufus of Ephesus (c. AD 100), whose dissections in apes led him to concur with the observations of Erasistratus that nerves of motion are distinguished from those of sensation, and to conclude that nerves originate from the brain.

The Galenic Period

The lasting work of early Greek antiquity that influenced medicine and science for fully 1,500 years was that of Galen of Pergamon/Pergamos/Pergamum (AD 129/130–200/201). In the era in which human dissection was proscribed, he performed vivisections on a variety of animals and examined the bones of humans that were available to him. He named the dura mater, pia mater, corpus callosum, the four ventricles, fornix, corpora quadrigemina, pineal and pituitary glands, and infundibulum. He described the intraventricular foramen (later named for Alexander Monro, Secundus [1733–1817]) and the cerebral aqueduct (later identified by Sylvius, see below) and the cervical, brachial, and lumbosacral plexuses, and he followed nerves from their origins to terminations in muscles and viscera. Galen discarded the Hippocratic notion that the brain is a gland, argued that it was the seat of intelligence, emotion, and sensation, and described it as a structure analogous to the bone marrow and continuous with the spinal cord. He initiated the idea of brain localization by declaring the frontal lobes to be the seat of the soul (*pneuma*) and the source of the "animal spirit." He introduced the concept of anatomical localization in clinical neurological science, holding that the "method of looking for the place chiefly affected is of great importance for all the organs, but particularly in disease of the brain" (Garrison/McHenry, 1969, p. 121).[1] At the center of Galen's physiological conceptions of brain function was the notion that natural spirit, a mysterious substance indispensable for life and originating in the liver,

transforms into vital spirit conveyed by the heart to the brain, and this in turn transforms into the more refined animal spirit. A necessary ingredient for this brain process was air inspired into the cerebral ventricles. These fanciful notions seem less ludicrous when terms such as oxyhemoglobin, cerebrovascular system, and propagation of electrical impulses in neural transmission replace the more vaguely conceived "spirituous substances." The comment of Robert Bentley Todd (1809–1860) in his discussion of the work of Thomas Willis is perhaps appropriate for Galen as well: "We may find in the writings of this great man the germs of many a theory which, in our times, has been brought forward with a more plausible aspect, disencumbered of the quaint phraseology and superabundant metaphor so common in his day" (Todd, 1845, p. 135).

The Middle Ages

Galen's voluminous contributions were summarized and disseminated in the *Continens Liber* of Rhazes (864–930 AD), which was translated into Latin in 1279, the *Canon* of Avicenna (980–1037) published in 1500, and the 200-volume work of the Benedictine monk Constantine (12th century). By the Middle Ages, mental faculties were thought to be localized either in the brain substance, as Galen had posited, or in the cerebral ventricles, as suggested by Herophilus of Chalcedon and medieval writers such as Nemesius, Bishop of Emesa (c. AD 390, published manuscript 1512) and St. Augustine (4th century). Little of substance was added to Galen's notions throughout this entire period, however, "with the exception of some therapeutic wrinkles" (Garrison/McHenry, 1966, p. 24).

Albert von Bollstädt (Albertus Magnus, 1193–1280) first depicted the cerebral ventricles in *Philosophia Naturalis* (published in 1496, according to Garrison/McHenry). He localized common sense in the frontal lobes, imagination in the midbrain, and memory in the cerebellum or in the four ventricles. Mondino dei Luzzi (Mundinus, 1275–1326) wrote his *Anothomia* in 1316 (first printed in 1478), which passed through numerous editions over the next 200 years. He summarized the anatomy known to Aristotle, Galen, and Avicenna, and he reintroduced human dissection, which had not been practiced since the time of the early Greeks. He ascribed a variety of qualities and attributes to the different components of the cerebral ventricular system. Fantasy and retention were in the anterior compartment of the lateral ventricle, special senses in the middle compartment, imagination and the ability to combine separate things in the posterior compartment. The third ventricle was endowed with the power of cognition and prognostication, and the fourth ventricle was concerned with the reception of impressions and memory (Clarke and O'Malley, 1996, p. 22). The drawings of Gregor Reisch (c. 1467–1525) in *Margarita Philosophica* (1503) further perpetuated the notion that complex functions reside in the ventricles, with functional specialization according to the different parts of the ventricular system. Diagrams of the brain, cranial nerves, optic chiasm, peripheral nerves, and muscles that began to approximate anatomic precision were those of Leonardo da Vinci (1452–1519), who also made the first successful wax casts of the cerebral ventricles. His anatomical drawings were not made available, however, until 1784. New realism was added to the published accounts of the nervous system in the

depictions of the brain by Lorenz Fries (Laurentius Phryesen, c. 1480–1532) in 1519, Jacopo Berengario da Carpi (Berengarius, c. 1470–1550) in 1523, Johann Eichman (Dryander) (d. 1560) in *Anatomia Capitis Humani* (the first anatomical work devoted to the head and brain) in 1536, and Charles Estienne (Stephanus, 1503–1564) in 1546. The major advance in neurological anatomy, however, awaited the work of Vesalius.

The Era of Vesalius

Whereas Galen had described the corpus callosum and the fornix in animals, the white matter and the gray matter of the brain were not differentiated from each other in antiquity, and the early Renaissance anatomists paid more attention to the ventricular system than to the brain parenchyma because the prevalent doctrine was that mental function resided in the ventricles.

With the publication in 1543 of Andreas Vesalius' (1514–1564) *De Humani Corporis Fabrica* (On the Structure of the Human Body), a new era of anatomical and scientific investigation and thought was introduced. "(T)he first period of Postclassical European anatomy, characterized by a helpless dependence upon the written word of Greek and Arab authorities, often erroneous, and based upon animal rather than human sources, was at an end" (Polyak, 1957, p. 92). In the seventh book of *Fabrica*, illustrated by the artist Jan Stephan Kalkar, a student of Titian, Vesalius was the first to distinguish the softer and yellowish cerebrum from the harder and whiter deeper substance below it that was continuous with the corpus callosum. He provided a comprehensive account of the corpus callosum, the first description of it in man, and he recognized that it linked the two halves of the brain. He also depicted the internal capsule, caudate nucleus, putamen, and globus pallidus, as well as the midbrain, pulvinar, corpora quadrigemina, pineal gland, pituitary gland, and superior and middle cerebellar peduncles.

Volcher Coiter (1534–1576) distinguished between the gray and white matter of the spinal cord in 1572, but this was not illustrated until 1666 by Gerard Blasius (1625–1692) in the first separate treatise of the spinal cord, *Anatome Medullae Spinalis et Nervorum*. Gross dissection of the white matter of the brain was performed in 1586 by Arcangelo Piccolhomini (1526–1605), who introduced the terms "cerebrum" for the cerebral cortex and "medulla" for the white matter. In 1573, Co(n)stanzo Varolio (or Variolus, 1543–1575), who examined the brain from its base up for the first time (as opposed to from the top down), described the lobes of the brain related to the different cranial fossae and described in detail the hippocampus, optic nerve, cerebral peduncle, and the "pons Varolii" that bears his name.

The Scientific Method from Willis to Vicq D'Azyr

When Thomas Willis (1621–1675) published *Cerebri Anatome* in 1664, he introduced a new level of anatomic accuracy to the understanding of the inner structures of the brain. His monograph provided the first reclassification of cranial nerves since Galen and contributed the word "neurology" (the doctrine of the nerves) to the lexicon. As stated by Polyak (1957, p. 105), Willis' functional interpretations were still based on

Galenic ideas of the production and distribution of "animal spirit." Unlike Galen, however, Willis thought these spirits were produced not in the white matter, but in the cerebral cortex. He endorsed the notion proposed by Erasistratus (3rd century BC) that convolutional complexity in humans is reflected in intelligence, and the cortex not only stored memories but was also the originator of memories and the organ of thought. Willis observed the corona radiata and the capsular striations through the corpus striatum. His notion of the "medulla oblongata" was that it comprised all the deep white matter, the ventricles, basal ganglia, thalamus, and brainstem, and he viewed it as a bifurcate structure resembling the letter Y with a limb in each cerebral hemisphere and the stem corresponding to the brainstem. He thought of it as a "royal highway" into which animal spirits constantly flow from their twin sources, the cerebrum and cerebellum, and are then carried into all parts of the nervous system. Spirits directed outward served a locomotor function, whereas spirits were directed inward in response to sensation.[2]

In 1664 Marcello Malpighi (1628–1694) used a primitive microscope to provide the first proof that the white matter was composed of "fibers." After boiling the brain in water, he traced the white matter fibers of the brain and cerebellum and observed that they take their origin from the top of the spinal marrow contained within the cranium ("medulla oblongata"). These fibers "ramify from four reflected crura of this medulla in all directions, until they end by their branched extremities in the cortex," where they were embedded like the roots of a plant (translated and quoted on p. 136 of Todd, 1845, derived from Malpighi, *Exercitatio Epistolica de Cerebro*, 1664. These ideas are further expanded in Malpighi, 1669).

In an essay in 1665 (published in 1671), Nicolaus Steno (Niels Stensen, 1638–1686) suggested that one way to study the white matter of the brain was to follow "the nerve threads through the substance of the brain to find out where they go and where they end" (translated in Clarke and O'Malley, 1996, p. 584). He concluded: "To say that the white matter is but a uniform substance like wax in which there is no hidden contrivance, would be too low an opinion of nature's finest masterpiece. We are assured that wherever in the body there are fibers, they everywhere adopt a certain arrangement among themselves, created more or less according to the functions for which they are intended. If the substance is everywhere of fibers, as, in fact, it appears to be in several places, you must admit that these fibers have been arranged with great skill, since all the diversity of our sensation and our movements depends upon this. We admire the skillful construction of the fibers in each muscle; how much more then ought we to admire it in the brain, where each of these fibers, confined in a small space, functions without confusion and without disorder."

Using a technique of scraping the white matter to display its fiber bundles, in 1672 Willis demonstrated an intricate arrangement of the medullary tracts, pathways, or cords within the substance of what was then termed the medulla oblongata. He was "astonished at the innumerable arrangements of nerve fibers distributed in wonderful order into the different parts of the entire body." These fibers conveyed animal spirits, "confined by certain bounds and limits, so to speak, within the compressed space of a single chamber, [that] attend to the infinite varieties of actions and passions" (quoted in Clarke and O'Malley, 1996, p. 584).

The scraping method of dissection that was suggested by Steno and performed by Willis to carry out detailed studies of the cerebral white matter was used by Raymond

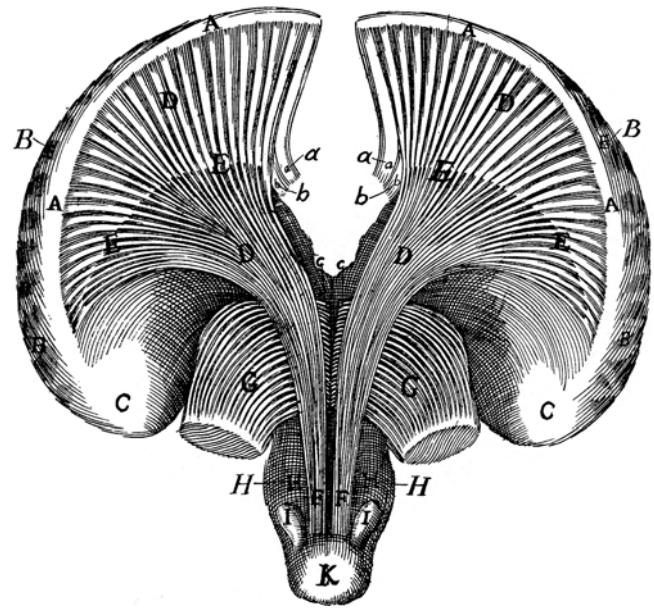

Figure 2-1
The illustration by Raymond Vieussens, figure 16 in *Neurographia* (1684), depicting "the base of the cerebrum, after the removal of the cerebellum and all the vessels, freed from nearly all its outer cineritious substance and shaved down" to show the fibers of the white matter.

de Vieussens (c. 1635–1715), who amended Malpighi's approach of boiling the brain in water. In his *Neurographia universalis* (1684), Vieussens readily distinguished the medullary white substance from the gray matter and showed that it "is composed of innumerable fibrils connected together and arranged into various fasciculi, which become very obvious when it is boiled in oil" (Todd, 1845, p. 136) (figure 2-1). Vieussens first observed the oval shape of the medullary white matter, introduced the term "centrum ovale," and demonstrated its continuity with the internal capsule, cerebral peduncle, and pyramidal fasciculi of the pons and medulla oblongata. He viewed the medullary fibers within the context of Galenic ideology. They "give the appearance of a spongy body which the animal spirit may permeate in many different and rather inexplicable ways, so that within it the spirit undergoes many different and inexplicable motions; because of their different arrangements different thoughts are aroused in the mind" (Clarke and O'Malley, 1996, p. 586).

The crossing of the pyramidal fibers below the pons was described by Domenico Mistichelli (1675–1715) in his 1709 treatise on apoplexy. In 1710 François Pourfoir de Petit (1664–1741) observed the same phenomenon in his *Lettres d'un medicine*. Based on clinical and experimental studies in dogs, he confirmed the observations of Hippocrates and Arateaeus that brain lesions are on the side opposite to the paralysis of the limbs. Pourfoir de Petit also noted that paralysis was complete and lasting only when the corpus striatum was damaged, whereas injury of the cerebral cortex alone produced only weakness. This led to the conclusion that animal spirits issued from the cortex, streamed through the fibers of the white matter, and crossed the corpora striata, made up of medullary (white matter) fibers, to form places where they could collect together.

Great importance was placed on the corpus callosum by Giovanni Maria Lancisi (1654–1720). In 1718 he stated that "it is quite clear that the part formed by the weaving together of innumerable nerves is both unique and situated in the middle [of the brain]; and so it can be said it is like a common marketplace of the senses, in which the

external impressions of the nerves meet. But we must not think of it as merely a storehouse for receiving the movement of structures: we must locate in it the seat of the soul, which imagines, deliberates, and judges" (quoted in Neuburger/Clarke, 1897/1981, p. 50, footnote 12).[3]

François Gigot de La Peyronie (1678–1747), too, concluded that the corpus callosum must be of the greatest importance for the support of life. Further, by relating cause and effect, he concluded that mental changes were observed only when the corpus callosum was diseased, and thus it was the seat of the intellectual faculties.

The work of Albrecht von Haller (1708–1777) is credited by Neuburger as having paved the way for future brain and spinal cord physiology. He differentiated between irritability and sensitivity in the nervous system, localized sensation to nerves and movement to muscles, and demonstrated the autonomous contractility of heart muscle. Haller believed that both the cerebral cortex and the dura mater lacked sensitivity, whereas the white matter of the brain was sensitive in all his experiments (Neuburger/Clarke, 1897/1981). He refuted the notion that the soul was located or distributed in the nervous system and introduced the idea of functional omnivalence—that any part of the brain (cerebrum and cerebellum) could function vicariously for another. There was, however, a distinction between the less significant cortex and the more important white matter that contained the "sensorium commune."[4]

On Feb. 2, 1776, Francesco Gennari (1752–1797) discovered the white matter streak in the occipital cortex; he designated it lineola albidior in 1782, and Heinrich Obersteiner (1847–1922) later named it the line of Gennari. This was the first anatomic underpinning of cortical heterogeneity and provided a rational basis for the ensuing notions of cortical localization.

