Understanding Neuropsychiatric Disorders: Insights from Neuroimaging

Edited by

Martha E. Shenton
Bruce I. Turetsky
Contents

List of contributors vii
Preface xiii

Section I – Schizophrenia
1 Structural imaging of schizophrenia 1
   Thomas J. Whitford, Marek Kubicki and Martha E. Shenton
2 Functional imaging of schizophrenia 30
   Godfrey D. Pearlson
3 Spectroscopic imaging of schizophrenia 48
   Jay W. Pettegrew, Richard J. McClure and Kanagasabai Panchalingam
4 Neuroreceptor imaging of schizophrenia 78
   Dean F. Wong, James Robert Brašić and Nicola Cascella
5 Neuroimaging of schizophrenia: commentary 88
   Nancy Andreasen

Section II – Mood Disorders
6 Structural imaging of bipolar illness 93
   Stephen M. Strakowski
7 Functional imaging of bipolar illness 109
   William M. Marchand and Deborah A. Yurgelun-Todd
8 Molecular imaging of bipolar illness 125
   John O. Brooks III, Po W. Wang and Terence A. Ketter
9 Structural imaging of major depression 139
   Anand Kumar and Olusola Ajilore
10 Functional imaging of major depression 151
    Simon A. Surguladze and Mary L. Phillips
11 Molecular imaging of major depression 170
    Julia Sacher and Gwenn S. Smith
12 Neuroimaging of mood disorders: commentary 197
    Paul E. Holtzheimer III and Helen S. Mayberg

Section III – Anxiety Disorders
13 Structural imaging of post-traumatic stress disorder 205
   Mark W. Gilbertson
14 Functional imaging of post-traumatic stress disorder 214
   Lisa M. Shin, Kathryn Handwerger Brohawn, Danielle L. Pfaff and Roger K. Pitman
15 Molecular imaging of post-traumatic stress disorder 229
   J. Douglas Bremner
16 Structural imaging of obsessive–compulsive disorder 236
   Andrew R. Gilbert, Alison M. Gilbert, Jorge R. C. de Almeida and Philip R. Szeszko
17 Functional imaging of obsessive–compulsive disorder 247
   Bon-Mi Gu, Do-Hyung Kang and Jun Soo Kwon
18 Molecular imaging of obsessive–compulsive disorder 260
   Martijn Figuee, Jan Booj and Damiaan Denys
19 Structural imaging of other anxiety disorders 274
   José Alexandre de Souza Crippa and Geraldo F. Busatto
20 Functional imaging of other anxiety disorders 288
   Oliver Tüscher, Daniel J. Zimmerman and David A. Silbersweig
Contents

Section IV – Cognitive Disorders
23 Structural imaging of Alzheimer’s disease 313
   Liana G. Apostolova and Paul M. Thompson
24 Functional imaging of Alzheimer’s disease 332
   Vanessa Taler and Andrew J. Saykin
25 Molecular imaging of Alzheimer’s disease 351
   Norbert Schuff
26 Neuroimaging of Parkinson’s disease 361
   Raúl de la Fuente-Fernández and A. Jon Stoessl
27 Neuroimaging of other dementing disorders 371
   William Hu and Murray Grossman
28 Neuroimaging of cognitive disorders: commentary 395
   Mony J. de Leon, Henry Rusinek, Wai Tsui, Thomas Wisniewski, Jerzy Wegiel and Ajax George

Section V – Substance Abuse
29 Structural imaging of substance abuse 403
   Sandra Chanraud, Anne Lise Pitel and Edith V. Sullivan
30 Functional imaging of substance abuse 429
   Omar M. Mahmood and Susan F. Tapert
31 Molecular imaging of substance abuse 446
   Brian C. Schweinsburg, Alecia D. Dager Schweinsburg and Graeme F. Mason
32 Neuroimaging of substance abuse: commentary 463
   Adolf Pfefferbaum

Section VI – Eating Disorders
33 Neuroimaging of anorexia and bulimia 465
   Guido K. W. Frank and Michael D. H. Rollin
34 Neuroimaging of obesity 487
   Gene-Jack Wang, Nora D. Volkow, Joanna S. Fowler and Panayotis K. Thanos
35 Neuroimaging of eating disorders: commentary 510
   Janet Treasure

Section VII – Developmental Disorders
36 Neuroimaging of autism spectrum disorders 517
   John D. Herrington and Robert T. Schultz
37 Neuroimaging of Williams–Beuren syndrome 537
   Andreia Santos and Andreas Meyer-Lindenberg
38 Neuroimaging of developmental disorders: commentary 555
   Nancy J. Minshew

Index 559
Contributors

Olusola Ajilore MD, PhD
Department of Psychiatry
University of Illinois at Chicago
Chicago, IL, USA

Jorge R. C. de Almeida MD, PhD
Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

Nancy Andreasen MD, PhD
Department of Psychiatry
University of Iowa
Iowa City, IA, USA

