Hodges' Frontotemporal Dementia

Second Edition

Clinical and scientific interest in frontotemporal dementia (FTD) and related disorders is rapidly growing, as can be seen by increasing attendance at the International Meeting on FTD as well as the burgeoning literature. There remains an important need for a book broadly focused on clinical, pathologic, and scientific aspects of FTD. The Hodges book is the major textbook resource in the academic book literature on this topic. Major advances have occurred since its last publication. New clinical diagnostic criteria were published in 2011, new pathologic criteria have been developed, and several major genetic discoveries have been made. Thus, it is time for a new edition.

We aim to continue the outstanding tradition of this book, targeting an audience of specialist and generalist neurologists, psychiatrists, geriatricians, neuropsychologists, neuropathologists, and basic scientists in relevant fields. In addition to addressing cutting-edge topics of interest to faculty-level clinicians and scientists, the book contains material accessible enough for trainees in these fields.

Bradford C. Dickerson, MD (Harvard) is an Associate Professor of Neurology, Harvard Medical School, Director of the Frontotemporal Disorders Unit, and Co-Investigator at the Alzheimer's Disease Research Center, Massachusetts General Hospital, Boston, MA, USA.

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Edited by
Bradford C. Dickerson

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To my wife, Dr. Allison Berger, and our daughters, Molly and Lilly, who teach me every day the importance of open communication and connection, and the joy of loving kindness and shared curiosity, all of which makes our lives so much more than they would be without each other.

–Your loving husband and father

To all the individuals with illnesses who entrust their lives to me, their families and caregivers; I treasure our partnerships in the journeys we take as we try to make sense of living with these tragic diseases and do everything we can to fight back.

I dedicate this book to Dr. Leyla de Toledo-Morrell: pioneering neuroscientist, talented teacher, dedicated mentor, and loving friend and "grandmother." Her passing in January 2015 left those of us lucky enough to know her with a deep hole in our lives.

–Brad Dickerson

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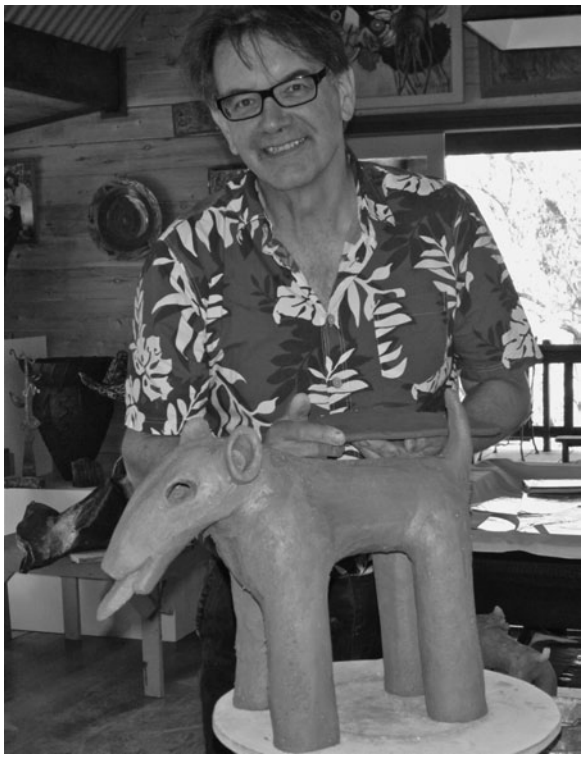
Dr. Dickerson runs a busy weekly clinic caring for patients with various forms of cognitive impairment and dementia, as well as providing training for clinical and research fellows. His research has focused primarily on the use of quantitative structural and functional neuroimaging techniques to understand the neurobiology of Alzheimer's disease, primary progressive aphasia, frontotemporal dementia, and other dementias, and on the relationships between imaging measures and behavior. He also investigates the neural substrates of changes in memory, affect, and other abilities in healthy young adults and in normal aging. He has taught widely to many audiences, and currently co-directs the annual Harvard Dementia CME course and the annual American Academy of Neurology Primer of Behavioral Neurology course. He has published more than 90 articles in peer-reviewed scientific journals as well as many book chapters, and has edited one book, *Dementia: Comprehensive Principles and Practice* (Oxford University Press).

He is the Principal Investigator on multiple NIH and foundation grants studying aging and dementia, and serves on the medical advisory boards for the Association for Frontotemporal Degeneration and the Massachusetts chapter of the Alzheimer's Association. He has won a number of awards, including the prestigious American Academy of Neurology Norman Geschwind Award in Behavioral Neurology and Honorable Mention for the Schwartz Center Award for Compassionate Care. When not practicing neurology, Brad enjoys spending time with his family and playing drums in his rock band with Allison …



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John is Professor of Cognitive Neurology based at Neuroscience Research Australia where he co-directs the Frontotemporal Dementia Research Group (FRONTIER http://www.ftdrg.org) and is a Principal Investigator of a NHMRC Program.

