

Principles of Behavioral and Cognitive Neurology

SECOND EDITION

M.-Marsel Mesulam

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Preface

The contributors to the first edition of this book were encouraged to emphasize principles rather than details. They were so successful that the book went through eight printings without appearing to become obsolete. Eventually, however, it became clear that new facts needed to be incorporated into a second edition. The magnitude of this venture was not fully realized until after the current project was initiated. Even authors whose task appeared to be as simple as updating an already excellent chapter decided to undertake an extensive and often complete rewriting. The second edition retains the spirit and philosophy of the first, but with an almost completely new content.

The first edition was published in 1985, at a time when basic neuroscience was undergoing several crucial developments: The connections of the monkey brain were being charted with axonally transported tracers, details of chemical neuroanatomy were being revealed with immunohistochemistry, neuronal physiology was being explored with single-unit recordings in behaving animals, and primate models of human neuropsychological syndromes were being established with the help of targeted ablations. These advances were incorporated into the first edition of this book and lent a new sophistication to the traditional interpretation of brain-behavior relationships. Functional imaging remained somewhat peripheral in the first edition. Although the methodology had been introduced a decade earlier, it had not yet started to yield truly novel information beyond what had been established by traditional behavioral neurology.

This second edition was written during another period of self-renewal for behavioral neurology, this time driven predominantly by developments in functional magnetic resonance imaging (fMRI). In the past, functional imaging was almost entirely confined to positron emission tomography. This expensive technology was available to very few centers, which became the privileged gatekeepers of research in this area. The advent of fMRI led to the radical democratization of this field. In many parts of the world, qualified investigators working in the vicinity of a research-friendly clinical radiology department can now access modern functional imaging technology. Although fMRI is not perfect, its widespread availability, flex-

ibility, and anatomical resolution have fueled much of the recent excitement in this field.

Research in behavioral neurology and neuropsychology had traditionally focused on patients with focal brain lesions. Paradigmatic patients such as Hughlings Jackson's Dr. Z., Paul Broca's Tan-tan, John Harlow's Phineas Gage, and Brenda Milner's H.M. provided lasting insights into the behavioral neuroanatomy of emotion, language, comportment, and memory. Despite these achievements, however, the epistemological limitations inherent in determining the function of an area on the basis of the dysfunction caused by its destruction are widely acknowledged. These limitations can be overcome by combining the clinical approach with functional imaging. Within the context of such a dual approach, focal lesions help to infer the location of areas that are critical for a given cognitive skill. The functional imaging of neurologically intact subjects performing the same cognitive task helps to assess the validity of these inferences and reveals the additional areas that participate in the neural coordination of that cognitive operation. The integration of these two complementary approaches leads to the identification of the large-scale neural networks that subserve individual cognitive domains.

There was a time when the cognitive scientists did not know much about the brain and the behavioral neurologist knew even less about cognitive neuroscience. The availability of functional imaging has changed this situation and has encouraged collaborative interactions between these two disciplines. The behavioral neurologist, who is now in a position to perform imaging studies on neurologically intact subjects, needs the expertise of the cognitive scientist for hypothesis-driven research and paradigm design. In turn, the cognitive scientist looks to the clinician for access to patients with focal lesions and for clinically based constraints (reality checks) to keep the interpretation of functional imaging experiments within the bounds of plausibility. This new and flourishing alliance of behavioral neurology/neuropsychology/neuropsychiatry with cognitive science has played a pivotal role in the further modernization of this field. Through this alliance, the cognitive scientist has become a bit of a behavioral neurologist, and the behavioral neurologist a bit of a cognitive scientist. The addition of the word "cognitive" to the title of this edition reflects this trend.

In contrast to the spectacular advances that have taken place in revealing the functional landscape of the human brain, little progress has been made in understanding its connectivity. Two levels of neural connectivity contribute to the functional organization of the brain. First, genetically determined axonal connections specify the type of information that a given area will process. Second, experience-induced modifications in the synaptic strengths of these connections enable the gradual accumulation of a knowledge base that is unique for each individual. Although corticocortical and corticosubcortical connections are very well delineated in the monkey brain, there is almost no corresponding information for the human brain. The literature tends to ignore this major gap and gives the misleading impression that the human brain is like a large monkey brain with similar, if not identical, connections. Anatomical, electrophysiological, imaging-based, and computational methods are currently being developed to explore the connectivity of

the human brain. These approaches are at embryonic but promising stages. This is an area that will almost undoubtedly witness very significant advances in the next decade.