Félix Vicq d'Azyr (1748–1794) independently confirmed Gennari's white line in 1781. In his 1786 *Traité d'anatomie et de physiologie*, one of the most extraordinary anatomical folios that had yet appeared, Vicq d'Azyr displayed the results of his dissections, which were facilitated by hardening the brain in alcohol—an innovation in the study of nervous system anatomy (figure 2-2). He identified the cerebral convolutions and internal structures of the brain. He described the mamillothalamic tract that bears his name, as well as the central sulcus (which François Leuret [1797–1851] in 1839 named for Luigi Rolando [1773–1831], who described it in 1809), the postcentral and precentral convolutions, and the insula (25 years before Reil). On horizontal sections of brain, he recognized the continuity of the white matter of the corpus callosum, the centrum ovale, and the white matter medial and lateral to the corpora striata. He described the anterior and posterior commissures that "are intended to establish sympathetic communications between the different parts of the brain, just as the nerves do between the different organs and the brain itself" (quoted in Clarke and O'Malley, 1996, p. 592). He differentiated for the first time the notion of commissural connections between the hemispheres as opposed to association pathways that run between the different regions of the same hemisphere. He included in the commissural category not only the corpus callosum and anterior and posterior commissures but also the quadrigeminal bodies, cerebral peduncles, pons, anterior medullary velum, interthalamic adhesion, infundibulum, and tuber cinereum. In the association system he considered the stria terminalis ("taenia semi-circularis"), fornix, peduncles of the pineal gland, and mamillothalamic tract. Vicq d'Azyr concluded that "everything is arranged in the system to multiply the connections

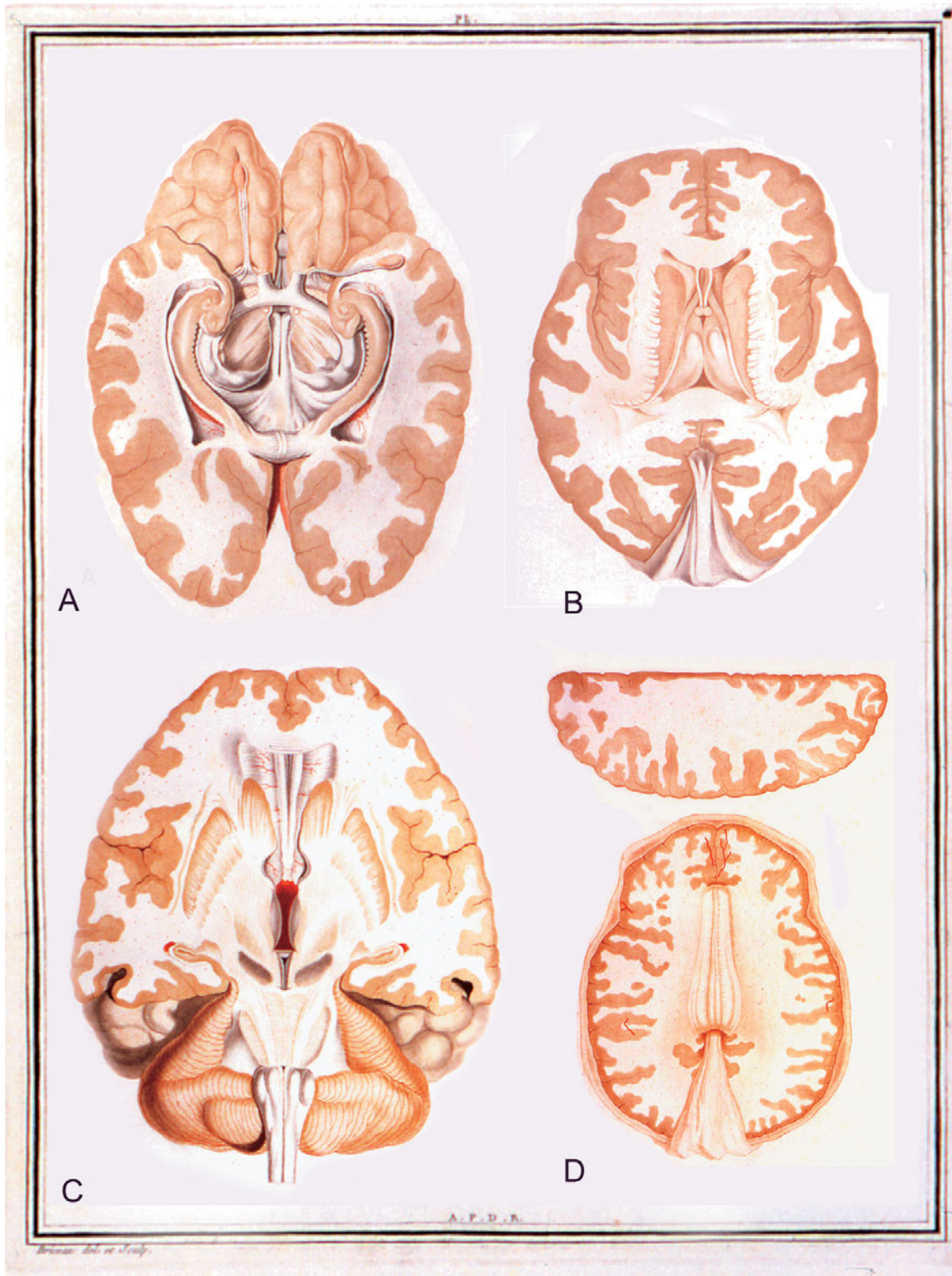

Figure 2-2

Images adapted from the atlas of Félix Vicq D'Azyr (*Traité d'anatomie et de physiologie,* 1786). Each of these four images occupies an entire page, and the decorative boundary that adorns each page is reproduced here. A, plate XX; B, plate XXII; C, plate IV; D, plate IX. The images in B through D are flipped vertically to show the frontal lobe at the top.

of different parts of the brain so that inconveniences which could result from difficulty occasioned in any part of the brain, are prevented" (ibid., p. 593). This concept presaged the role of synaptic plasticity in functional recovery.

The Era of Gross Dissection

The investigations of Willis, Steno, Malpighi, Vieussens, and others resulted in the initial recognition that the cerebral white matter was heterogeneous and complex. A completely new understanding of the organization of the white matter became possible, however, with the evolution of new brain-fixation techniques and the novel approaches to gross dissection of its internal structure that these techniques facilitated. In 1809 Johann Christian Reil (1759–1813) realized that using fresh unfixed tissue resulted in decaying material in which many original structures and relationships were lost. After soaking the brain in alcohol with potash or ammonia added, he investigated the white matter of the cerebral hemispheres (figure 2-3) and introduced the term "corona radi-

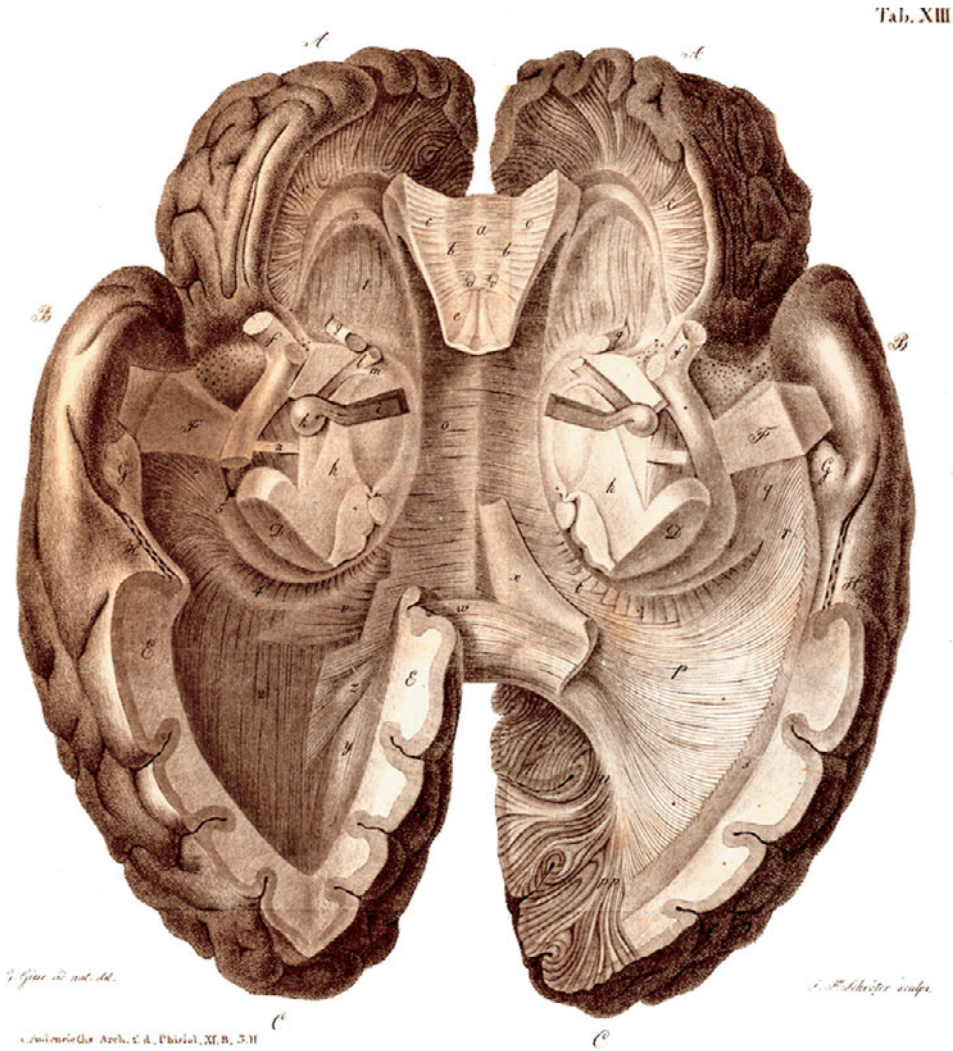

Figure 2-3
Tafel XIII of Johann Christian Reil (*Archiv für die Physiologie*, 1812, volume XI) to show his gross dissection of the human brain viewed from below.

ata" to describe the radiation of fibers in Vieussens' centrum ovale.[5] He emphasized the close relation between these fibers, the internal capsule, and the cerebral peduncles, described the corpus callosum, anterior commissure, and uncinate fasciculus, and recognized the external capsule. He regarded the fibers that lead toward the occipital pole as being a caudal extension of the corona radiata, described the insular cortex that bears his name, and suggested that the cerebral convolutions were the seat of mental processes: "Around these centers [the basal gray masses] are all the convolutions of the hemispheres like the rays of the sun, or like rivulets that absorb their life spirits from the ocean; around these [centers] lie the main instruments of the soul; around them originate the organs of artistic perception, of the ability for induction and representation" (Reil, 1809d, p. 207; also quoted in Clarke and O'Malley, 1996, p. 391).

Haller's notions of equipotentiality survived into the 19th century, supported, for example, by Reil, Jean Marie Pierre Flourens (1794–1867), and others, despite Robert Boyle's (1627–1691) earlier conclusion that there was a motor area in the brain. Boyle had demonstrated the presence of a motor area in a patient with a palsy of the arm from a depressed skull fracture that resolved when the depressed bone was raised. Similarly, in his writings between 1738 and 1744, Emanuel Swedenborg (1688–1772), who recognized that fibers descend from the brainstem to the spinal cord and proposed the concept of an upper-motor and lower-motor neuron, defined the location of the motor area in the cerebral cortex. According to Garrison/McHenry (1969, p. 108), Swedenborg placed the representation of the extremities in the upper frontal convolutions, the abdomen and thorax in the middle frontal convolutions, and the head and neck in the lower frontal convolutions.

Against this background, the genius of Franz Joseph Gall (1758–1828), in collaboration with Johann Kaspar Spurzheim (1776–1832), led to a fundamental shift in the concept of brain structure and function. Best known for the spurious field of phrenology that Gall and Spurzheim promoted, their anatomy and conceptions of the nervous system represented a completely new direction that would prove to be validated repeatedly. Contemporary systems neuroscience has its origins in Gall's work.

Gall and Spurzheim initiated the concept that brain function is based on the preeminent importance of cerebral cortex ("the convolutions are of an essential nature and necessary for intellectual functions" [quoted in Clarke and O'Malley, p. 394]), that there is functional specialization of different parts of the cortex, that the cortex is the originator of the connecting fibers of the white matter, and that there is specificity of the connections of the different regions of the cortex. The publication in 1810 of *Anatomie et physiologie du systeme nerveux* also provided a fundamentally novel understanding of the organization of the white matter pathways in the cerebral hemispheres (figure 2-4). This work on the intracerebral white matter was designed to elucidate the connections between the postulated surface organs of the cortex, and it provided anatomical support for their notion that functional differences of the cortical organs were the result of different peripheral connections as well as discrete central relationships. Their diagrams of blunt dissection of fiber bundles established that white matter consists of tracts connecting cortical gray matter regions that they considered to be the organ of mental activity. Whereas callosal and association systems had been proposed by Vicq d'Azyr, Gall and Spurzheim proposed the existence of projection systems as opposed to association systems. The projection system ("divergent, or sortant") was equivalent to the afferent and efferent projection fibers that link the cortex with subcortical regions, brainstem, and spinal cord. Association fibers

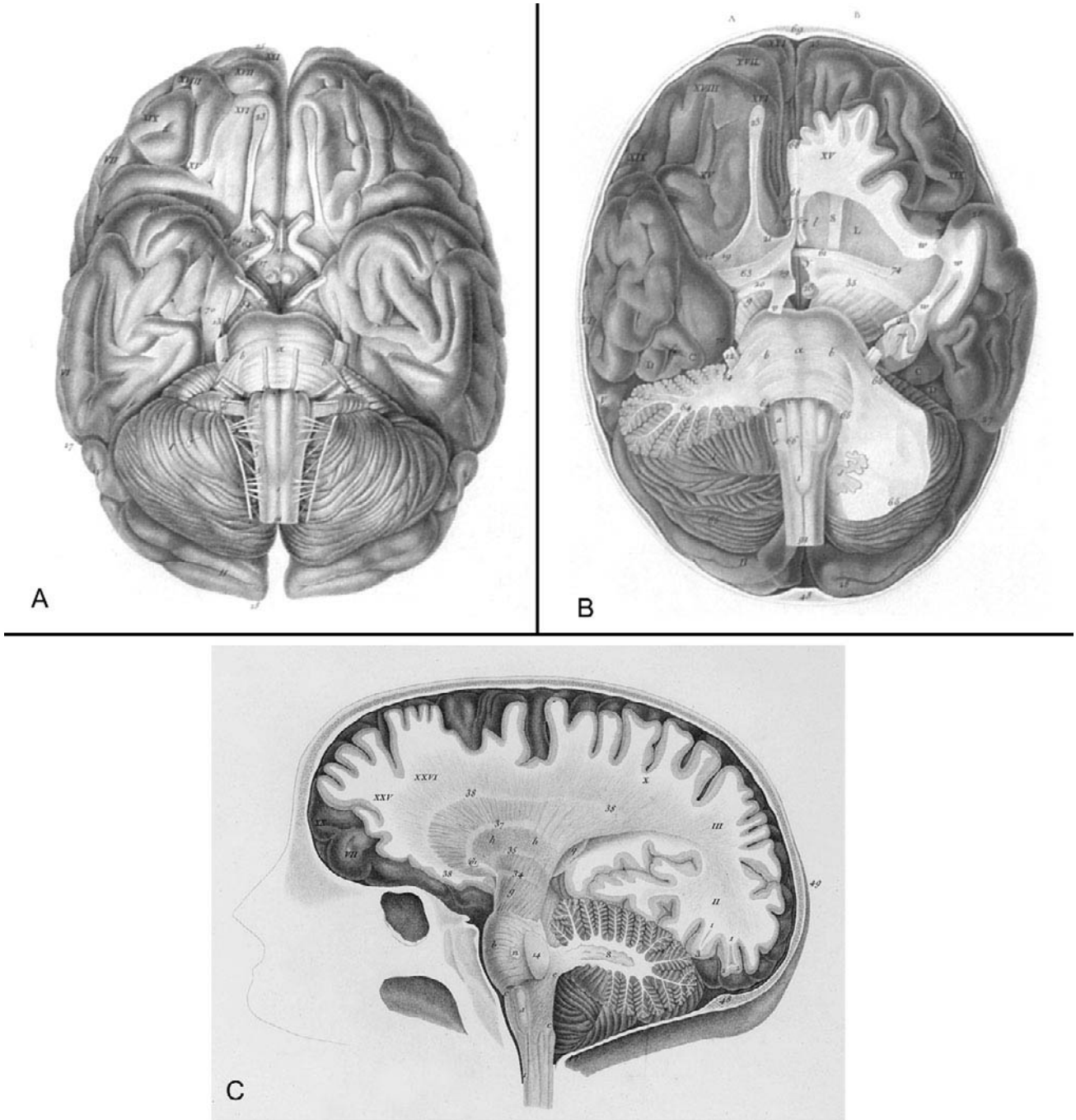

Figure 2-4
Images from the atlas of Franz Joseph Gall and Johann Kaspar Spurzheim (*Anatomie et physiologie du systeme nerveux*, 1810) showing cerebral convolutions and dissections revealing differentiating features of cerebral cortex and white matter. A, plate IV; B, plate XIII; C, plate X.

("convergent, or retrant"), were an entirely intracerebral system greatly developed in humans, being more numerous and containing larger bundles of fibers than the projection system. Further, these association fibers were of two kinds: short or arcuate fibers, and long fibers that connect parts of the different cerebral lobes. Commissural fibers that link the two hemispheres were considered by Gall to be part of the association system.