Liana G. Apostolova MD, MSCR
Department of Neurology
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, CA, USA

Jan Booij MD
Department of Nuclear Medicine
University of Amsterdam
Amsterdam, The Netherlands

James Robert Brašić MD, MPH
The Russell H. Morgan Department of Radiology and Radiological Science
The Johns Hopkins University School of Medicine
Baltimore, MD, USA

J. Douglas Bremner MD
Department of Psychiatry and Radiology
Emory University School of Medicine
Atlanta, GA, USA

Kathryn Handwerger Brohawn PhD
Department of Psychology
Tufts University
Medford, MA, USA

John O. Brooks III MD, PhD
Department of Psychiatry
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, CA, USA

Geraldo F. Busatto MD
Department of Psychiatry
University of São Paulo
São Paulo, SP, Brazil

Nicola Cascella MD
Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University School of Medicine
Baltimore, MD, USA

Sandra Chanraud PhD
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Stanford, CA, USA and Neuroscience Program
SRI International Menlo Park, CA, USA

José Alexandre de Souza Crippa MD, PhD
Department of Neuroscience and Behavioral Sciences
University of São Paulo
Ribeirão Preto, SP, Brazil

Raúl de la Fuente-Fernández MD
Division of Neurology
University of British Columbia
Vancouver, BC, Canada

Mony J. de Leon EdD
Department of Psychiatry
New York University School of Medicine
New York, NY, USA

Damiaan Denys MD, PhD
Department of Psychiatry
University of Amsterdam
Amsterdam,
The Netherlands
List of contributors

Martijn Figee MD
Department of Psychiatry
University of Amsterdam
Amsterdam, The Netherlands

Guido K. W. Frank MD
Department of Psychiatry
University of Colorado School of Medicine
Aurora, CO, USA

Joanna S. Fowler PhD
Department of Psychiatry
Mount Sinai School of Medicine
New York, NY, USA and
Medical Department
Brookhaven National Laboratory
Upton, NY, USA

Ajax George MD
Department of Radiology
New York University School of Medicine
New York, NY, USA

Alison M. Gilbert PhD
Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

Andrew R. Gilbert MD
Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

Marek Kubicki MD, PhD
Department of Psychiatry
VA Boston Healthcare System and
Department of Psychiatry
Brigham and Women's Hospital
Harvard Medical School
Boston, MA, USA

Anand Kumar MD
Department of Psychiatry
University of Illinois at Chicago
Chicago, IL, USA

Jun Soo Kwon MD, PhD
Interdisciplinary Program in Brain Science and
Department of Psychiatry
Seoul National University College of Medicine
Seoul, Korea

Richard J. McClure PhD
Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

Omar M. Mahmood PhD
Psychology Service
VA San Diego Healthcare System and
Department of Psychiatry
University of California, San Diego
San Diego, CA, USA

Paul E. Holtzheimer III MD
Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine
Atlanta, GA, USA

William Hu MD, PhD
Department of Neurology
University of Pennsylvania School of Medicine
Philadelphia, PA, USA

Do-Hyung Kang MD, PhD
Department of Psychiatry
Seoul National University College of Medicine
Seoul, Korea

Terence A. Ketter MD
Department of Psychiatry and Behavioral Sciences Stanford University School of Medicine
Stanford, CA, USA

Murray Grossman MD
Department of Neurology
University of Pennsylvania School of Medicine
Philadelphia, PA, USA

Bon-Mi Gu MSc
Interdisciplinary Program in Brain Science
Seoul National University College of Medicine
Seoul, Korea

John D. Herrington PhD
Center for Autism Research
Children's Hospital of Philadelphia
Philadelphia, PA, USA
William M. Marchand MD
Department of Psychiatry
University of Utah School of Medicine
Salt Lake City, UT, USA

Graeme F. Mason PhD
Department of Psychiatry and
Department of Diagnostic Radiology
Yale University School of Medicine
New Haven, CT, USA

Sanjay J. Mathew MD
Department of Psychiatry and Behavioral Sciences
Baylor College of Medicine
Houston, TX, USA

Helen S. Mayberg MD
Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine
Atlanta, GA, USA

Andreas Meyer-Lindenberg MD PhD
Department of Psychiatry and Psychotherapy
University of Heidelberg and
Central Institute of Mental Health
Mannheim, Germany

Nancy J. Minshew MD
Department of Psychiatry and
Department of Neurology
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

James W. Murrough MD
Department of Psychiatry
Mount Sinai School of Medicine
New York, NY, USA

Kanagasabai Panchalingam PhD
Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

Godfrey D. Pearlson MD
Olin Neuropsychiatry Research Center
Institute of Living
Hartford, CT, USA and
Department of Psychiatry
Yale University School of Medicine
New Haven, CT, USA

Jay W. Pettegrew MD
Departments of Psychiatry, Neurology, Behavioral and Community Health Sciences,
University of Pittsburgh School of Medicine and
Department of Bioengineering
University of Pittsburgh
Pittsburgh, PA, USA