Experience-induced modifications of synaptic strengths are particularly difficult to identify. We tend to think of plasticity as a phenomenon confined to early life. In fact, dendritic and synaptic remodeling occurs throughout the life span and helps us learn new associations, adapt to new situations, and compensate for the wear and tear of everyday life. These dynamic aspects of brain structure are very poorly understood, even in simple animal models. A deep understanding of exactly how a new face or new word alters the synaptology of the human brain is unlikely to become available for decades to come. Major technological and conceptual leaps in the basic neurosciences will be required to initiate progress in this aspect of human neurobiology.

In these cost-conscious times, clinicians are asked to justify their existence by the value they add to patient care. The behavioral neurologist has traditionally been consulted to localize brain lesions, determine whether symptoms which seem to defy plausibility (such as those of temporolimbic epilepsy or Capgras's syndrome) are neurological (organic) or psychiatric, and chart a course for treatment and rehabilitation. The remarkable advances in neuroimaging may initially seem to have marginalized the contributions of the clinician to lesion localization. It is worth considering, however, that a specialized understanding of brain-behavior relationships is often necessary to assess the relevance of neuroimaging results. In the dementias, furthermore, early diagnosis depends on the neuropsychological detection of abnormalities at a time when imaging studies can be entirely normal. Insights into the intricacies of neurobehavioral syndromes and into their modes of recovery also fall within the expertise of clinicians in this field. This specialized knowledge improves the quality of differential diagnosis, prognosis, and rehabilitation planning. The behavioral neurologist and neuropsychiatrist provide additional expert guidance for the pharmacological treatment of cognitive and behavioral impairments. Considering the large number of medical and neurological diseases that impair mental function, it would seem that the services of the behavioral neurologist, neuropsychologist, and neuropsychiatrist will continue to attract considerable demand.

This second edition maintains the general structure and objectives of the first. The chapters are comprehensive and authoritative. The purpose is to provide a clinically inspired but scientifically guided approach to behavioral and cognitive neurology. Chapter 1 provides a broad overview of behavioral neuroanatomy as a background for all the other chapters. This chapter also includes a review of frontal syndromes, the limbic system, hemispheric asymmetry, and large-scale distributed networks. Chapter 2 offers a systematic approach to formal and bedside neuropsychological testing. Chapters 3–7 contain detailed reviews of confusional states, neglect syndromes, memory disorders, aphasia-alexia-agraphia, aprosodia, and complex visual deficits. They link clinical observations to the neurobiology of the relevant syndromes. The chapters on language and memory have new authorship in this edition. Chapters 8–10 focus on diseases of great interest to behavioral and

cognitive neurology, namely temporolimbic epilepsy, major psychiatric syndromes, and the dementias. The last two of these chapters, those on the psychiatric syndromes and dementia, are new and address areas that were not covered in the first edition.

I want to thank Fred Plum who asked me to edit the first edition and Fiona Stevens, Susan Hannan, and Nancy Wolitzer who have skillfully guided the transformation of this second edition from manuscript to finished book.

Chicago, Ill.
May 1999

M.-M. M.

Preface to the First Edition

One factor that has contributed prominently to the rapid growth and evolution of contemporary behavioral neurology is the distinctly multi-disciplinary approach to patient care and research. The phenomenal progress in the basic neurosciences, for example, has provided a source of new direction and enthusiasm for the clinician. In turn, clinical observations are once again beginning to guide basic experimentation, as they had done so fruitfully during the earlier days of both disciplines. Many of the recent developments in the areas of attention, emotion, memory, and dementia owe their impetus to this fertile interaction.

Since the single most fundamental aspect of behavioral neurology is the systematic assessment of mental state, the neuropsychologist has played one of the most important roles in the development of the entire field. The relationship between psychiatry and neurology is also central to behavioral neurology. Although this interaction is not new, it is undergoing a welcome revival. For example, temporo-limbic epilepsy is now regularly included in the differential diagnosis of atypical psychiatric problems; some cases of shyness and childhood depression have been linked to a developmental right hemisphere dysfunction; and it is now generally accepted that substantial alterations of mood, personality, and comportment may arise as the sole manifestation of focal injury not only in the frontal lobes but also in various parts of the right hemisphere. These are only some of the developments that have fueled the intensity of the interchange between psychiatry and neurology.

This is not to say that there is an inexorable movement toward reclassifying all psychiatric diseases within the neurologic nosology. In fact, for the vast majority of patients who seek outpatient psychiatric help, a neurologic approach is no more useful (or desirable) than a chemical analysis of the ink would be for deciphering the meaning of a message. However, new discoveries on the cerebral organization of emotion and personality are prompting the inclusion of neurologic causes into the differential diagnosis of many conditions that have traditionally been attributed to idiopathic psychiatric disorders.