The importance of the anatomical studies of Gall and Spurzheim was recognized by their contemporary Alexander Monro, Tertius (1773–1859), professor of anatomy at the University of Edinburgh, like his father and grandfather before him. Monro wrote that "(t)he Plates of the brain of Drs Gall and Spurzein, are, taken as a whole, far superior to any that have been published; and by their method of exhibiting the brain, they have thrown much light upon the relative situation of parts" (Monro, 1813, p. 135).

John Gordon (1786–1818) published a scathing critique of the anatomical work of Gall and Spurzheim, quoting their work liberally in order to belittle it. As Gordon (1817, pp. 126–135) points out, Gall and Spurzheim noted that all white matter comprises fibers (although this was not a new observation); that all white matter originates and ends in the cerebral cortex; and that the cerebral convolutions contain both converging (association) and diverging (projection) fibers. Gordon was incensed by the statement of Gall and Spurzheim that the corpus callosum fibers are topographically arranged—frontal lobe fibers in the genu, fibers from the pericentral region in the body of the corpus callosum, and parietal and occipital lobe fibers in the caudal part of the corpus callosum, including the splenium. Further, Gall and Spurzheim concluded that the anterior commissure contains fibers that have their origins in the rostral part of the temporal lobe and in the ventral part of the frontal lobe. The anatomical conclusions of Gall and Spurzheim that Gordon enumerated have subsequently been validated repeatedly, as the results of our monograph also confirm. In hindsight, and perhaps to Gordon's chagrin, it transpires that the principles of cerebral white matter organization that were postulated by Gall and Spurzheim were prescient and accurate.

Neuburger also acknowledged that "Gall, who, as no one before him, succeeded in analyzing the structure of the white matter . . . was the first to claim that mental activities were localized in the cortex alone, (and) the white matter he relegated to the role of a system of conduction and projection" (Neuburger/Clarke, 1897/1981, p. 277). It took some time for the new ideas about white matter to become accepted, as reflected in the 1823 statement of François Magendie (1783–1855), who recognized the central role in locomotion played by "the white matter fibers that radiate from the pyramids to the cerebral hemispheres" but considered "that properties relating to movements reside chiefly in this (white matter) part of the brain" (Neuburger/Clarke, 1897/1981, p. 275).

Gall's "doctrine of plurality of cerebral organs" was favorably looked upon by Karl Friedrich Burdach (1776–1847), whose three-volume work between 1819 and 1826 defined and designated fiber bundles through gross dissection (figure 2-5). Burdach identified the tapetum, cingulum, uncinate fasciculus, and arcuate or superior longitudinal fasciculus, as well as other systems that he termed the inferior longitudinal fasciculus, and the "baseos internus" (Burdach, 1826, vol. 3, p. 959). The existence of intracerebral association fibers was proposed by Vicq d'Azyr and Gall and Spurzheim, and a preliminary characterization was attempted by Reil, but Burdach was the first to identify, characterize, and name these association fiber bundles in more detail.[6]

Intricate gross dissections of white matter were pursued subsequent to these early works and illustrated magnificently. Herbert Mayo (1796–1852) illustrated the fiber bundles in his engravings in 1827 (figure 2-6). Friedrich Arnold (1803–1890) depicted the fiber systems in his atlas (Arnold, 1838a) and described them (Arnold, 1838b), including bundles later to be named for him (the frontopontine tract [Arnold's bundle]

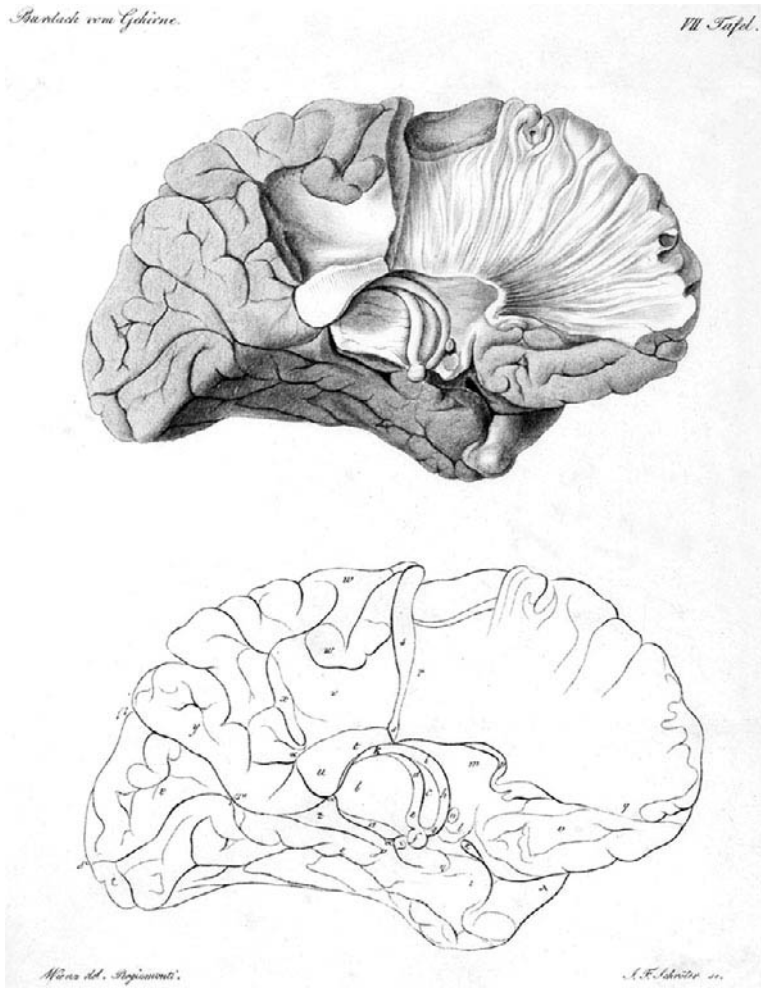

Figure 2-5
Tafel VII from Karl Friedrich Burdach (*Vom Baue und Leben des Gehirns, Zweyter Band*, 1822) showing gross fiber dissection in the white matter of the frontal lobe.

and the temporothalamic fasciculus [Arnold's tract]; Arnold, 1851). He also observed the arcuate fibers linking adjacent gyri (figure 2-7) that had been described by Gall and Spurzheim (later called the fibrae arcuateae of Arnold). Achille-Louis Foville (1799–1878) diagrammed his gross fiber dissections in 1844, focusing on the corpus callosum (figure 2-8). He showed longitudinal fibers from the occipital lobe progressing rostrally, but he was not able to discern their destination.

Louis-Pierre Gratiolet (1815–1865) was the first to parcellate the cerebral hemisphere into lobes. The names he gave them remain in use today, including the Sylvian fissure, after Franciscus de le Boë, or Sylvius (1614–1672) who described it (as acknowledged by Caspar Bartholin the Younger [1655–1738] in 1641) and published his description in 1663 (Clarke and O'Malley, 1996, p. 390). Gratiolet also made a systematic study of the white matter in monkeys using the technique of gross dissection. He observed the anterior commissure, corpus callosum, and U-shaped association fibers connecting adjoining gyri of the same hemisphere. His notable additions to the description of white matter systems were the fibers that originated from Reil's corona radiata, the radiations from the quadrigeminal body, medial geniculate nucleus, and cerebellum, and most particularly the optic radiations (of Gratiolet), a fiber system coming via the optic

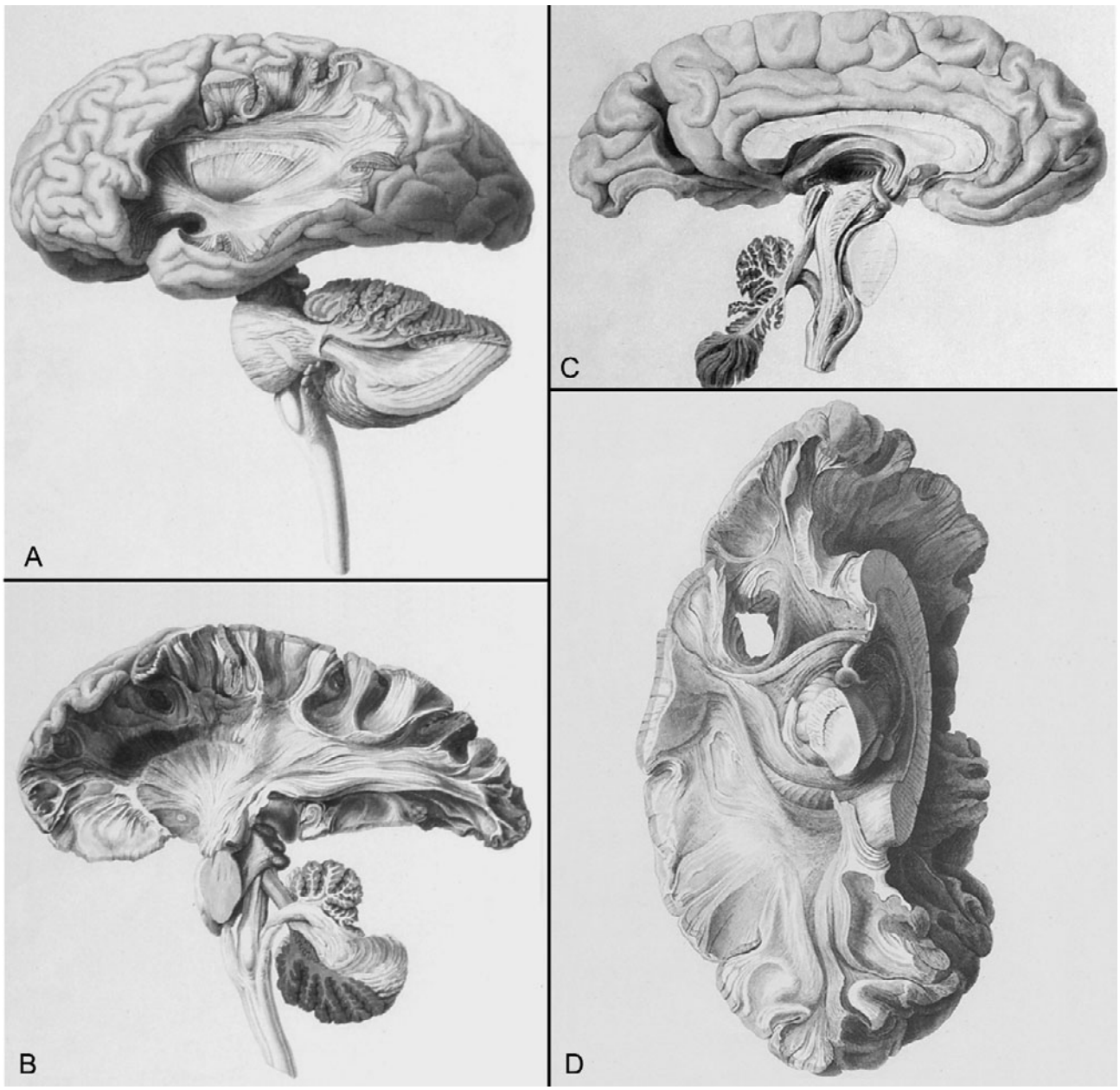

Figure 2-6
Depictions of white matter dissections of the cerebral hemisphere, cerebellum, and brainstem by Herbert Mayo (1827) in his *A Series of Engravings Intended to Illustrate the Structure of the Brain and Spinal Cord in Man*. A, plate III; B, plate IV; C, plate V; D, plate VI. The uncinate fasciculus and superior longitudinal fasciculus are seen in A, and the arcuate or U-fibers are shown in B and D. The medial hemisphere in C is dissected in D and shown from the ventral aspect.

tract and leading to the posterior part of the cerebral cortex, including the parietal and occipital lobes (figure 2-9). Gratiolet's observation that a fiber system of a sensory (visual) modality leading all the way to the cortex, and terminating in only a restricted part of the cortex, had far-reaching significance: it was the first confirmation of a special sensory tract above the level of the brainstem. Flourens, a figure of great stature and in-

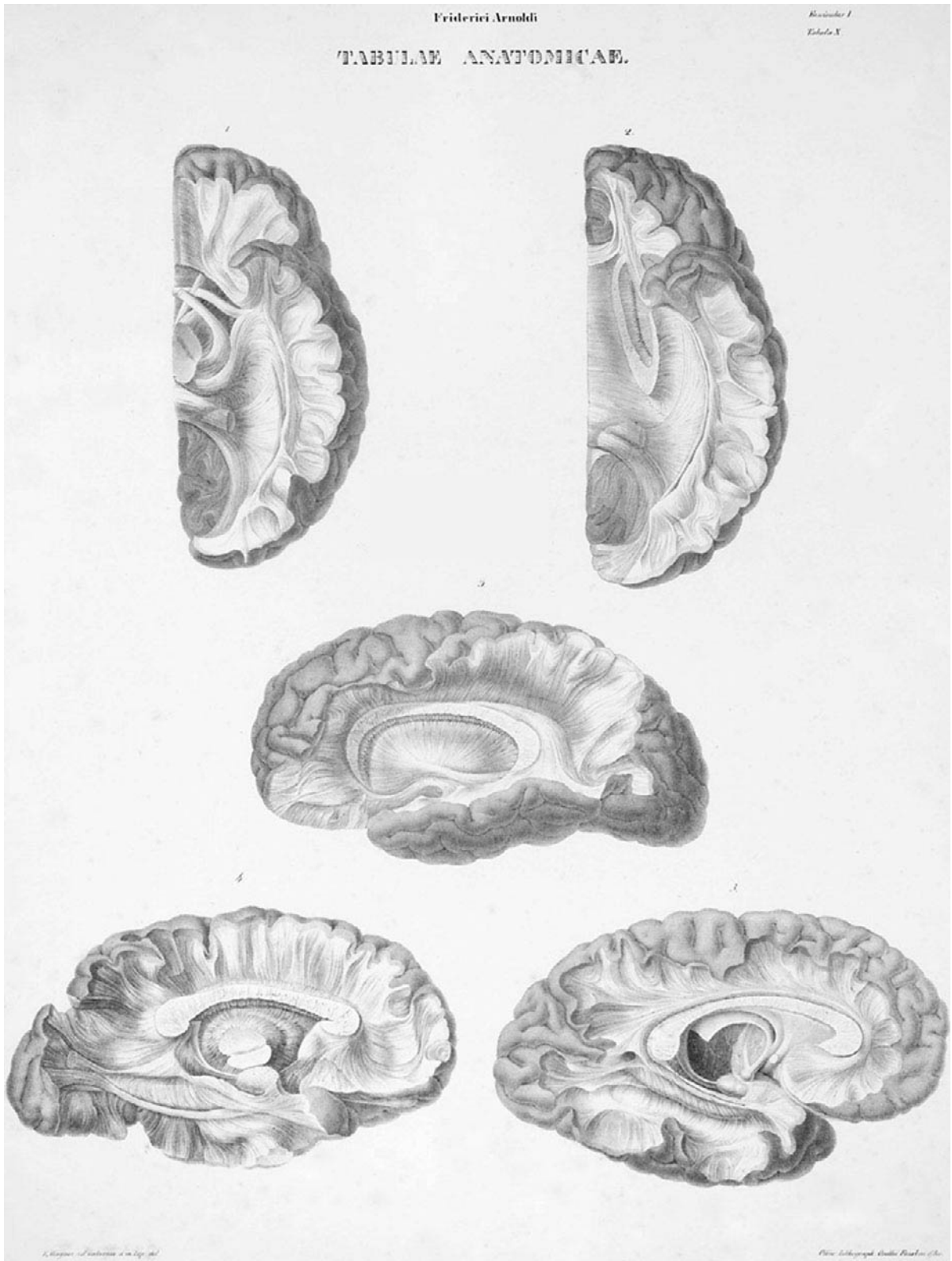

Figure 2-7
Images from the *Tabulae Anatomicae* of Friedrich Arnold (1838), Tafel X, in which his gross dissections of the white matter reveal the arcuate fibers that were named for him.