John qualified in Medicine from London University with honours (1975) and undertook periods of psychiatric and neurologic training in Southampton, Oxford, and San Diego and obtained his MD in 1988. From 1997 to 2007 he was the MRC Professor of Behavioural Neurology with joint appointments in the Department of Clinical Neuroscience at Addenbrooke's Hospital and the MRC Cognition and Brain Sciences Unit, Cambridge. He moved to Sydney in 2007 as an ARC Federation Fellow and established FRONTIER with support from the ARC and NHMRC.

He has a long-standing interest in many aspects of cognition, particularly in the context of neurodegenerative disorders. His current research focuses on aspects of frontotemporal dementia. He is the author of over 450 journal articles and five books including *Cognitive Assessment for Clinicians* (Oxford University Press, 2007), *Early-Onset Dementia* (Oxford University Press, 2001), and *Frontotemporal Dementia Syndromes* (Cambridge University Press, 2007).

Foreword

First described in 1892, frontotemporal dementia (FTD) and related disorders are finally gaining public and scientific interest as the decades of labeling every cognitive disease of aging "Alzheimer's disease" are dwindling. FTD is a devastating disease for patients and caregivers that usually begins to be noticed in people in their 40s, 50s, and 60s, while people are expected to be active participants in career, family, and community. This young age of onset combined with a commonly psychiatric presentation means that there are often many alternate diagnoses proposed before the correct one is identified. Patients and families often go through years of searching for the correct diagnosis and understanding what is happening. Unfortunately by the time an accurate diagnosis is made, oftentimes the supportive relationships that hold families together are already deeply strained owing to the exceptionally difficult behaviors, poor judgment, and personality changes frequently seen in patients with FTD. This situation can be dangerous for patients with a progressive neurodegenerative disease if they are left without any support before the disease is identified.

With new technologies and clinical insights, patient diagnoses are becoming more precise, and scientists are working to understand the molecular drivers of each type of FTD spectrum disorder. This rigorous approach is bringing us closer to treatments than we have ever been, and a treatment for FTD could unlock treatments for Alzheimer's disease, Parkinson's disease, Creutzfeldt–Jakob disease, and others. The active search for reliable biomarkers is a hot area of research now. Such biomarkers could provide an objective diagnosis much earlier when treatment could start before symptoms emerge. These biomarkers could also provide measures of treatment success in clinical trials, which could help identify a cure.

Regular international meetings bring together scientists and clinicians from each continent to share the discoveries and challenges seen in diverse cultures and geographies. This worldwide sharing also crosses disciplinary boundaries to include neurologists, psychiatrists, geriatricians, neuropsychologists, neuropathologists, nurses, genetic counselors, and basic scientists to provide a truly broad understanding of the changes in the brain in FTD. This comprehensive review of FTD brings together the latest findings from the rich international community of researchers growing larger each year. Covering the clinical phenotypes, diagnostic issues, pathology, and treatment, the editor of this edition has brought these discoveries together in one place. This outstanding edition is a must-read for anyone interested in dementia.

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Preface

I am honored to serve as the editor of *Hodges' Frontotemporal Dementia* (second edition), which I have worked to refine as a clinically oriented book aiming to provide a comprehensive reference for the frontotemporal dementia (FTD) spectrum of neurodegenerative diseases. When I was asked to carry on the tradition of this volume started by Professor John Hodges, I wanted to honor the tradition John started in the first edition of this book while expanding it to include the many new insights and advances by the broad international FTD clinical and research community that have developed over the past eight years since its original publication. I named the revision of this book after John to honor his groundbreaking clinical, research, and teaching/mentorship contributions to the fields of FTD, primary progressive aphasia (PPA), memory, behavioral neurology, and neurodegenerative disease research.

The first edition of this book has filled a very special niche, and I hope the second edition will continue in this vein. The FTDs are rare but important diseases that are slowly yielding their secrets to the international community of investigators dedicated to unlocking them. It is remarkable to witness the growth of the diverse but strongly collaborative group of clinicians and scientists around the world, and the ways in which patients and families join efforts to advance our collective knowledge of these diseases and attempts to treat them.