Attitudes that once considered the organic approach as the insensitive sledgehammer of psychiatry and the area of behavior as the soft underbelly of neurology

are rapidly changing. Behavioral neurology is now firmly established as a *bona fide* specialty that includes, among other fields of interest, the borderland area between neurology and psychiatry. It also provides an outlook that focuses on the behavioral consequences of almost all neurologic diseases and of many medical conditions that influence brain physiology. The clinical mandate of behavioral neurology is vast and its future is bright. The growth of this field promises to be of major benefit to a large group of patients, who can hope to receive a new understanding for conditions that have not been of central interest to the mainstream of modern medical, neurologic, and psychiatric practices. These developments are also likely to have a considerable impact on the scientific investigation of brain-behavior relationships.

This book aims to provide a background for some of the major areas in behavioral neurology. Chapter 1 contains a survey of anatomic and physiologic principles that guide the interpretation of brain-behavior interactions. Chapter 2 gives an overview of the mental state assessment and its correlations with cerebral damage. This chapter also places a special emphasis on the examination of elderly and demented patients. Chapters 3 through 7 contain in-depth analyses of major behavioral areas: attention, memory, language, affect, and complex perceptual processing. Chapter 8 is somewhat unique in dealing with a single disease process. This appeared justified in view of the remarkable spectrum of psychiatric and endocrinologic conditions that are seen in conjunction with temporolimbic epilepsy. Chapters 9 through 11 survey recent advances in the behavioral application of evoked potentials, regional metabolic scanning, and quantitative computerized tomography.

Each chapter in this book contains a broad range of information, which can provide not only an introductory background for clinicians who are new to the field but also an update for the expert. However, this book will not accomplish its full purpose unless it also proves useful to the basic neuroscientist who is interested in bridging the gap between the experimental laboratory and the human brain.

During the preparation of this book, it has been a pleasure to work with Fred Plum, M.D., Editor-in-Chief of the Contemporary Neurology Series, Sylvia K. Fields, Ed.D., Senior Medical Editor at F.A. Davis, Ann Huehnergath, Production Editor, and the other F.A. Davis staff members who have directed the production process. I also want to thank my secretary, Leah Christie, who diligently participated in the preparation and editing of almost every chapter in this book.

M.-M. M.

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Contributors

DAVID BEAR, M.D.
Director of Telepsychiatry
Acadia Hospital
Professor of Psychiatry
University of Massachusetts
Worcester, Massachusetts, USA

ANTONIO DAMASIO, M.D., PH.D.
M.W. Van Allen Professor and Head
Department of Neurology
University of Iowa College of Medicine
Iowa City, Iowa, USA

HANNA DAMASIO, M.D.
Professor and Director
Human Neuroanatomy and Neuroimaging
Laboratory
Department of Neurology
University of Iowa College of Medicine
Iowa City, Iowa, USA

HANS J. MARKOWITSCH
Professor
Abteilungssprecher
Facultät für Psychologie und
Sportwissenschaft
Abteilung für Psychologie
Universität Bielefeld
Bielefeld, Germany

M.-MARSEL MESULAM, M.D.
(EDITOR)
Ruth and Evelyn Dunbar Professor of
Neurology and Psychiatry
Director, Cognitive Neurology and
Alzheimer's Disease Center
Northwestern University Medical School
Chicago, Illinois, USA

MARGARET G. O'CONNOR, PH.D.
Director of Neuropsychology
Behavioral Neurology Unit
Beth Israel Deaconess Medical Center
Assistant Professor of Neurology
Harvard Medical School
Boston, Massachusetts, USA

ROBERT POST, M.D.
Chief of Biological Psychiatry Branch
National Institute of Mental Health
Bethesda, Maryland, USA

MATTHEW RIZZO, M.D.
Professor, Department of Neurology
Division of Behavioral Neurology &
Cognitive Neuroscience
University of Iowa College of Medicine
Iowa City, Iowa, USA

ELLIOT F. ROSS, M.D.
Professor, Department of Neurology
University of Oklahoma Health Science
Center
Director, Center for Alzheimer's and
Neurodegenerative Disorders
Department of Veterans Affairs Medical
Center
Oklahoma City, Oklahoma, USA

DONALD L. SCHOMER, M.D.
Chief, Division of Clinical
Neurophysiology and the
Comprehensive Epilepsy Program
Associate Professor of Neurology
Department of Neurology
Beth Israel Deaconess Medical Center
Boston, Massachusetts, USA

MARGITTA SEECK, M.D.
Department of Neurology
University Hospital of Geneva
Geneva, Switzerland

PAUL SPIERS, PH.D.
Visiting Scientist
Clinical Research Center
Massachusetts Institute of Technology
Boston, Massachusetts, USA

DANIEL TRANEL, PH.D.
Professor and Chief, Benton
Neuropsychology Laboratory
Department of Neurology
Division of Behavioral Neurology &
Cognitive Neuroscience
University of Iowa College of Medicine
Iowa City, Iowa, USA