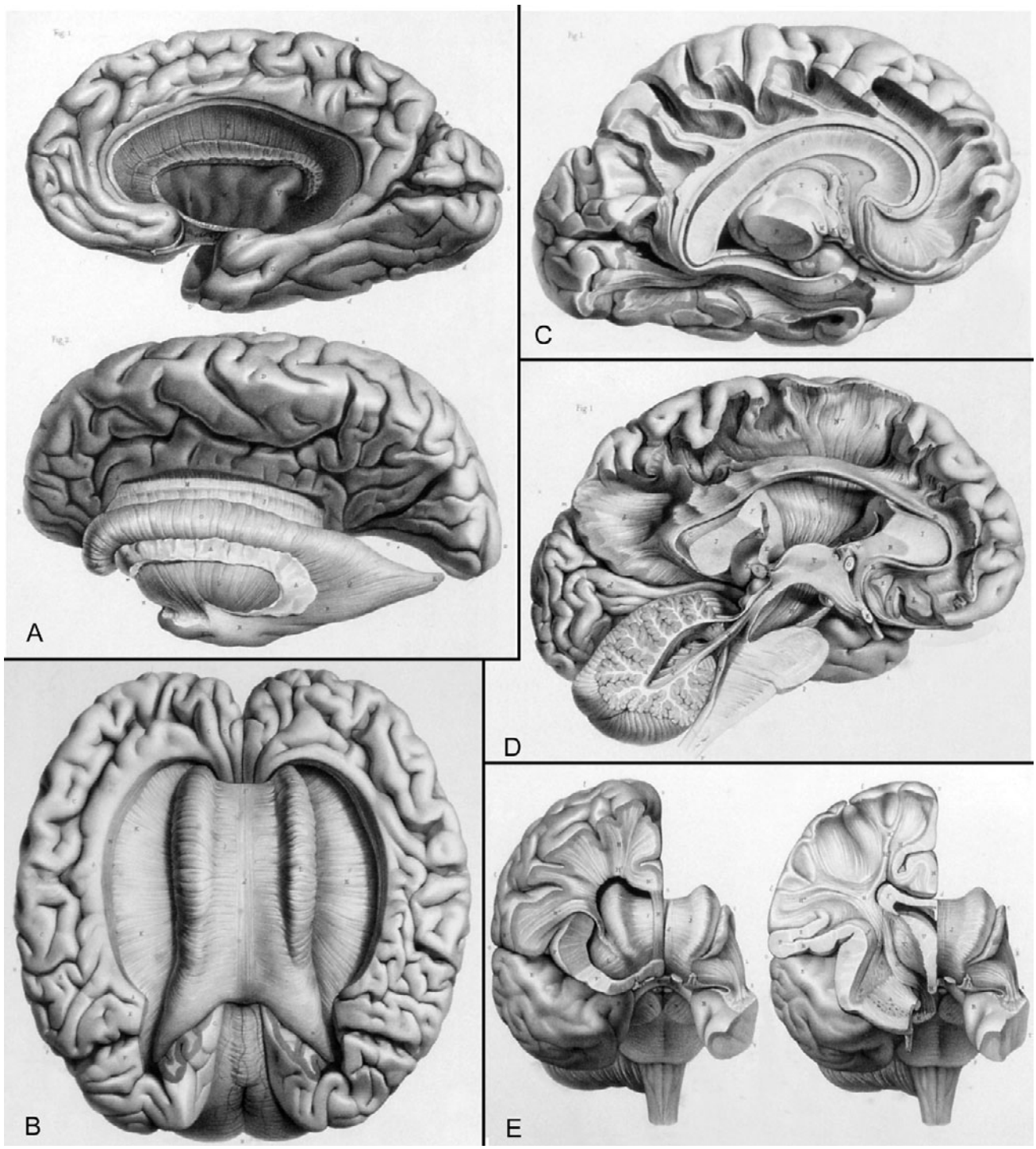

Figure 2-8

Selected illustrations from Achille-Louis Foville's (1844) *Traité complet de l'anatomie*. A, Plate 16 shows the gyral surface of the medial hemisphere and a schema of the ventricular system. B, Plate 15 depicts a dorsal view of the dissected corpus callosum linking the two hemispheres. C, Plate 14 shows Foville's notion of the transected corpus callosum and the cingulum bundle. D, Plate 18 shows corona radiata fibers, the cingulum bundle, and the superior cerebellar peduncle. E, Plate 19 is an anterior view of the dissected hemispheres showing the corpus callosum, corona radiata, and internal capsule.

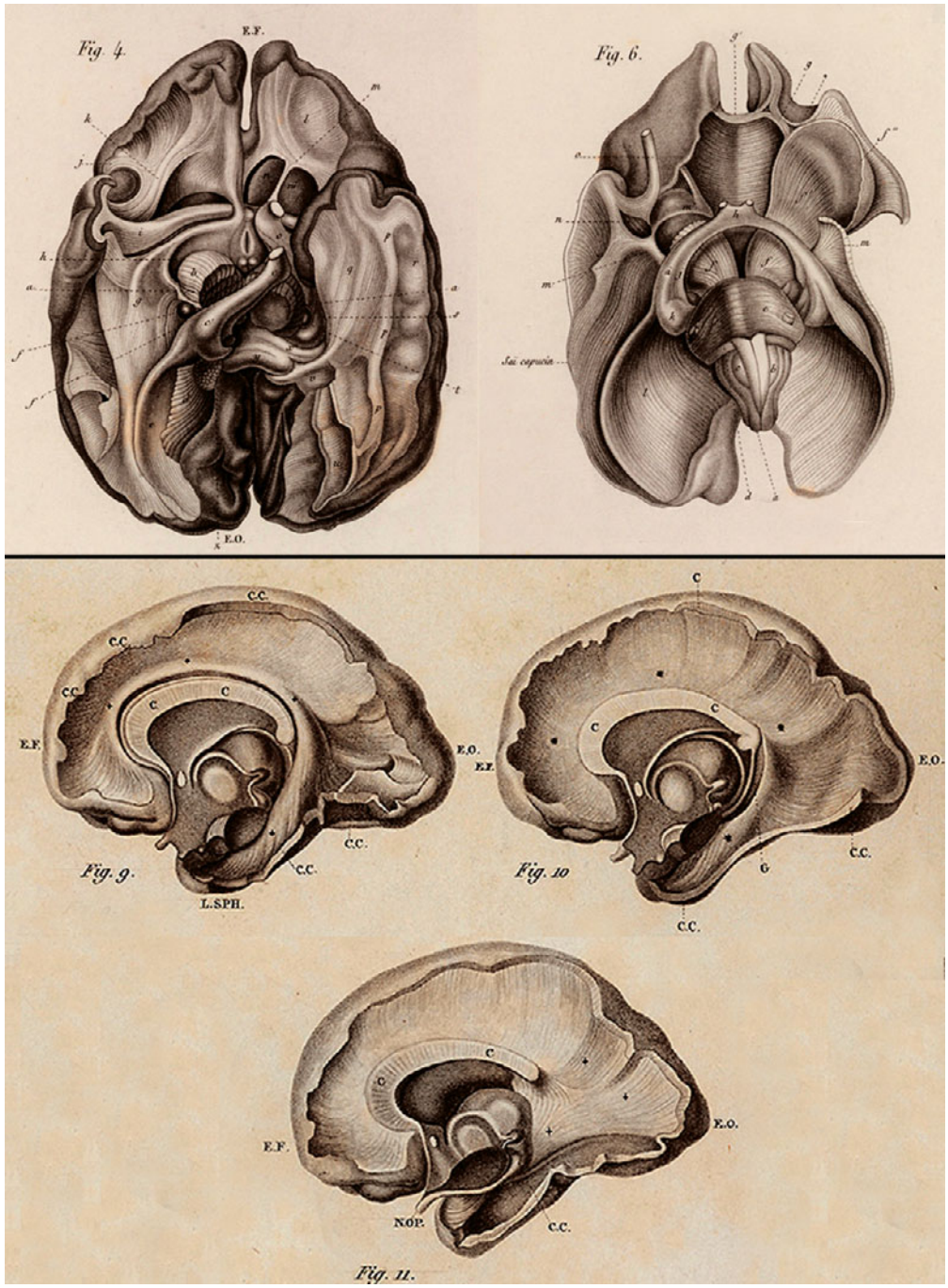

Figure 2-9

Gross dissections by Louis-Pierre Gratiolet (adapted from Leuret and Gratiolet, 1839, *Anatomir comparée du système nerveux*) depicting the fiber bundle that came to be known as the optic radiation. Fig. 4 and Fig. 6 (top) are monkey brain dissections, from Plate XXVII. Label "e" in Fig. 4 (adjacent to "d" and caudal to "c'") refers to the roots of the optic nerve. Label "l" in figure 6 refers to the radiation ("expansion") of the optic nerve into the right hemisphere. Fig. 9, Fig. 10, and Fig. 11 (bottom) are from Plate XXX, depicting the fetal human brain. *Fig.9 labels*: +, ring formed by the white matter fibers of the medial edge of the hemisphere ("l'ourlet"– literally, hem); CC, cerebral cortex; C, corpus callosum. *Fig. 10 labels* *, radiation of the corpus callosum into the hemisphere. *Fig 11 labels:* +, radiation of the optic nerve into the hemisphere.

fluence at the time, strongly opposed Gall's cortical localization theory and phrenology and believed in the functional omnivalence (equivalence) of the cerebrum and cerebellum. He did, however, propose that vision is localized in the cerebral cortex and argued against the notion that the cerebral cortex in some way presides over sensory functions without being able to see, hear, or feel. Gratiolet's observations provided support for Flourens' view that the cerebral hemisphere is indeed directly related to the sense organs, and therefore the brain could not be exclusively a substratum of so-called psychic function above the level of sensory experience. "(T)he cerebral cortex had to be recognized not as a kind of anatomical abstraction outside the so-called somatic sphere, but as the highest level of nervous system whose roots reach to the very confines of bodily organization" (Polyak, 1957, p. 137). However, in contrast to Flourens' omnivalence theory that the entire cerebral hemisphere was a uniformly organized substratum with homogeneous function, Gratiolet had determined that the visual pathways terminated in a distinct area of the cortex, and there were large parts of cortex outside the reach of these fibers.

Gross dissections of the fiber systems of the brain have continued sporadically into the present era. The results of some of these efforts, and the differing interpretations surrounding the published observations, are considered in more detail in chapters that deal with the individual bundles. In the early 20th century attempts were made to delineate association fiber systems using what were considered to be enhanced techniques of gross or blunt white matter bundle dissection (see, e.g., Hoeve, 1909; Jamieson, 1908–9; Johnston, 1908). Investigators at that time confirmed many of the findings of a century earlier, but they continued to debate the nomenclature and the possible origins and terminations of the tracts identified with these techniques. Thus, Trolard dissected the fiber systems around the claustrum (1905) and the inferior longitudinal and arcuate fasciculi (1906); Curran (1909) believed he had identified an inferior fronto-occipital fasciculus as well as the uncinate, arcuate, and transverse occipital fasciculi; Davis (1921) dissected the inferior longitudinal and uncinate fasciculi and the geniculocalcarine tract and Curran's (probably spurious) inferior fronto-occipital fasciculus; Ranson (1921) described subcortical fiber systems, including the temporothalamic fibers that bear the name Arnold's tract (the temporopulvinar bundle of Arnold, according to Ludwig and Klingler [1956] and Klingler and Gloor [1960], as opposed to the frontopontine system [Arnold's bundle]); and Rosett (1933) unsuccessfully attempted to clarify the nature of the subcallosal bundle. Klingler amended the technique of gross dissection by freezing the brain after fixation in formaldehyde. This facilitated his meticulous dissections of the white matter and made it possible to delineate fiber bundles with greater clarity (Ludwig and Klingler, 1956), albeit, so contemporary findings indicate, without necessarily resulting in greater anatomic accuracy. Gross dissections have also been performed more recently by Kertez and Geschwind (1971), Gluhbegovic and Williams (1980), Ross (1980), Heimer (1983, 1995), Ebeling and von Cramon (1992), and Türe with Yasargil et al. (1997, 2000). Wendell Krieg (1906–1997) provided schematic representations of the fiber systems in three-dimensional format in the rat (Krieg, 1947) and monkey (Krieg, 1954, 1975), as derived from myelin-stained material.

Controversy has surrounded this method from its earliest days in the 1500s.[7] The gross dissection method left many questions unanswered. The course and arrangement

of the fiber bundles could not be determined, and it was not clear whether fibers terminated in the cortex, originated in it, or simply turned around and passed back again to the brainstem. Todd (1845) encapsulated the problem thus (pp. 133–137): "The problem which the anatomist has to solve is, Given certain columns or bundles of fibers in the medulla oblongata, to determine how they connect themselves with the other segments of the brain. (I)n the statements of all anatomists, who avail themselves of no other aid than that which the naked eye affords, there is much that must necessarily be uncertain or doubtful. (I)t will not suffice to display the direction of all the fibres, nor indeed is any mode of preparation adequate for that purpose. Nor is there any other mode of removing these uncertainties than by the successful application of extensive and patient microscopic analysis to the whole cerebral structure." Advances in the understanding of the cerebral white matter had to wait for the development of the compound achromatic microscope in the 1820s,[8] the new understanding in the 1840s that white matter fiber bundles were comprised of axons derived from nerve cells, and the progressive elaboration of fixation and staining techniques.

Todd's conclusion that gross fiber dissection had inherent limitations was echoed by Charles Edward Beevor (1854–1908) in 1891 (p. 135): "The method by dissection of the brain with the scalpel has been much employed, and though it is doubtless of value in tracing out the coarser strands, it is open to the objection that the parts are very much displaced by the operation necessary to follow out the fibres, and also that relations may be artificially produced which do not actually exist. Moreover it is quite impossible to trace the fibres to their ultimate ending, as this can only be accomplished by the use of the microscope." These concerns were supported by subsequent events. The study of white matter fiber systems by gross fiber dissection was marked by confusion and uncertainty, as described in detail in the relevant sections of our text. This development notwithstanding, some contemporary authors (e.g., Türe et al., 1997, 2000) have taken to resurrecting this approach.

The Neuron Theory

The early tractographers performed their gross dissection of cerebral white matter unaware that the neuron was an independent entity and that the fibers were composed of axons derived from nerve cells. The more detailed understanding of the cerebral white matter was therefore dependent upon the discovery of the neuron and the microscopic and staining techniques that would facilitate the finer analysis of the fiber bundles. A brief synopsis is relevant here, given the central importance of this concept to the technique used in the current investigation.

The existence of the nerve fiber was discovered before the nerve cell body. Using the crude microscope that he had invented, in 1674 Antoni van Leeuwenhoek (1632–1723) examined the optic nerve of a cow and saw filamentous particles. In a letter written in 1677, he provided the first account of the peripheral nerve fiber, reporting that the nervous system "consisted of diverse, very small threads or vessels lying by one another" (translated and quoted in Clarke and O'Malley, 1996, p. 32). The Galenic view

was that spirituous substances were conveyed by hollow nerve passages, and Leeuwenhoek wondered whether the vessels that he had seen "might not be those that conveyed the animal spirits through the spinal marrow." Malpighi determined in 1681 that gray matter was made up of cellular follicles, white matter of fine excretory ducts. Giovanni Alfonso Borelli (1608–1679) challenged the concept of nerves as hollow tubes, believing instead that they "are channels filled with a certain spongy substance, like the pith of the elder tree. This spongy pith of the fibres is easily moistened by the spirituous juice of the brain, to which they are directly attached . . ." (*De motu animalium*, Rome, 1680–1681, 2 volumes, translated and quoted in Clarke and O'Malley, 1996, p. 164).

The nerve fiber was identified as the ultimate structure of peripheral nerve in 1781 by Felice Gaspar Ferdinand Fontana (1730–1805), who termed it the primitive nerve cylinder. Using the new achromatic compound microscope, Christian Gottfried Ehrenberg (1795–1876) demonstrated the existence of nerve fibers within the medullary substance of the cerebral white matter in 1833. Gabriel Gustave Valentin (1810–1883) documented the existence of the nerve cell in 1836 and identified the nerve cell body, including the nucleus, nucleolus, and parenchyma. He believed, however, that the nerve cell and the nerve fiber were not connected but merely juxtaposed. In 1838, for the first time, Robert Remak (1815–1865) described both myelinated and unmyelinated nerve fibers and suggested that the nerve fiber and nerve cell, which had previously been described separately by a number of observers, were in fact joined. Knowledge of the anatomy of nerve cells and fibers was further advanced by Jan Evangelista Purkyně (Purkinje) (1787–1869), who also identified the cerebellar cortical neuron that bears his name (Purkyně, 1837). Theodor Schwann (1810–1882) described the myelin sheath investing the axon and in 1839 enunciated the cell theory that "there is one common principle of development for the most diverse elementary parts of the organism, and this principle is the formation of cells."[9] Adolph Hannover (1814–1894) developed a fixation technique using chromic acid and illustrated its results describing myelinated fibers (Hannover, 1840). He observed axons lining the floor of the fourth ventricle, extending down into the spinal cord, and being as thick as peripheral nerve fibers, with a very similar appearance. He observed there were transverse fibers in the spinal cord of animals, running individually as well as in bundles, and he substantiated Remak's assertion by being the first to observe that fibers in the brain originate from brain cells and retain a lifelong, permanent connection with these central structures. The origin of myelinated fibers from nerve cells in the central nervous system as well as in peripheral ganglia was further established by Rudolf Albert von Koelliker (1817–1905), who also concluded that all nerve fibers are connected with nerve cells (von Koelliker, 1849), and by Otto Friedrich Karl Deiters (1834–1863), whose name is eponymously linked with the lateral vestibular nucleus. Augustus Volney Waller (1816–1870) sectioned the glossopharyngeal and hypoglossal nerves of frogs in 1850 and observed degeneration of the distal portions of these nerves. This observation led to the idea that the cell body is a nutritional and trophic center and that the nerve fiber is dependent upon it. It also formed the basis of later tract-tracing and connectivity studies using the principle of degeneration.

