White Matter Dementia

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Christopher M. Filley
University of Colorado School of Medicine
Denver Veterans Affairs Medical Center

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To all the patients who have contributed to my understanding of the brain in the course of their suffering

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Foreword

For years, the scientific community has focused on the influence of gray matter on cognition at the expense of white matter. In the past 30 years, advances in imaging tools have allowed us to delineate the relative contributions of white and gray matter in higher cortical function. In 1988 Chris Filley introduced the term "white matter dementia" when it became clear that white matter loss could produce cognitive decline and, when sufficiently severe, dementia.

Dr. Filley has thoughtfully considered the role of white matter in health and disease for more than 30 years, and *White Matter Dementia* is the constellation of his thinking on this critically important topic. "Corticocentrism," a term used by Dr. Filley to emphasize the lack of interest in white matter, sets the stage for this book, which provides a thorough and highly innovative review of white matter and cognition. His extensive experience with patients has shaped the scholarly approach to a topic on which he has performed his own pioneering research. This book takes the reader on a journey through white matter disorders and white matter dementia to diagnosis, prognosis, treatment, and a look at what's coming. This is a huge range of material with the fresh perspective of an experienced behavioral neurologist.

Dr. Filley describes a broad spectrum of disorders ranging from Alzheimer's Disease to traumatic brain injury and chronic traumatic encephalopathy, drug-induced white matter injury, vascular dementia, primary leukoencephalopathies, and a wide range of neuropsychiatric disorders. The early clinical manifestations of white matter dysfunction are detailed, and Dr. Filley guides the reader to a practical approach to the evaluation of white matter manifestations of brain disease. Augmented by scholarly discussions of white matter anatomy, both macroscopic and microscopic, the biological features of oligodendroglia, and gray and white matter connections and circuitry, *White Matter Dementia* is an intriguing read. The behavioral neurology of white matter is the unifying thread of this impressive and unique book.

I am proud to endorse this book and think it serves an incredibly valuable educational need. It will be an important part of any complete neurology library. We're inching closer to viable treatments for neurodegenerative diseases, and we need to have a complete picture get us across the finish line. This book brings us one step closer to the day when clinicians will be able to recognize the clinical manifestations of white matter disease, understand the biological cause, and provide effective treatments for the patient.

Bruce L. Miller, MD
A.W. and Mary Margaret Clausen Distinguished Professor in Neurology
Director, Memory and Aging Center
Joint Appointment in Psychiatry
UC San Francisco School of Medicine

Preface

My interest in the white matter of the brain as it contributes to human behavior dates back more than 30 years. In medical school during the late 1970s, I was taught that white matter had little or nothing to do with cognition, but even at that stage of my education I was not persuaded. Only as I completed residency and fellowship training, however, did I gain critical insight into this question, and joining the faculty of the University of Colorado in 1984 offered many opportunities to explore the topic in earnest. Since then, the journey in pursuit of white matter–behavior relationships has proven endlessly fascinating.

As a behavioral neurologist regularly called upon to evaluate people with cognitive loss or dementia, I naturally think in great detail about the neuroanatomic basis of cognition. Beginning with the principle that all mental operations are products of the brain, and recognizing that the brain is a highly evolved organ with almost overwhelming structural and functional complexity, is it possible to delineate neuroanatomic categories that can meaningfully shed light on cognitive dysfunction? The cerebral cortex has a long and cherished history in human neuroscience as the primary locus of higher function, and is rightly the topic of intensive study in this respect. Less well appreciated but still recognized in the architecture of cognition is the subcortical gray matter, which attracts attention as a parallel substrate of cognitive function. Between these two general gray matter areas, as every student of neuroscience knows, lies the white matter, which until recently received the least attention of all.

In this book, I have attempted to apply the idea that white matter plays a key role in cognition to the important clinical problem of dementia. The result is the concept of white matter dementia, a theoretical construct intended to help organize thinking with regard to the neural foundations of human cognition. Introduced in 1988, the syndrome of white matter dementia has served to contextualize a wide variety of observations that have been made with modern neuroimaging, offering a framework for understanding how the connectivity of the brain complements the operations of gray matter. This book reviews the original formulation of the idea, its refinement and clarification, its current position relative to trends in neuroscience (including connectomics and systems biology), and its promise for stimulating further investigation.

I am particularly indebted to Nick Dunton at Cambridge University Press for approaching me with the idea of writing this book. Many other individuals have informed, encouraged, advised, and corrected me along the long course of completing this work, and their contributions have been invaluable: C. Alan Anderson, James P. Kelly, David B. Arciniegas, Elizabeth Kozora, C. Munro Cullum, B. K. Kleinschmidt-DeMasters, Bruce L. Miller, Herbert H. Schaumburg, Jeremy D. Schmahmann, John Hart Jr., Erin D. Bigler, Marco Catani, Michael P. Alexander, Mario F. Mendez, Bruce H. Price, Allan H. Ropper, Josette G. Harris, Jose M. Lafosse, Erin D. Bigler, Jim Grigsby, Jack H. Simon, Mark S. Brown, Steven P. Ringel, John R. Corboy, Mark C. Spitz, Daniel I. Kaufer, Deborah A. Hall, Brian D. Hoyt, Michael R. Greher, Thomas R. Wodushek, Christopher Domen, Brianne M. Bettcher, Neill R. Graff-Radford, Ronald C. Petersen, Brian D. Berman, Bruce R. Ransom, Mark P. Goldberg, Melissa E. Murray, Bernard Michel, Francois Boller, Gorazd B. Stokin, Wendy B. Macklin, John R. Sladek, Leroy Hood, and R. Douglas Fields. Kristie Fields provided secretarial support, and Kenneth L. Tyler helped make possible the academic environment in which the ideas in this book could take shape and find expression. I am grateful to all.