Although I had talked with and learned from patients and family members suffering with "Pick's disease" in the early 1990s when I worked at the Alzheimer's Association, it was not until 2002 that I diagnosed and treated my first patient, Joe J., as a neurology resident. From that time forward, with the encouragement and support of colleagues and mentors, I have been captivated by the special needs of patients and families living with these mysterious illnesses – not to mention the fascinating science of these diseases – and I vowed to try to contribute to efforts to improve their plight. As my interest deepened in PPA and semantic memory impairment, I started the Massachusetts General Hospital (MGH) PPA Program in the fall of 2007 with Daisy Sapolsky, who was introduced to me by my good friend and colleague (and her future husband) Dr. Leigh Hochberg. Drs. David Caplan, Marsel Mesulam, and Sandy Weintraub, along with Paige Nalipinski and Joyce Shapiro Gordon (senior speech pathologists at MGH), helped us start our clinical research program in PPA. Once we "hung our shingle," we were fortunate to have many colleagues who referred patients and families to our program. As we worked with increasing numbers of people, I began turning a substantial portion of my effort to PPA, FTD, and related disorders. Dr. Anne Young, Chief of Neurology at MGH, and Drs. John Growdon and Brad Hyman enthusiastically supported my proposal to start a specialized clinical and research unit dedicated to FTD, and the MGH FTD Unit was born in the fall of 2008. We have since had the good fortune of working with many wonderful patients, families, and colleagues, and have received funding from the NIA, NINDS, NIMH, Alzheimer's Association, and Association for FTD, as well as multiple philanthropic organizations and generous families; we have evaluated and treated more than 300 patients over the past eight years.

On November 13, 2014, shortly after the 9th International Conference on FTD, we held our fourth Boston-area MGH FTD Unit Caregiver Education and Support day. As I talk with my colleagues around the world, we share similar stories of the power that programs such as this offer. Bringing together the community of patients, families, other loved ones, clinicians, researchers, and other dedicated professionals, programs like this one help us realize how critical it is to have dedicated interdisciplinary teams working on FTD and networks of caring individuals putting effort toward improving the lives of those affected by these illnesses. As most people in this community

recognize, this is a defining feature of the international FTD research and clinical community – it is a closeknit, collaborative "family."

This book is designed to improve knowledge about the FTD spectrum and competence in its clinical management, hopefully translating into improved early detection, accurate diagnosis, and compassionate comprehensive care and treatment. Written primarily for clinicians, this volume takes a multidisciplinary approach to understanding FTD and is aimed toward neurologists, psychiatrists, geriatricians, psychologists, genetic counselors, speech pathologists, nurse specialists, internists, primary care physicians, social workers, occupational and physical therapists, clinical pharmacists, research scientists, and other health professionals involved in the diagnosis, management, and investigation of FTD and related illnesses.

The first part of the book provides an historical introduction by John Hodges and a broad overview of the complex relationships between these illnesses by Paul McMonagle and Andy Kertesz. The second part of the book delves more deeply into clinical phenotypes, with sections on each of the major syndromes by Matthew Jones and David Neary (overview), Katya Rascovsky (behavioural variant FTD), Chiara Cerami and Stefano Cappa (PPA), Sharon Abrahams and Tom Bak (the FTD-ALS spectrum), and Barbara Borroni and Antonella Alberici (progressive supranuclear palsy and corticobasal degeneration). The next section reviews a clinical approach to the diagnostic assessment of FTD spectrum illnesses, with chapters by Chiadi Onyiki, Simon Ducharme, and myself (overview of clinical assessment), Teresa Torralva, Macarena Martinez Cuitiño, and Facundo Manes (neuropsychology), Jonathan Rohrer (imaging), Nick Verwey, Yolande Pijnenburg, and Philip Scheltens (cerebrospinal fluid biomarkers), and Beth McCarty Wood and Jill Goldman (genetic counseling). The next section then provides an up-to-date survey of neuropathology by Ian Mackenzie. Gabor Kovacs, and Manuela Neumann, genetics by Marc Cruts and Christine Van Broeckhoven, and pathophysiology and animal models by Brian Warmus and Erik Roberson. Finally, the last section reviews treatment of FTD, including quantification of impairment in everyday life by Claire O'Connor and Eneida Mioshi, practical management by Ted Huey and Masood Manoochehri, current and future pharmacologic therapy by Richard Tsai and Adam Boxer, and the family's perspective by Susan Dickinson and Jill Shapira.

Besides providing cutting-edge reviews of the literature, one of my goals was to obtain personal perspectives and "clinical pearls" by internationally respected leaders in the field. I hope that specialists will find this book useful as an up-to-date reference work, while less specialized clinicians will take away valuable principles useful in daily clinical practice, and trainees at all levels will enjoy an opportunity to appreciate the broad array of disciplines that FTD touches. Ultimately, FTD will be conquered by the concerted efforts of this international army of experts from across many fields of basic and clinical neuroscience, in close partnership with patients and families, advocacy and support communities, funding agencies and philanthropists, and industry groups.