The evolution of the concept of the neuron and the improvements in the available microscopes prompted the development of better staining techniques to enhance the visualization of neural structures. Louis-Antoine Ranvier (1835–1922) used a new silver

impregnation method to describe the node that bears his name in 1871. Franz Nissl (1860–1919) first described the constituents of the nerve cell body using basic aniline dyes (Nissl, 1892). Joseph von Gerlach (1820–1896) used the carmine stain to develop his nerve net theory in 1872 based on observations in the spider and started a controversy (nerve net vs. neuron theory) that continued until the turn of the 20th century. Camillo Golgi (1843–1926) published in 1883 a new staining technique that combined potassium bichromate and silver nitrate and that was considerably better than any previous technique; it permitted visualization of the nerve cell, its axon (nerve extension), and dendrites (protoplasmic extensions). He described neurons with long axons (Golgi type I cells) and those with short axons (Golgi type II cells.) His observations led him to a firm belief in the nerve net theory. Paul Ehrlich (1854–1915) developed the methylene blue stain that outlined the nerve cell and all its processes, including nerve endings and myelinated nerve fibers. The neuron doctrine was introduced by Wilhelm His (1831–1904) in 1887. Using the approach of developmental histology, he determined that "each nerve fiber originates as a process from a single cell. This is its genetic, nutritive and functional center; all other connections of the fiber are either indirect or secondary" (His, 1887, translated in Clarke and O'Malley, 1996, p. 102). Auguste-Henri Forel (1848–1931) used Golgi staining and the retrograde degeneration technique of Johann Bernhard Aloys von Gudden (1823–1886) to demonstrate that a nerve network does not exist. Forel also showed that each nerve cell is in contact with but not in continuity with its neighbor (the contact theory of Forel) and that nerve fibers originate only from nerve cells. Further, whereas a fiber will degenerate if the nerve cell is damaged, as Waller had shown, the nerve cell itself will degenerate if its axon is damaged.

Santiago Ramón y Cajal (1852–1934) provided independent histological confirmation in 1888 of the contiguity of nerve cell elements. Cajal's study of basket cells and Purkinje neurons in the cerebellar cortex, and then of neurons in the cerebral cortex, laid to rest the neural net theory of Golgi and established the neuron doctrine. (Heinrich Wilhelm Gottfried von Waldeyer-Hartz [1836–1921)] introduced the term "neuron" [Waldeyer, 1891], and the term "neuron doctrine" evolved thereafter.) In his Croonian lecture, Cajal (1894) summarized the understanding of the nerve cell and the fibers that make up the white matter systems. "In a synthetic manner one can say that the whole nerve center is the result of association of the four following paths: the nerve cells with short axis cylinders, that is, branching in the very thickness of the gray matter; the terminal nerve fibers which come from other centers or distant regions of the same center; nerve cells with a long axis cylinder, that is, extending as far as the white matter; the collaterals which originate either during the passage of axis cylinder extensions of the cells with long processes [axons] across the gray matter, or during the course of the tubes [*bundles*] of white matter." (Proc. R. Soc. 1894;55:444–468. Translated in Clarke and O'Malley, 1996, p. 123). The development of *in vitro* neuronal cell culture in 1907 by Ross Granville Harrison (1870–1959) initiated a new field of cytology and provided decisive confirmation of the neuron doctrine.

Rudolf Virchow (1821–1902) described and named the neuroglia (nerve glue) in 1856. The role of neuroglia in neural transmission and maintenance of neuronal integrity has been recognized in recent years. The glia are relevant to our study of the fiber pathways because their morphology, including the size, orientation, and cell pack-

ing density, serves as a guide to the orientation of the fiber bundles and for the comparison of the major fiber bundles between species.

Microscopic Study, Clinicopathologic Correlations

Along with further refinements in the optical physics of the microscope, laboratory techniques improved in the 1800s, permitting thin sections of brain to be made that could be stained for the analysis of normal and degenerated nerve fiber tracts. These new techniques revealed the relationship between the cortical neurons and the axons in the white matter and a previously unimagined level of detailed organization of the cerebral cortex, the subcortical nuclei, and the fiber systems that connect them. Fixation of the brain was a crucial step in the microscopic analysis. It was first hardened in alcohol (Reil, 1809a–d), then in chromic acid (Hannover, 1840) and chromic salts that were used for staining. Formaldehyde was not introduced until 1893 by Ferdinand Blum (1865–1957), and its utility was confirmed by Hermann (1894). The serial sectioning method that Benedict Stilling (1810–1879) introduced (Stilling, 1842) could be applied routinely to the hardened brain, and the use of the microtome (George Adams [1750–1795], 1798) and paraffin (Klebs, 1869) and celloidin embedding (Duval, 1879) facilitated evaluation of the microscopic features of the nerve cells and fibers that were made more visible with the new dyes and techniques. These included carmine (Corti, 1851; Gerlach, 1858; Goeppert and Cohn, 1849; Hartig, 1854; Osborne, 1857), aniline dyes (Perkin, 1861), hematoxylin (e.g., Gage, 1892–3), the "black reaction" of osmic acid that Camillo Golgi described in 1873 (Golgi, 1883) and that was extensively used by Ramón y Cajal in his investigations (1899–1904), and the special stains of Paul Ehrlich as discussed in his encyclopedia of 1903, Vittorio Marchi (1851–1908) in 1885, Franz Nissl in 1892, and Max Bielschowsky (1869–1940) in 1902. The myelin stain was developed by Carl Weigert (1845–1904) in 1882 (Weigert, 1884) and enhanced by Pal (Wethered, 1888).

Ludwig Türck (1810–1868) used Stilling's serial section technique to study degenerated pathways following brain lesions (Neuburger, 1910; Türck 1849, 1850, 1851). He described the anterior corticospinal tract that was named for him by Jean-Martin Charcot (1825–1893) in 1875 (Charcot, 1878). (The temporopontine tract was incorrectly named for Türck, an error that dates from Meynert, 1885. See Schmahmann et al., 1992.) Türck's discovery of this method of tract tracing through degeneration was essentially simultaneous with the well-known work of Waller in 1850. von Gudden further developed the degeneration method of tracing nerve fibers, producing secondary atrophy of nerve centers and their connections by removing sense organs such as the eye or cranial nerves. He defined the decussation of the visual pathway in the optic chiasm of the rabbit, showed that if a cerebral hemisphere is removed and the thalamus left intact, a decrease in the size of the thalamus results (von Gudden, 1870), and observed that degeneration of the proximal end of a divided nerve is directed toward the cell body (Gudden's law). The secondary degeneration technique was adapted by Gudden's student, Constantin von Monakow (1853–1930), to study corticothalamic and other subcortical connections (von Monakow, 1882a,b, 1885, 1895) and by Sir David Ferrier (1843–1928) and Gerald Francis Yeo (1845–1909) to study motor pathways in the inter-

nal capsule (Ferrier and Yeo, 1884; Schäfer, 1883); it remained the principal method of neuroanatomical tract-tracing studies for a century.

In a series of papers from 1867 to 1872, Theodore Hermann Meynert (1833–1892) applied the improved histological techniques to study the cerebral white matter systems in the bat (Meynert, 1872; see translated works in Stricker, 1872, and Meynert, 1885, and figure 30.1 A-D). He established with greater clarity the three principal types of white matter systems that had first been suggested in 1786 by Vicq D'Azyr (callosal and association systems) and in 1810 by Gall and Spurzheim (projection systems, and association [including callosal] systems). These systems described by Meynert were (1) the association systems including the short arcuate fibers (the fibrae arcuateae of Arnold, 1838a,b, that Gall and Spurzheim, 1810, had previously identified, or the U-shaped fibers of Meynert) and the long association fibers by means of which various parts of the cerebral cortex are interconnected and communicate with each other; (2) the commissural pathways linking the two hemispheres; and (3) the afferent and efferent projection systems between the cerebral cortex and subcortical structures that facilitate somatotopic representation in the cortex. Meynert also identified the afferent systems entering the cerebral hemispheres from the cerebellum. (These influential ideas and illustrations of Meynert, including the prevailing misconception that the basal ganglia contribute to the cerebral peduncle, are incorporated in his 1872 writings and diagrams, reproduced in the Notes.[10])

Paul Emil Flechsig (1847–1929) used the carmine stain and Weigert's myelin stain to study the evolving patterns of myelination through development in a body of work extending over five decades (from 1872 to 1927). Flechsig's efforts laid the foundation for a number of fundamental concepts of brain organization. He provided a comprehensive and enduring understanding of myelinogenesis in the human brain. He determined that different tracts develop myelin sheaths at different periods of prenatal and postnatal life and that fibers belonging to the same system mature at approximately the same time, whereas those of anatomically and functionally different tracts do so at different periods. He introduced the "fundamental law of myelinogenesis" that the sequence of myelination during individual development repeats their phylogenetic appearance. This was an extension of the "biogenetic law" of Ernst Haeckel (1834–1919) that "ontogeny recapitulates phylogeny" (Haeckel, 1879, 1902).[11] Based on his study of myelination patterns of cerebral white matter, Flechsig described projection[12] and association fibers, developed the concept of cerebral "association areas," and expanded the notion of sensory versus association cortex.[13] He described the course of the pyramidal tracts from the cerebrum through the internal capsule to the spinal cord and showed that the basal ganglia do not contribute anatomically to the pyramidal tract. He demonstrated the auditory radiations and the loop of the visual radiations in the temporal lobe that later came to bear the name of Meyer.

Flechsig believed that the great fiber tracts that myelinate by the end of intrauterine existence and the first few weeks of extrauterine life together constitute Meynert's projection system and make up Reil's corona radiata. He concluded that the association areas are essentially devoid of projection systems, having no or very few direct connections with peripheral receptor organs. Rather, the sensory afferents are conveyed to the association cortices by means of the short "association fibers of Meynert" and by callosal fibers. Further, "lesions involving the sense centers are followed by a train of

symptoms of an entirely different character from those which accompany lesions of the association centers" (Barker, 1899, p. 1074). According to Barker (1899, pp. 1081–1082), Flechsig's ideas met with some opposition. Monakow was among "a number of leading neurologists and psychiatrists . . . unwilling to grant that the areas of the cortex to which projection fibers are distributed are as limited as Flechsig would have us believe. Thus, von Monakow asserts that projection fibers go to nearly all parts of the cortex, though certainly some parts of it receive fewer by far than others. Von Monakow bases his objection upon the results of his studies of secondary degenerations. He believes . . . that the sense areas occupy much more extensive fields of the cerebral surface than those indicated by Flechsig in his diagrams. . . . Flechsig responded to these comments by pointing out 'that lesions of the parietal cortex have been followed in a number of instances by degenerations of projection fibers, but in all such instances he believes the cortical nodule had affected bundles of projection fibers belonging to other parts of the cortex, but situated beneath the area diseased. The results of experimental degenerations in animals following extirpation of cortical zones can not properly be directly applied to human beings, for in man there is a development of the association centers not reached in the brain of any other animal.' "

The work of Flechsig had a profound influence on myelination studies later conducted by Paul Ivan Yakovlev (1894–1983), and Flechsig's thinking about the association areas played an important role in Norman Geschwind's reinvigoration and expansion of the ideas about higher-order brain function and disconnection syndromes.

In 1892 and 1893, Heinrich Sachs used histological and degeneration studies to accurately define the sagittal stratum that includes, in part, the optic radiation, and he divided it into external and internal segments. He also identified transverse fibers within the occipital lobe that came to bear his name. Wladimir Muratoff (1893a,b; Muratow, 1893) identified a longitudinally oriented subcallosal fasciculus in dogs. In cases of agenesis of the corpus callosum, Onufrowicz (1887) along with his mentor Forel (1881, 1907) became convinced of a fronto-occipital fiber bundle in their erroneous interpretation of what Sachs (1892) and Moriz Probst (1901a) subsequently identified as misdirected callosal fibers.

Apart from his important contributions in the field of aphasiology and cortical localization, Carl Wernicke (1848–1900) published an atlas of myelin-stained serial sections of the human brain in the coronal (1897), axial (1900), and sagittal planes (1903). Projection systems were darkly stained, whereas long association fibers had poor myelin staining properties, with the exception of the cingulum bundle and the uncinate fasciculus, which were prominent. He identified a fasciculus of the caudate nucleus, the superior longitudinal fasciculus lateral to and more lightly staining than the corona radiata, the uncinate fasciculus, the cingulum bundle including a ventral component, and an inferior longitudinal fasciculus that is anatomically identical to the external aspect of the sagittal stratum. He identified a vertical fiber tract intrinsic to the occipital lobe, later named for him, and a "corona radiata temporalis" in the temporal stem, that was also named Wernicke's bundle. Wernicke used this anatomic knowledge to further understand and explain clinical disorders of higher function.

Joseph Jules Dejerine (1849–1917), like Wernicke, contributed significantly to the field of clinical neurology by describing a number of clinical syndromes. In 1895 he published his enduring anatomical work, *Anatomie de systeme nerveux*, in which he de-

scribed the association fiber pathways in detail (figures 2-10 and 2-11) and included scholarly accounts of the historical development of notions concerning the fiber systems. He used myelin-stained normal human material and the Marchi technique to study degeneration in clinicopathological cases to understand which areas of cortex these pathways connect. Dejerine's concepts of the white matter systems have been the preeminent authority on this topic for over a century. A brief summary will not suffice; rather, his conclusions are discussed in detail in the sections of our monograph that deal with each of the individual fiber bundles. His historical accounts and descriptions attempted to resolve the discrepancies regarding the various pathways, and we take our cue from Dejerine in the present work, using contemporary tract-tracing methodology (autoradiography) to try to settle unresolved issues regarding the fiber systems in the monkey brain. Dejerine's student Vialet (1893) also used myelin-stained material to define the transverse fiber systems intrinsic to the occipital lobe, one of which bears his name (the ventral occipital transverse fascicle).

Dejerine matched his anatomical investigations with clinical observations in patients, and his description (Dejerine, 1892) of alexia without agraphia resulting from a lesion of the left occipital lobe together with a lesion of the splenium of the corpus callosum is the first account of a disconnection syndrome. Clinical neurology was emerging as a discipline at this time, and many of the seminal observations and interpretations of Charcot and his students in the latter part of the 19th century dealt explicitly with the clinical consequences of white matter lesions as manifested, for example, in multiple sclerosis.

A greater appreciation of the complexity of the white matter fiber pathways had thus become apparent, and their crucial importance was recognized in linking cortical areas with each other and with subcortical sites, peripheral sensory receptors, and motor effector organs. Santiago Ramón y Cajal in 1933 discussed the understanding at that time[14] and recognized the challenges posed by the lack of adequate information concerning the detailed connections of these areas: "In summary, at this very moment the little we know about the kinds of neuro-neuronal connections in the cerebral cortex agrees in principle with the arrangement of the connections made in other parts of the brain. The elucidation of the manner of connection between the innumerable endogenous, exogenous, collateral, and terminal branches originating in thalamic, callosal, and association fibers in every way constitutes at present an overwhelming problem. It will put to the test the sagacity and patience of many generations of future neurologists" (Cajal, 1933). The era of connectional neuroanatomy would begin to address these deficiencies and further elucidate the role of the fiber systems.

Cortical Cytoarchitecture and Connectional Neuroanatomy

The fibers in the cerebral white matter link different cortical and subcortical areas, and so an appreciation of the organization of cerebral cortex with respect to its architecture and connections is relevant. Cortical architectonics and connectional neuroanatomy are both vast disciplines that cannot be summarized here, but it is useful to consider some major milestones in the development of these disciplines, particularly as they relate to a comprehensive understanding of the white matter tracts.