SANDRA WEINTRAUB, PH.D.
Associate Professor and
Head of Neuropsychology, Northwestern
University Medical School
Department of Psychiatry and Behavioral
Sciences
Cognitive Neurology and Alzheimer's
Disease Center
Northwestern University
Chicago, Illinois, USA

Behavioral Neuroanatomy

Large-Scale Networks, Association Cortex, Frontal Syndromes, the Limbic System, and Hemispheric Specializations

M.-MARSEL MESULAM

Faced with an anatomical fact proven beyond doubt, any physiological result that stands in contradiction to it loses all its meaning. . . . So, first anatomy and then physiology; but if first physiology, then not without anatomy.

—BERNHARD VON GUDDEN (1824–1886), QUOTED BY KORBINIAN BRODMANN, IN LAURENCE GAREY'S TRANSLATION

I. INTRODUCTION

The human brain displays marked regional variations in architecture, connectivity, neurochemistry, and physiology. This chapter explores the relevance of these regional variations to cognition and behavior. Some topics have been included mostly for the sake of completeness and continuity. Their coverage is brief, either because the available information is limited or because its relevance to behavior and cognition is tangential. Other subjects, such as the processing of visual information, are reviewed in extensive detail, both because a lot is known and also because the information helps to articulate general principles relevant to all other domains of behavior.

Experiments on laboratory primates will receive considerable emphasis, especially in those areas of cerebral connectivity and physiology where relevant information is not yet available in the human. Structural homologies across species are always incomplete, and many complex behaviors, particularly those that are of greatest interest to the clinician and cognitive neuroscientist, are either rudimentary or absent in other animals. Nonetheless, the reliance on animal data in this chapter is unlikely to be too misleading since the focus will be on principles rather than specifics and since principles of organization are likely to remain relatively stable across closely related species.

The nature of the relationship between brain structure and behavior is a central theme for all chapters in this book. Neuroscience texts tend to highlight the relatively invariant relationships between anatomy and function. Damage to the optic

tract or striate cortex, for example, always leads to a contralateral homonymous hemianopia and a thoracic cord transection always leads to paraplegia and incontinence. The approach to cognition and comportment was initially based on the expectation that analogous relationships would be uncovered and that it would be possible to identify centers for “hearing words,” “perceiving space,” or “storing memories.” These expectations need to be modified to accommodate modern observations which show that the structural foundations of cognitive and behavioral domains take the form of partially overlapping large-scale networks organized around reciprocally interconnected cortical epicenters.^{329,334,339} The components of these networks can be divided into *critical* versus *participating* areas. Lesions which irreversibly impair performance in a cognitive domain help to identify network components that are *critical* for its integrity, whereas activations obtained by functional imaging when subjects are performing tasks related to the same domain also reveal the areas that *participate* in its coordination. The traditional approach based on the investigation of patients with focal brain disease can thus be integrated with functional imaging experiments in order to obtain a more complete picture of the relationships between brain structure and behavior.

At least five large-scale networks can be identified in the human brain: (1) a right hemisphere-dominant spatial attention network with epicenters in dorsal posterior parietal cortex, the frontal eye fields, and the cingulate gyrus; (2) a left hemisphere-dominant language network with epicenters in Wernicke’s and Broca’s areas; (3) a memory-emotion network with epicenters in the hippocampo-entorhinal regions and the amygdaloid complex; (4) an executive function-comportment network with epicenters in lateral prefrontal cortex, orbitofrontal cortex, and posterior parietal cortex; and (5) a face-and-object identification network with epicenters in lateral temporal and temporopolar cortices. The neuroanatomical building blocks and overall organizational principles of these networks are reviewed in this chapter. The purpose is to provide a broad perspective which can serve as a background for the more detailed discussions in Chapter 3 (spatial attention), Chapters 4, 8, and 9 (memory and emotion), Chapters 5 and 6 (language), and Chapter 7 (face and object recognition).

II. PARTS OF THE CEREBRAL CORTEX

The human cerebral cortex contains approximately 20 billion neurons spread over nearly 2000 square centimeters of surface area.^{394,520} The study of the cerebral cortex can be quite challenging. There is no universal agreement on terminology, no distinct boundaries that demarcate one region from another, and, in most instances, no clear correspondence among lobar designations, traditional topographic landmarks, cytoarchitectonic boundaries, and behavioral specializations. Furthermore, one part of the brain can have more than one descriptive name, and cytoarchitectonic (striate cortex), functional (primary visual cortex), topographic (calcarine cortex), and eponymic (Brodmann’s area [BA] 17) terms can be used interchangeably to designate the same area.