I greatly appreciate the efforts of the contributors, who took time out from their usual activities to distill their knowledge for this book. Nicholas Dunton, Kirsten Bot, and Charlotte Thomas at Cambridge University Press were invaluable in helping me to develop this project and nurture it to completion. In addition, I would like to thank Susan Dickinson, Nadine Tatton, Sharon Denny, Matt Sharp, and Helen Ann Comstock, as well as the AFTD board members, whose tireless efforts on behalf of the FTD community through the Association for FTD are outstanding. In addition, I treasure the partnership of colleagues from the Massachusetts/New Hampshire chapter of the Alzheimer's Association, including Paul Raia, Jerry Flaherty, Lindsay Brennan, Susan Rowlett, Nicole McGurin, Brooke Patterson, Nancy Nichols, Lenore Jackson-Pope, and Jim Wessler. I would like to extend special thanks to my mentors and colleagues who have sculpted my thinking in so many ways: Tony Phelps, Sheryl Williams, Leyla deToledo-Morrell, Marsel Mesulam, Sandy Weintraub, Mario Mendez, Martin Samuels, Marilyn Albert, Reisa Sperling, Kirk Daffner, Deborah Blacker, Brad Hyman, John Growdon, David Caplan, Jeremy Schmahmann, Bruce Price, Keith Johnson, Anne Young, Merit Cudkowicz, Bruce Rosen, Matthew Frosch, Steve Haggarty, Jim Gusella, Rudy Tanzi, Mykol Larvie, Maurizio Fava, Paige Nalipinski, Joyce Shapiro Gordon, Janet Sherman, Doreen Rentz, Barbara Maxam, Randy Buckner, Daphne Holt, Nikos Makris, and Lisa Feldman Barrett. Special thanks to Liz and George Krupp for your generous support through your Tom Rickles fund in honor of your dear brother, and also to Marie and Brandt Henderson and many other individuals who have contributed critical financial support to our program. Many mentors

and colleagues in the broader FTD community have provided incredibly generous inspiration, encouragement, and wise counsel as I have developed our FTD clinical research program, including Bruce Miller, Marsel Mesulam, Sandy Weintraub, Dino Ghetti, Bill Seeley, Marliu Gorno-Tempini, Emily Rogalski, Howie Rosen, Adam Boxer, Brad Boeve, Dave Knopman, Jon Rohrer, Kate Rankin, Gil Rabinovici, Katya Rascovsky, Murray Grossman, Tiffany Chow, Mario Mendez, and John Hodges. I am very lucky to have the partnership of several special people in the Boston-area FTD community, including Emily Levy, Barbara Neufeld, Amy Almeida, Genevieve Wanucha, and especially Katie Brandt. The ADRC Longitudinal Cohort team has been critical to our efforts, including Jeanette Gunther, Kelly Hennigan, Larissa Collins, Frannie Hatling, Amy Zoller, Kyleen Swords, Jillian Kizielewicz, and Jon Hirschberger. So much of our clinical and research effort has been carried out by outstanding fellows, students, and other trainees, including Daisy Hochberg, Kimiko Domoto-Reilly, Luce Pellerin, Liang Wang, Stephane Poulin, Kristin Lindquist, Maria Gendron, Belen Pascual, Kevin Bickart, Yakeel Quiroz, Mandana Modirrousta, Joan Camprodon, Chenjie Xia, Mark Eldaeif, David Perez, Ryan Darby, Simon Ducharme, Mia Minen, Elena Ratti, Megan Quimby, Claire Cordella, Rani Sarkis, Sara Mitchell, Jaya Padmanabhan, Abid Qureshi, and Tamar Gefen. Special thanks to my good friends and colleagues David Wolk and Ali Atri. Finally, I am immensely grateful for the dedication of many wonderful individuals in the FTD Unit and other collaborators, including Daisy Hochberg, Kimiko Domoto-Reilly, Scott McGinnis, Diane Lucente, Akram Bakkour, Aly Negreira, Mike Brickhouse, Mark Hollenbeck, Mike Stepanovic, Megan Quimby, Christina Caso, Katie Kelly, Sara Makaretz, Liz Lynch, and especially our stellar "front office" team, including Jackie Mazzie, Karolina Ballester, Ayana Cole, Brianna O'Connell, and Rose Gallagher.

Most important, for their love, support, and inspiration, I thank my family, including Allison Berger, Molly Dickerson, Lilly Dickerson, Jeannae Dickerson, Jim Dickerson, Sarah Dickerson, Lewis Berger, Ileana Berger, and Stacie, Isabel, Avery, Vivian, and Karl Siebrecht.

And I want to give special acknowledgment to the many patients, family members, caregivers, and others who have entrusted me with intimate details from your lives and the humbling opportunity to learn from and with you during this journey, and to offer you the opportunity to join forces in our fight against these terrible diseases. I will do my best to help ensure that your contributions help pave the way toward deeper knowledge of these diseases and ultimately better treatments. We strive toward a world without FTD, and while we work toward a cure, we give the best care we can.