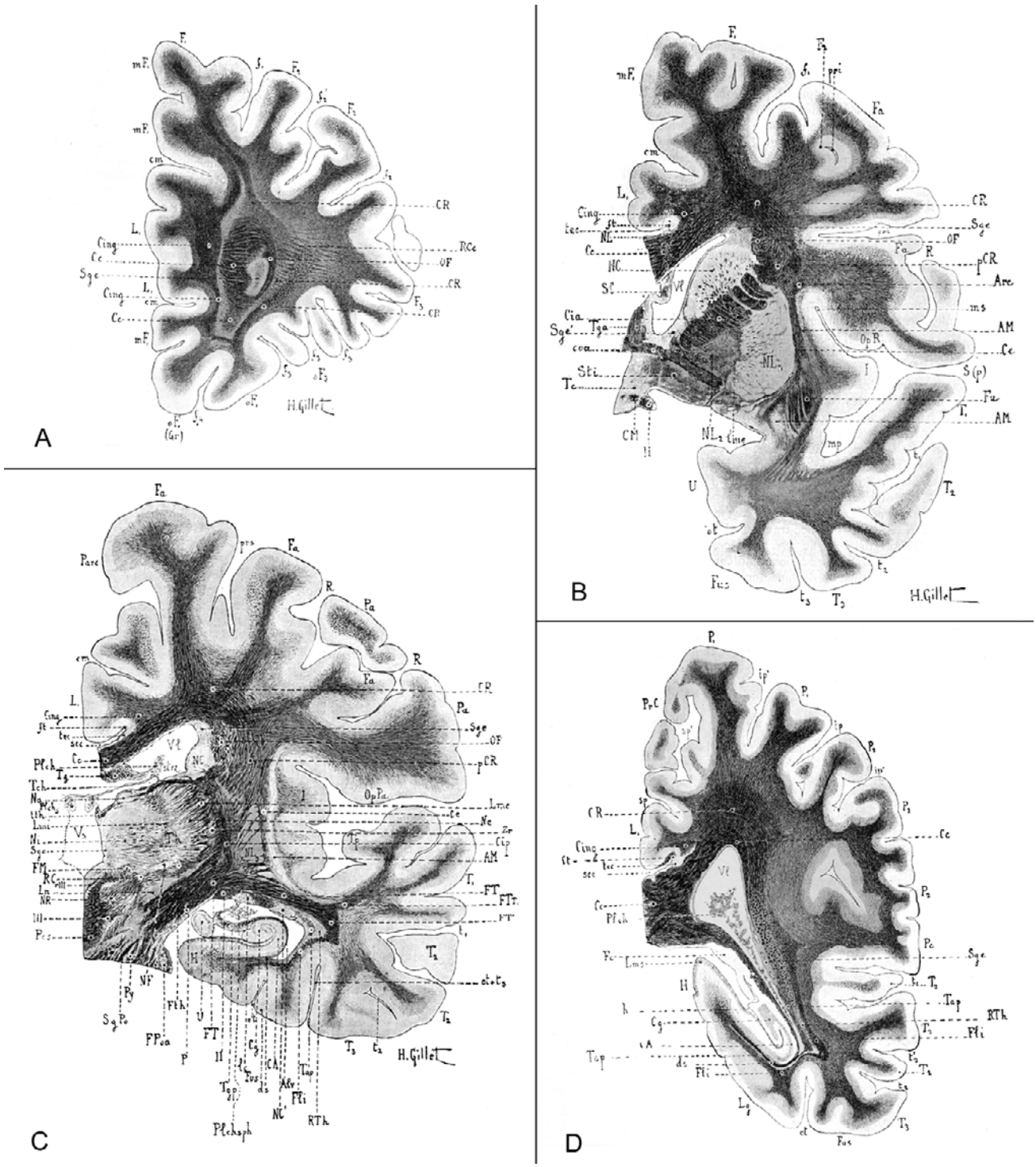

Figure 2-10

Images from Joseph Jules Dejerine's (1895) *Anatomie des centres nerveux* showing coronal sections of human brain stained for myelin. A, Prefrontal region in figure 390, page 785. B, Section through the anterior commissure and rostral temporal lobe in figure 382, page 764. C, Section through the frontoparietal region and thalamus in figure 387, page 774. D, Section through the parieto-occipital region, splenium of the corpus callosum, and the sagittal stratum, figure 383, page 767.

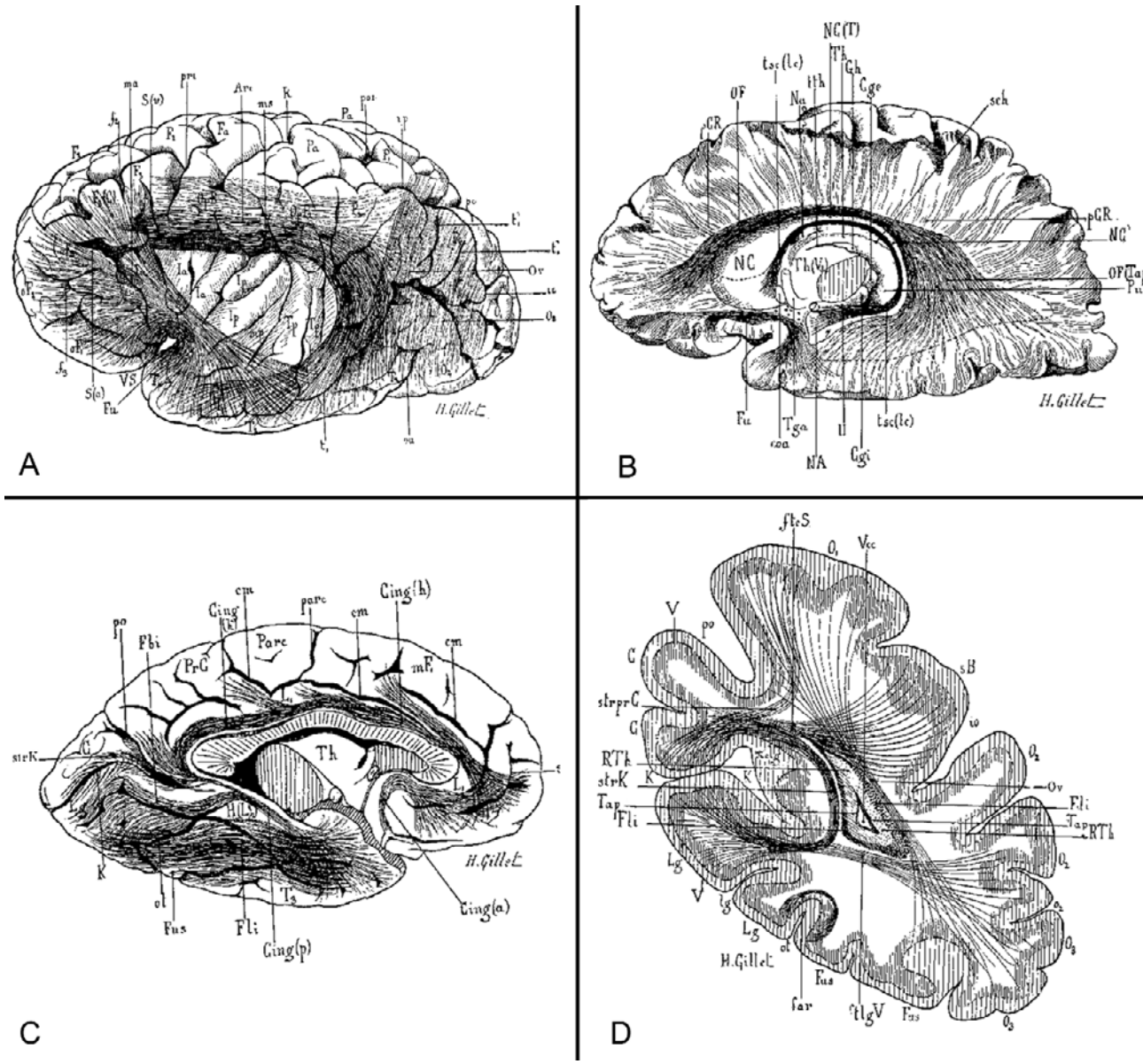

Figure 2-11

Diagrams from Dejerine's (1895) *Anatomie des centres nerveux* summarizing some of the major pathways of the human brain discussed in his work. A, Dejerine's notion of the arcuate and uncinate fasciculi and the vertical occipital fibers in figure 377, page 757. B, The uncinate fasciculus, fronto-occipital fasciculus, and corona radiata are shown in figure 381, page 762. C, The cingulum bundle and inferior longitudinal fasciculus are shown in figure 374, page 752. D, This schematic coronal section depicts the intrinsic fibers of the occipital lobe, including the occipitovertical fascicle, or perpendicular occipital fascicle of Wernicke (Ov), the occipital transverse fascicle of the cuneus of Sachs (ftcS), the occipital transverse fascicle of the lingual lobule of Vialet (ftlgV), the stratum proprium of the cuneus (strprC), and the stratum calcarinum (strK) or U-fiber layer of the calcarine fissure, in figure 389, page 783.

The origins of cortical architectonics were embedded in the notion that the cerebral cortex was functionally heterogeneous, as suggested by Gall and Spurzheim, and anatomically differentiated since the identification by Gennari, Vicq d'Azyr (and Samuel Thomas von Soemmering [1755–1830]; Clarke and O'Malley, 1996, p. 423) of an anatomic difference between the visual area and the remainder of the cerebral cortex. The presence of myelinated fibers within the cerebral cortex was noted in 1840 by Jules-Gabriel-François Baillarger (1815–1890),[15] who mounted thin sections on glass, examined them against the light, and saw lamination in the cerebral cortex for the first time.[16]

The attempts to establish a scientific basis for the system of cortical architecture began with the definitive work using aniline dyes in the monkey by Korbinian Brodmann (1868–1918) in 1905, by Alfred Walter Campbell (1905), Cécile Vogt (1875–1962), and Oskar Vogt (1870–1959) in 1919, and by A. Earl Walker (1938) and Gerhardt von Bonin and Percival Bailey (1947). Architectonic studies in humans were performed by Brodmann in 1909, Constantin von Economo (1876–1931) and Georg N. Koskinas (1925), and Semen Aleksandrovich Sarkisov (1955). These investigators focused on architecture as a specific and defining hallmark of cerebral cortex. Myeloarchitectonic studies of the cortex based on the differential arrangement of the bands of Baillarger were also performed by several investigators (e.g., Hopf, 1954; Vogt and Vogt, 1919). These studies notwithstanding, although architectonic analysis was well accepted for differentiation of subcortical structures in the brainstem, vigorous objections were raised against the architectonic approach being applied to the cerebral cortex during the 1940s and 1950s. These analyses were criticized as being subjective and unreliable, the architectonic differentiation of cortex was considered an isolated anatomic feature of limited value, and the potential significance of this field of inquiry was minimized (e.g., Karl Spencer Lashley [1890–1958]). This type of criticism almost resulted in the premature death of cytoarchitectonics as a discipline. After a lull in the awareness of the relevance of cortical architecture, there was resurgence in the latter part of the 20th century of the appreciation of the importance of this approach (e.g., the work of Friedrich Sanides [1914–1984], Galaburda and Sanides, 1980; Pandya and Sanides, 1973; and Sanides, 1968, 1972; as well as Barbas and Pandya, 1987, 1989; Braak, 1978; Galabura and Pandya, 1983; Hackett et al, 2001; Pandya and Yeterian, 1990; Preuss and Goldman-Rakic, 1991a,b; Rajkowska and Goldman-Rakic, 1995a,b; Seltzer and Pandya, 1978, 1989b; Weller and Kaas, 1987). The relevance of architectonic analysis of the cerebral cortex has subsequently become established in all fields of investigation of the organization and function of the nervous system. In recent years the use of immunocytochemistry and histochemical methods has allowed investigators to further identify subtleties of cortical and subcortical architecture and connections (Huntley and Jones, 1991; Jones, 2003; Morel et al., 1993), and observer-independent methodology has lent further credibility to these approaches (Schleicher et al., 1999). Indeed, cytoarchitectonic analysis is increasingly relevant in the study of structure–function correlations in the human brain when combined with functional imaging data. To this end, Zilles et al. (see Amunts and Zilles, 2001) have suggested that cytoarchitectonic mapping in the human may be based on a definition of areal borders using multivariate statistical analysis, quantitative analysis of similarity and dissimilarity in architecture between cortical areas, and probabilistic mapping of cytoarchitectonic areas in three-dimensional reference space.

Improvements in techniques made it possible to study neural connections in experimental animals with greater precision. This resulted in a vast literature detailing cortical connections in nonhuman primates and other animal models. In the latter part of the 19th and earlier parts of the 20th century, the Marchi method (Marchi and Algeri, 1885) was the principal method used to study neuronal connectivity (e.g., Mettler, Minkowski, Sunderland, Krieg, Crosby, Shower, Hearst, Milch, LeGros Clarke, and Yakovlev). The silver impregnation method of Max Bielschowsky introduced in 1902 represented an improvement upon a similar technique of Cajal. Both the Marchi and Bielschowsky methods were difficult and capricious. The Marchi method was dependent upon degenerating myelin product, and therefore nerve terminals could not be visualized. The Bielschowsky stain did not allow full impregnation of all degenerating fibers. These technical considerations limited the utility of both these methods. The silver impregnation technique introduced by Glees (Glees, 1946; Marsland et al., 1954) was used, for example, by Adey and Meyer (1952), but this method also had limited application because of the difficulty of differentiating intact versus degenerating nerve terminals.

The double silver impregnation technique developed by Walle J.H. Nauta (1916–1994; Nauta and Gygax, 1951, 1954) represented a considerable advance. Unlike the Marchi and Bielschowsky methods, the Nauta-Gygax stain suppressed the distal part of the normal nerve fibers and more readily demonstrated the degenerated nerve fibers. The late 1950s and early 1960s witnessed refinements in this silver impregnation method. The improvements in methodology led to an expansion in the number of anatomical studies being performed; of particular interest here are the corticocortical studies of association areas (e.g., Jones and Powell, 1970; Kuypers et al., 1965; Myers, 1962; Pandya and Kuypers, 1969). This accelerated investigation into cortical connectivity. By the middle and latter part of the 1960s, further improvements in the silver impregnation technique (e.g., Fink-Heimer, 1967; see Heimer, 2003) allowed the visualization of the finer endings of the nerve terminals at the level of the bouton. Several modifications of these methods were used for connectivity studies. These techniques all required the induction of a lesion that would result in focal pathology at a distant site after an appropriate time interval, which could be demonstrated by the silver impregnation. The idiosyncrasies inherent in these methods limited enthusiasm for performing these studies and for the results obtained. Whereas these methods demonstrated the cortical and subcortical areas that were anatomically linked, they could not reliably and consistently demonstrate the fiber pathways that subserve these connections.

The method of strychnine neuronography facilitated the physiological study of cortical connections and was first applied to the study of the sensory cortex in cat and monkey (Dusser de Barenne, 1916, 1924a,b). This approach was further used to examine the visual (McCulloch, 1944), auditory (Bailey et al., 1943a; Petr et al., 1949; Sugar et al., 1948), and somatosensory domains (French, 1948; Sugar et al., 1950), as well as the frontal lobe and limbic system (Pribram et al, 1950; Pribram and MacLean, 1953). In addition, Bailey et al. (1943b) defined physiological connections between remote regions of the cerebral hemispheres in monkey and chimpanzee that suggested they were linked by long association fiber bundles similar to those identified in the human. These studies indicated that area 18 in the dorsal parastriate cortex projected to prefrontal cortex area 8; the inferior temporal region area 20 projected to the parastriate cortex area 18; and

area 38 in the rostral inferotemporal region projected to area 47 in the orbitofrontal cortex. The authors concluded that they had identified the origins and terminations of homologues of long association bundles previously recognized in the human, namely the superior longitudinal fasciculus, the inferior longitudinal fasciculus and vertical occipital fascicle of Wernicke, and the uncinate fasciculus, respectively. Thus the strychnine neuronography method enhanced the understanding of the origins and terminations of cortical connections, but its widespread used was hampered by multiple limitations.

A major technological advance in the field of connectional neuroanatomy occurred in the early 1970s. Whereas previous anterograde tract-tracing methods relied upon the ablation–degeneration and subsequent silver impregnation technique, the autoradiographic method developed by Cowan et al. (1972) represented a novel physiological approach to the tracing of neuronal connections. Moreover, in addition to the visualization of the nerve endings, the radioisotope technique also displayed the course of the axons leading from the injection site to their distant terminations. Freed from the unpredictability of the silver degeneration technique, the isotope methodology readily gained acceptance and became widely used as a method to study anterograde connections. Using this approach, a number of studies in the monkey have outlined corticocortical connections (e.g., Amaral et al., 1983; Amaral and Price, 1984; Baleydier and Mauguiere, 1980; Galaburda and Pandya, 1983; Gattas et al, 1997; Jones et al., 1978; Porrino et al., 1981; Preuss and Goldman-Rakic, 1989; Rockland and Pandya, 1979; Seltzer and Pandya, 1978, 1989a; Tranel et al., 1988; Ungerleider et al., 1989; Van Essen et al., 1986; Weller and Kaas, 1983), as well as subcortical connections (e.g., Asanuma et al., 1983; Giguere and Goldman-Rakic, 1988; Jones and Burton, 1976; Schmahmann and Pandya, 1989, 1991, 1993, 1995, 1997a,b; Schmahmann et al., 2004b; Siwek and Pandya, 1991; Tusa and Ungerleider, 1988; Yeterian and Pandya, 1985; Yeterian and Van Hoesen, 1978). Some of these studies have also delineated hemispheric fiber systems (e.g., Mufson and Pandya, 1984; Petrides and Pandya, 1984, 1988, 2002a; Schmahmann and Pandya, 1992, 1994; Ungerleider et al., 1989), but it has been less widely appreciated that this technique is ideally suited for the study of the origins, trajectories, and terminations of the long association pathways in the experimental animal.

The use of retrograde degeneration as a scientific method for studying connections has been known since the 1800s (e.g., Gudden, Monakow, Nissl). This approach suffered the same limitations as the earlier anterograde degeneration techniques. By the early 1970s, physiological retrograde tract tracing became possible with the use of injected horseradish peroxidase (HRP), which results in labeling of neurons in the cortical and subcortical areas that project to the site of the injection (LaVail and LaVail, 1972). Neurons with HRP that had been transported from the injection site in a retrograde manner were rendered visible by the brown reaction product using diaminobenzidine and were enhanced by the blue reaction product using benzidine dihydrochloride (Mesulam, 1976, 1978) and by conjugating HRP with wheat germ agglutinin (Harper et al., 1980). As effective as this method was for determining neurons of origin that project to the injection site, it did not in general provide a satisfactory visualization of fiber tracts.

Similarly, fluorescent retrograde tracers (Keizer et al., 1983; Kuypers et al., 1980) that were easy to use and allowed one to study projections to multiple areas simultaneously in the same animal, and trans-synaptic viral tract tracing techniques (e.g., Ugolini et al., 1987; Middleton and Strick, 1994) that enhanced the ability to analyze connec-

tions did not provide adequate visualization of the fiber pathways. Within the past several years, other anterograde tracers and mapping techniques have been introduced, including *Phaseolus vulgaris* leukoagglutinin (PHAL; Gerfen and Sawchenko, 1984; Tourtellotte and Van Hoesen, 1992) and biotinylated dextrans (Veenman et al., 1992). Whereas these approaches demonstrate individual axons with great precision, they are not suitable for tract tracing of fiber systems on a larger scale.

A limitation of the autoradiographic technique is that it can be used only in the experimental animal. Magnetic resonance imaging (MRI) in humans can provide exquisite detail of cerebral anatomy *in vivo*, and the further development of MRI techniques promises to reveal anatomic details at a very high level of resolution. As discussed in chapter 1, diffusion tensor imaging, MR tractography, and diffusion spectrum tractography can visualize white matter pathways *in vivo,* but they do not demonstrate the origins or terminations of the pathways. Further, they rely heavily on *a priori* knowledge of the anatomy of these fiber systems based upon the Talairach atlas (Talairach and Tournoux, 1988) and the understanding of the white matter tracts derived from Dejerine's (1895) epic work. Without a clear and accurate notion of where the fiber tracts are expected to lie in the human as determined by experimental work in the monkey, however, spurious results may be produced and misconceptions regarding these white matter bundles are likely to be created or perpetuated. Cognitive and psychiatric manifestations, as well as motor manifestations, following white matter lesions in patients are being identified with increasing sophistication (see Filley, 2001). We hope that these clinical observations and the evolving *in vivo* white matter tractography, together with the understanding of the fiber pathways that our monograph presents, will facilitate insights into the cerebral white matter in humans.

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Approach to the Study of the Fiber Tracts

PART II

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Materials Analyzed

3

The preceding chapter dealt with the attempts by many pioneering investigators to delineate the fiber pathways of the cerebral hemisphere using the techniques available to them, notably gross dissection and lesion-degeneration studies. The current resurgence of interest in the white matter fiber pathways in the normal and diseased states is matched by increasingly accurate methods for the exploration of these tracts, including neuroimaging methods in the human brain, and anterograde tracing techniques in the experimental animal. In this chapter we outline the different methods that we used to study the association, commissural, and projection fiber pathways in the rhesus monkey brain.

Autoradiography

Material was available to us from the brains of 36 adult rhesus monkeys that were used in previous studies. These brains were prepared with the anterograde tract-tracer technique using radiolabeled isotopes.[1] The intensity of the autoradiographic label has remained robust, as the photomicrographs demonstrate. The case numbers and locations of the isotope injections in the brains we have studied are listed in table 3-1 and shown in the diagrams in figure 3-1. The distribution of the isotope-labeled fibers and terminations was charted onto corresponding coronal sections of a standard brain.

Nissl-Stained Template Brain

The brain of a healthy adult rhesus monkey was used to represent the findings in all cases. This brain was embedded in celloidin and prepared with the Nissl stain (cresyl violet).[2]

Cytoarchitecture of Rhesus Brains

Cerebral Cortical Architecture

Cortical architectonic areas were identified on the Nissl-stained sections of the celloidin-embedded template brain. The architectonic features were also verified in each of the experimental cases. The cerebral cortical nomenclature systems used in this work are derived from the maps of Brodmann (1908, 1909) and Bonin and Bailey (1947) and from the following investigators, atlases, and published papers. For visual areas we have followed Gattass and Gross (1981), Ungerleider and Desimone (1986), Colby et al. (1988), Krubitzer and Kaas (1990), and Felleman and Van Essen (1991). For

Table 3-1
Case Numbers by Lobe and Architectonic Area

Parietal Lobe

1. Superior parietal lobule: area PGm, encroaching upon area PEc
2. Superior parietal lobule: medial part of area PEc at the junction of area PE
3. Superior parietal lobule: lateral part of area PEc at the junction of area PE
4. Inferior parietal lobule: caudal part of area PG and in area Opt
5. Inferior parietal lobule: rostral inferior parietal lobule, area PF
6. Inferior parietal lobule: middle part of the parietal operculum

Superior Temporal Region

7. Caudal part of the superior temporal gyrus involving area Tpt
8. Caudal part of the superior temporal gyrus in areas paAlt and Tpt
9. Midportion of area TPO, ventral superior temporal gyrus area TAa, caudal area KA
10. Rostral part of area TS3
11. Areas Pro, TS1 encroaching on TS2

Inferior Temporal Region

12. Ventral part of the temporal lobe, area TE2 and TE3
13. Ventral temporal region, area TF
14. Rostral superior temporal sulcus involving area IPa, lateral border of hippocampus
15. Medial part of the inferior temporal gyrus in area TE1 and TE2
16. Rostral temporal lobe in the midportion of area TE2

Occipital Lobe

17. Medial preoccipital gyrus, medial area 19 (area PO), and area PGm
18. Dorsal preoccipital gyrus, area DP, and upper part of area V4D
19. Dorsal area V4 and adjacent area V4T
20. Ventral preoccipital gyrus above inferior occipital sulcus, in area V4
21. Ventral area V4, with some encroachment in ventral area V3

Cingulate Gyrus

22. Retrosplenial cortex in area 30 and in area 23
23. Rostral cingulate gyrus in area 24

Motor Cortex

24. Frontal operculum in the precentral aspects of areas 1 and 2
25. Ventral area 4, face representation
26. Area 4 behind the arcuate spur, in hand representation
27. Dorsal precentral gyrus area 4, trunk representation
28. Dorsal area 4, foot representation
29. Medial part of the superior frontal gyrus, rostral area MII, face representation

Prefrontal Region

30. Medial surface of the prefrontal cortex involving mainly area 32
31. Above the midportion of the principal sulcus in area 46d
32. Middle part of ventral area 46 in both the sulcal and gyral cortices
33. Orbital frontal cortex in the orbital part of area 47/12

Premotor Region (cases used in chapter 22 only)

34. Area ProM in the frontal operculum
35. Ventral premotor area 6v
36. Dorsal premotor area 6d

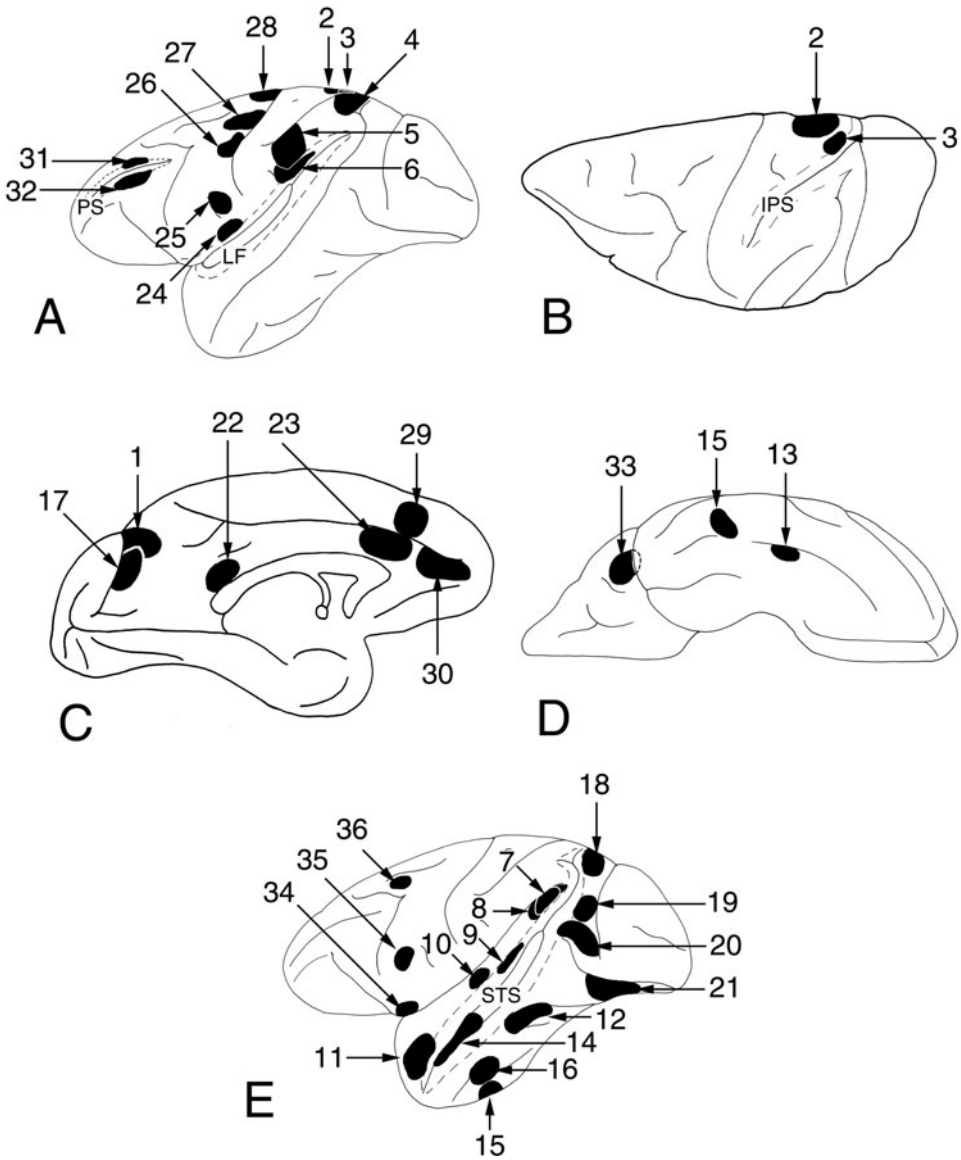

Figure 3-1

Summary diagrams of the cerebral hemisphere of a rhesus monkey showing the locations of the isotope injections in the experimental cases studied. A, Lateral view of the cerebral hemisphere with the principal sulcus (PS) and the Sylvian (lateral) fissure (LF) opened to show the buried cortex. Injections are in the parietal, precentral motor, and prefrontal regions. B, Dorsal view showing the injection sites in the superior parietal lobule. The intraparietal sulcus (IPS) is opened to expose the hidden cortex. C, Medial view of the hemisphere with injections in the medial parietal, medial preoccipital, medial prefrontal, and cingulate cortices. D, Basal surface of the hemisphere, with injections in the ventral temporal and orbitofrontal regions. E, Lateral view of the hemisphere with the superior temporal sulcus (STS) opened to reveal the cortex in its banks, and injections in the superior and inferior temporal regions, parastriate cortices, and premotor region. The numbers correspond to the cases in this series. Cases 1 through 33 were examined in detail throughout the monograph; cases 34 through 36 were used to determine the location of commissural fibers within the corpus callosum, as discussed in chapter 22.

parietal lobe we have followed Pandya and Seltzer (1982) and Seltzer and Pandya (1980), for the superior temporal regions Seltzer and Pandya (1978, 1989b) and Galaburda and Pandya (1983), for the superior temporal sulcus and inferotemporal area Seltzer and Pandya (1978), for the parahippocampal gyrus Rosene and Pandya (1983) and Blatt et al. (2003), for the prefrontal cortex Petrides and Pandya (1994), and for the cingulate gyrus Vogt et al. (1987). *The Rhesus Monkey Brain in Stereotaxic Coordinates* (Paxinos et al., 1999) was also used to assist with the identification of architectonic regions and for comparison with contemporary architectonic nomenclatures.

Subcortical Nuclei and Nuclear Divisions

Standard nomenclature systems are used to designate the major subcortical gray matter structures. Nomenclature used in the text to describe the thalamic nuclear subdivisions is derived from Olszewski (1952), but we also consulted the nomenclatures of Jones (1985) and Ilinsky and Kultas-Ilinsky (1987). Thalamic nuclear subdivisions are not identified in the photomicrographs and diagrams, but the descriptions of the thalamic terminations are included in the text and correspond to published anterograde studies of corticothalamic terminations (e.g., Asanuma et al., 1985; Beck and Kaas, 1998; Fitz-Patrick and Imig, 1978; Graham et al., 1979; Künzle and Akert, 1977; Pandya et al., 1994; Selemon and Goldman-Rakic, 1988; Yeterian and Pandya, 1985, 1988, 1997). Pontine nuclear subdivisions are according to Sunderland (1940a), Nyby and Jansen (1951), and Schmahmann and Pandya (1989).

Many of the cortical areas studied in this work have projections to the nuclei of the basis pontis. These are presented briefly along with the report of the trajectories of the subcortical fiber bundles in the individual case descriptions. A number of investigators have studied these corticopontine pathways, and reference to their work, as well as detailed analyses of the projection patterns in the cases analyzed in the present material, may be found in the previously published reports of Schmahmann and Pandya: posterior parietal cortices (1989), superior temporal region (1991), inferior temporal region (1991, 1993), parastriate and parahippocampal areas (1993), prefrontal cortices (1995, 1997a), and precentral motor and supplementary motor areas (Schmahmann et al., 2004b).

White Matter Architecture

The arrangement of the fibers in the white matter has traditionally been studied using stains that specifically identify myelin. We have used a novel approach, however, that relies on Nissl-stained sections to locate and identify the fiber pathways of the cerebral hemispheres. We studied the Nissl-stained template brain under 40× magnification and evaluated the orientation of the axons within the fiber bundles, including their direction and their position relative to cortical and subcortical landmarks. In addition, the orientation, packing density, and patterns of arrangement of the glia within the white matter were useful for distinguishing the fiber systems. The differential arrangement of fibers using this technique is readily apparent, and the outline of the different fiber pathways is clearer than that seen with conventional myelin stains that mask the fine discriminative detail (figures 3-2 and 3-3). Using this technique we identified major fiber structures, namely the corpus callosum, sagittal stratum, and internal capsule. In addi-

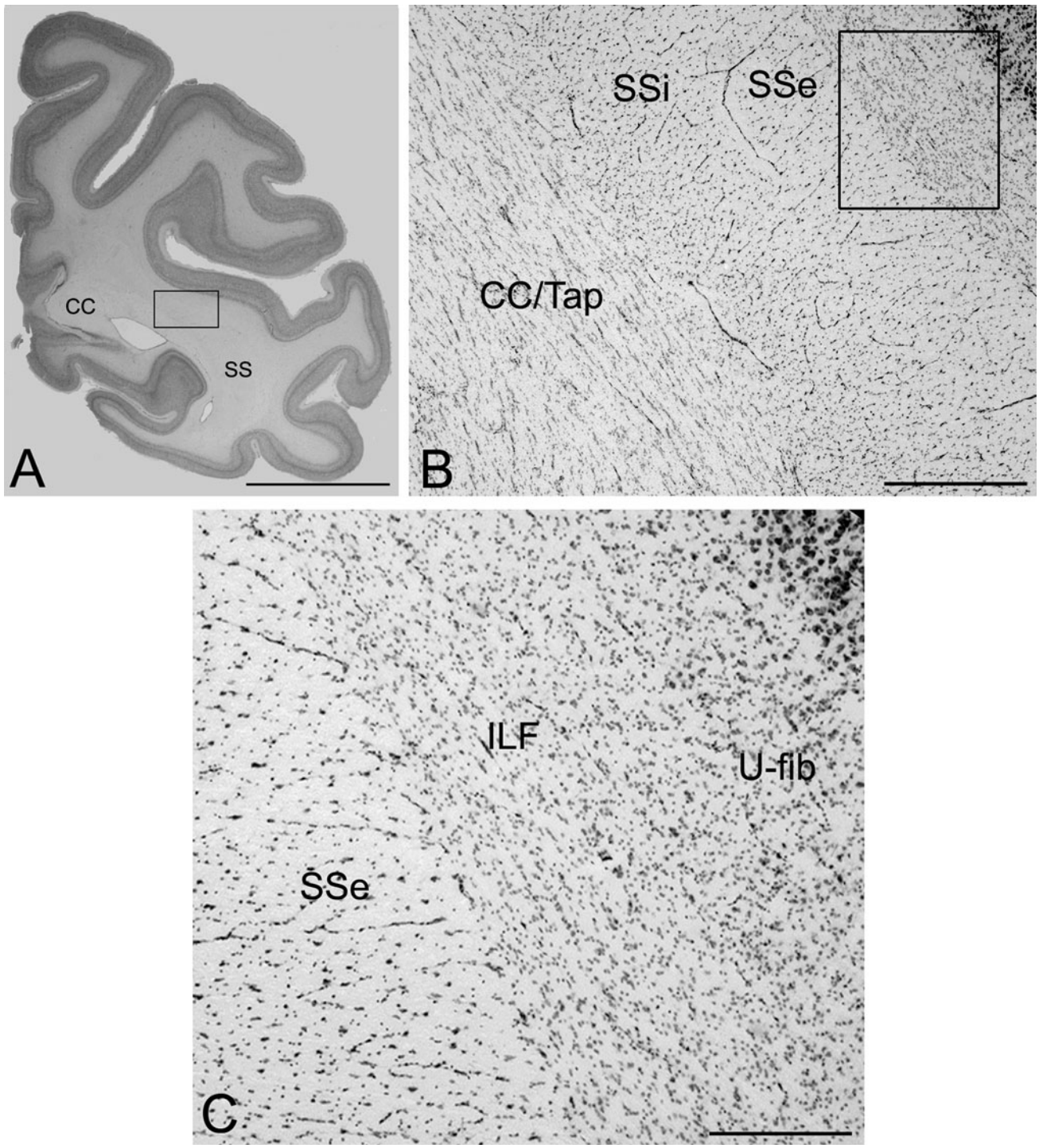

Figure 3-2

Light-field photomicrographs prepared with a Nissl stain. A is a coronal section through the parietal lobe (Mag = 0.5×, bar = 0.5 cm). B is a high power photomicrograph of the rectangular area outlined in A showing the differential distribution of glia in the tapetum of the corpus callosum (CC/Tap), the internal segment of the sagittal stratum (SSi), and the external segment of the sagittal stratum (SSe) (Mag = 2×, bar = 1 mm). C is a higher power magnification of the area outlined in B showing the differential arrangement of the glia in the SSe, the inferior longitudinal fasciculus (ILF) and the local U-fibers (U-fib) (Mag = 4×, bar = 0.5 mm).

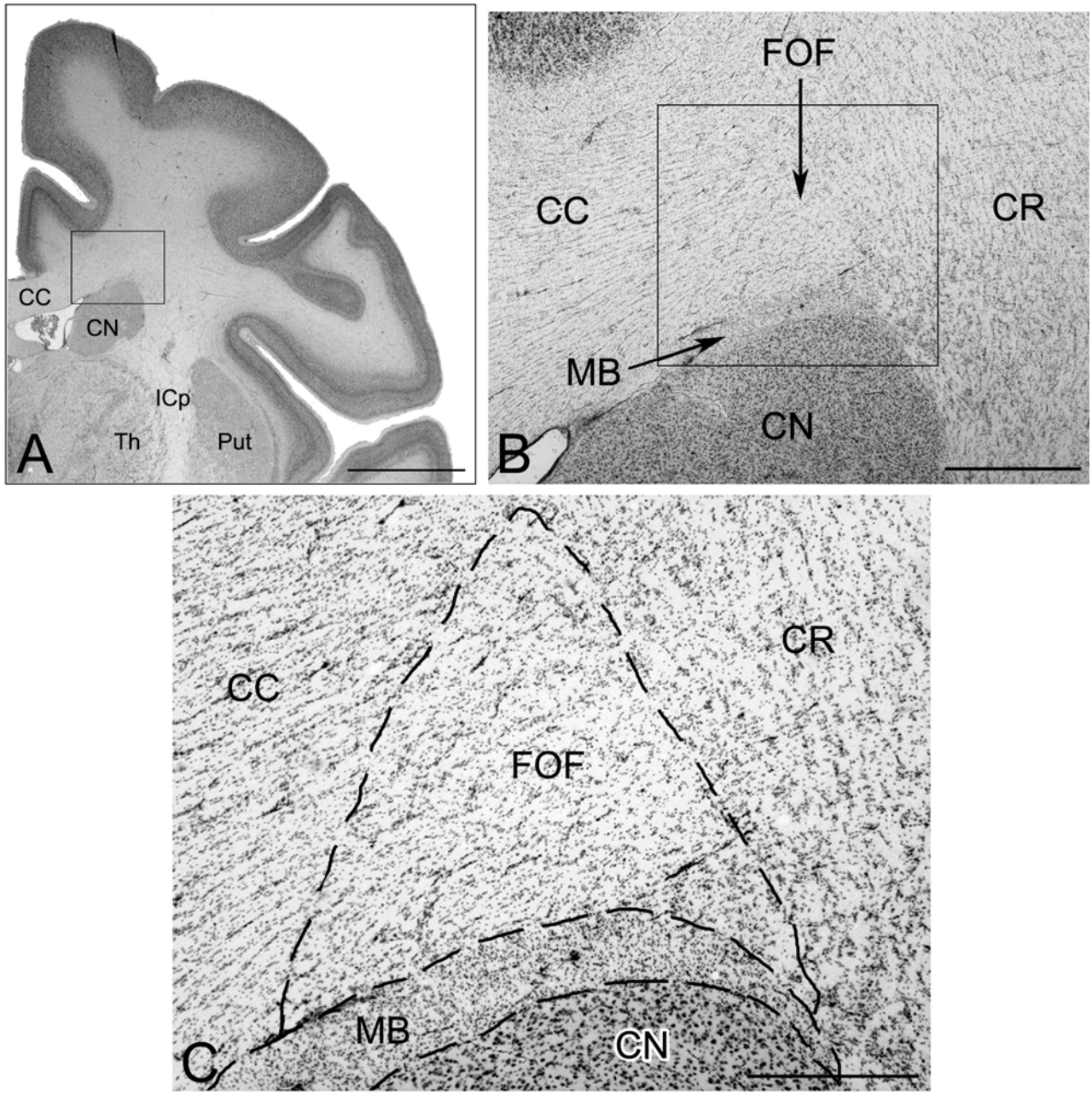

Figure 3-3

Light-field photomicrographs prepared with a Nissl stain. A is a partial view of a coronal section at the fronto-parietal junction (Mag = 0.5×, bar = 1 cm). CC, corpus callosum; CN, caudate nucleus; ICp, posterior limb of the internal capsule; Put, putamen; Th, thalamus. B is a high power photomicrograph of the area outlined in A showing the differential organization of the glia in the corpus callosum, corona radiata (CR) fronto-occipital fasciculus (FOF) and the subcallosal fasciculus of Muratoff (Muratoff bundle, MB) (Mag = 2×, bar = 1 mm). C is a higher magnification view of the area outlined in B demarcating the boundaries of the fronto-occipital fasciculus (FOF) and the subcallosal fasciculus of Muratoff (MB) (Mag = 4×, bar = 0.5 mm).

tion, we could distinguish the subcallosal fasciculus of Muratoff, the fronto-occipital fasciculus, the superior longitudinal fasciculus (SLF) and its three divisions, SLF I, SLF II, and SLF III, the middle longitudinal fasciculus lying in the white matter of the superior temporal gyrus, the inferior longitudinal fasciculus in the parieto-occipital and temporal lobes, and the uncinate fasciculus, extreme capsule, and arcuate fasciculus. The corticosubcortical bundle that divides into corticothalamic and corticopontine/corticospinal systems could also be distinguished using this methodology, having been guided by the experimental isotope cases. This approach helped define the stem portion of the major fiber pathways and allowed the tracts to be distinguished from each other. The anatomical definition of the boundaries of the fiber systems was then able to provide a framework within which the constituents of the fiber pathways could be determined in the different brains.

Rationale for Use of a Standard Template Brain

To understand the organization of the different fiber bundles within the cerebral white matter and to attempt to determine the topographic arrangement of fibers within the fiber bundles, it was necessary to compare the location of the fibers between different experimental cases. This was accomplished by using a single template brain to represent the data. For each experimental case, the autoradiographic data determined by dark-field microscopy were charted directly onto drawings of equivalent coronal sections of the template brain. This method facilitated the comparative analysis of the organization of the fiber pathways in the different experimental cases.

Selection of Template Brain Sections

Twenty-one coronal sections from the normal brain in the rostrocaudal axis were selected to represent the findings for the majority of cases studied. In some instances, notably to represent the motor cases in which most of the fiber pathways dissipate within a short rostrocaudal distance, two additional intervening sections were used. Each section was selected to represent a particular anatomic feature within the coronal level identified. Thus, for example, template brain section 41 is at the genu of the corpus callosum, section 65 contains the anterior commissure as it crosses midline, section 78 reflects the most rostral part of the thalamus, section 89 contains the rostral tip of the intraparietal sulcus and the midpart of the lateral geniculate nucleus, and in section 113 the caudal end of the splenium of the corpus callosum is evident.

Drawing of Template Sections

The selected sections were traced at 9× on an Aus-Jena overhead magnification system. Sections delineated the outlines of the cortex and boundary of the white matter, the ventricular system, and the subcortical nuclei. In addition, the locations of the major fiber tracts such as the corpus callosum and anterior commissure were identified at this

low-power magnification, whereas light microscopy was required for identification of less obvious fiber systems.

Selection of Matching Coronal Sections of the Experimental Brains with Reference to the Template Brain

The preliminary step in the analysis of the experimental brains was to determine which rostrocaudal section corresponded with the selected sections in the template brain. Slides for each experimental case were studied, and sections were chosen that corresponded to the anatomical landmarks identified on the template sections. In some cases it was apparent that the plane of coronal section did not match the corresponding section from the template brain exactly. Further, individual variation of sulcal and gyral pattern at this gross morphological level was also observed. In these instances, the sections that corresponded most closely with the essential anatomical features of the template section were chosen. In rare instances, the mismatch between the experimental case and the template were troublesome enough that autoradiographic findings identified on the experimental slide could not be completely represented on the corresponding template section. In these sections, autoradiographic information was transferred to the adjacent template brain section that most closely correlated with the observed finding in the experimental case.

Identification of Autoradiographic Staining, and Transfer of Data onto the Template Brain

The selected sections from the experimental cases were studied under dark-field and light-field microscopy. Labeled fibers were identified under dark-field microscopy at a magnification of 4× and 10×. Light-field microscopy was used to verify the location of the labeled fibers within the identified fiber tracts. Sections adjacent to those selected for charting were studied as well to help understand the details of the fiber systems.

Registration marks were placed on the tracing of each template section previously drawn using the overhead magnification system. These drawings were then photocopied, and these copies were used to chart the labeled fiber pathways and terminations in the experimental cases. Isotope-labeled fibers and terminations in each experimental slide were hand-drawn on the corresponding template section. The precise location, orientation, and extent of the fibers were assessed by visual inspection. The corresponding location on the template of the fibers in the experimental brain was derived from the similarity of the sections of the template brain and the experimental brain, and from the determination by glial pattern of the location of the fiber bundles both within the template brain and in the experimental brain.

Preparation of Line Diagrams

Outlines of the template sections, including the registration crosses, were traced onto vellum using Koh-I-Noor Rapidograph pens and scanned into Adobe Photoshop 5.5. The hand-drawn charting (on the template) of the fibers in each section of the exper-

imental cases was then traced in a similar manner. These depictions of the fibers were then scanned into Adobe Photoshop, and the background was rendered invisible. The fiber tracings with the registration marks were then overlaid onto the template brain, the registration marks were aligned using the "Free Transform" and "Move" tools in Photoshop, and the fiber tracing and template outline were then merged in the final illustration. Labels and arrows were placed on the illustrations using Adobe Photoshop 5.5 or Adobe Illustrator 8.0.

The composite illustrations of the fibers within each of the major cerebral hemispheric lobes were rendered by adding one additional feature to the above method. Fibers in each case were color-coded in Photoshop by selecting the fibers, using the "Fill" tool to give them a chosen color, and then overlaying them onto the template brain using the registration marks as described above. In this manner, the cases within a single lobe could be overlaid onto the same template and the location of the fibers compared from one case to another, as depicted in the summary diagrams for the cases in each lobe (e.g., rostral vs. caudal regions in the parietal lobe). Likewise, the fibers emanating from the different lobes were then color-coded for use in the final summary series of coronal sections (prefrontal region coded red, parietal lobe coded purple, and so forth). In the chapters devoted to individual bundles, the fibers in each experimental case were copied and pasted onto the outlines of the bundle derived from the final composite color figure.

Photomicrography

Dark-field photomicrographs of the fiber pathways and terminations were obtained by using a Nikon Eclipse E800 microscope equipped with a 0.5× stage. Images were captured by a Spot digital camera (Diagnostic Instruments, Inc.) and imported into Photoshop 5.5. Low-power (0.5×) or high-power (4×) magnification images were merged in photomontages, and background artifact in the image was removed using the "Rubber Stamp" tool in Photoshop. Photomicrographs were labeled using Adobe Illustrator 8.0. Light-field microscopic images of the template brain were obtained using the same equipment and computer software.

It may be useful to compare the sections of the template brain used in this work with those in *The Rhesus Monkey Brain in Stereotaxic Coordinates* (Paxinos et al., 1999). Levels of coronal section in our work correspond to those of the Paxinos atlas in the following manner. In this work, sections 20 through 165 are derived from 145 rostral-to-caudal sections, prepared in the coronal stereotaxic plane, at a thickness of 36 to 40 μm, every 10th section processed as described above. In Paxinos et al. there are 135 sections (in figures 7 through 142), prepared in the stereotaxic plane with respect to the interaural line, at a thickness of 45 μm, every 10th section processed. Our section 20 corresponds to Paxinos figure 7 at interaural 37.83 mm, bregma 15.93 mm. Our Section 165 corresponds to Paxinos figure 142, interaural −23.55 mm, bregma −45.45 mm. The most rostral part of the genu of the corpus callosum in our template (section 38, also shown in section 41) corresponds to Paxinos figure 24, interaural 30.00 mm, bregma 8.10 mm. The most caudal part of the splenium of the corpus callosum in our template (section 113) corresponds to Paxinos figure 92, interaural −0.65 mm, bregma −22.55 mm. The anterior commissure in our template (section 65) corresponds to Paxinos figure 50, interaural 18.30 mm, bregma −03.60 mm.