Danielle L. Pfaff BA
Department of Psychology
Tufts University
Medford, MA, USA

Adolf Pfefferbaum MD
Neuroscience Program
SRI International
Menlo Park, CA, USA and
Department of Psychiatry and Behavioral Science
Stanford University School of Medicine
Stanford, CA, USA

Mary L. Phillips MD
Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

Anne Lise Pitel PhD
Department of Psychiatry and Behavioral Science
Stanford University School of Medicine
Stanford, CA, USA

Roger K. Pitman MD
Department of Psychiatry
Massachusetts General Hospital
Harvard Medical School
Boston, MA, USA

Scott L. Rauch MD
Department of Psychiatry
McLean Hospital
Harvard Medical School
Belmont, MA, USA

Michael D. H. Rollin MD
Department of Psychiatry, Division of Child and Adolescent Psychiatry, and The Children’s Hospital
University of Colorado
School of Medicine
Aurora, CO, USA
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henry Rusinek PhD</td>
<td>Department of Radiology&lt;br&gt;New York University School of Medicine&lt;br&gt;New York, NY, USA</td>
</tr>
<tr>
<td>Julia Sacher MD, PhD</td>
<td>PET Centre&lt;br&gt;Centre for Addiction and Mental Health&lt;br&gt;Toronto, ON, Canada</td>
</tr>
<tr>
<td>Andreia Santos PhD</td>
<td>Central Institute of Mental Health&lt;br&gt;Mannheim, Germany</td>
</tr>
<tr>
<td>Andrew J. Saykin PhD</td>
<td>Department of Radiology and Imaging Sciences&lt;br&gt;Indiana University School of Medicine&lt;br&gt;Indianapolis, IN, USA</td>
</tr>
<tr>
<td>Norbert Schuff PhD</td>
<td>Center for Imaging of Neurodegenerative Diseases at the Veterans Affairs Medical Center and&lt;br&gt;Department of Radiology and Biomedical Imaging&lt;br&gt;University of California San Francisco&lt;br&gt;San Francisco, CA, USA</td>
</tr>
<tr>
<td>Robert T. Schultz PhD</td>
<td>Department of Pediatrics&lt;br&gt;University of Pennsylvania School of Medicine and&lt;br&gt;Center for Autism Research&lt;br&gt;Children's Hospital of Philadelphia&lt;br&gt;Philadelphia, PA, USA</td>
</tr>
<tr>
<td>Alecia D. Dager Schweinsburg PhD</td>
<td>Department of Psychiatry&lt;br&gt;Yale University School of Medicine&lt;br&gt;New Haven, CT, USA</td>
</tr>
<tr>
<td>Brian C. Schweinsburg PhD</td>
<td>Department of Psychiatry&lt;br&gt;Yale University School of Medicine&lt;br&gt;New Haven, CT, USA</td>
</tr>
<tr>
<td>Martha E. Shenton PhD</td>
<td>VA Boston Healthcare System and&lt;br&gt;Department of Psychiatry&lt;br&gt;Brigham and Women's Hospital&lt;br&gt;Harvard Medical School&lt;br&gt;Boston, MA, USA</td>
</tr>
<tr>
<td>Lisa M. Shin PhD</td>
<td>Department of Psychology&lt;br&gt;Tufts University&lt;br&gt;Medford, MA, USA and&lt;br&gt;Department of Psychiatry&lt;br&gt;Massachusetts General Hospital&lt;br&gt;Harvard Medical School&lt;br&gt;Boston, MA, USA</td>
</tr>
<tr>
<td>David A. Silbersweig MD</td>
<td>Department of Psychiatry&lt;br&gt;Brigham and Women's Hospital&lt;br&gt;Harvard Medical School&lt;br&gt;Boston, MA, USA</td>
</tr>
<tr>
<td>Gwenn S. Smith PhD</td>
<td>Department of Psychiatry and Behavioral Sciences&lt;br&gt;The Johns Hopkins University School of Medicine&lt;br&gt;Baltimore, MD, USA</td>
</tr>
<tr>
<td>A. Jon Stoessl MD</td>
<td>Division of Neurology&lt;br&gt;University of British Columbia&lt;br&gt;Vancouver, BC, Canada</td>
</tr>
<tr>
<td>Stephen M. Strakowski MD</td>
<td>Department of Psychiatry&lt;br&gt;University of Cincinnati&lt;br&gt;Cincinnati, OH, USA</td>
</tr>
<tr>
<td>Edith V. Sullivan PhD</td>
<td>Department of Psychiatry and Behavioral Sciences&lt;br&gt;Stanford University School of Medicine&lt;br&gt;Stanford, CA, USA</td>
</tr>
<tr>
<td>Simon A. Surguladze MD, PhD</td>
<td>Institute of Psychiatry&lt;br&gt;King’s College London&lt;br&gt;London, UK</td>
</tr>
<tr>
<td>Philip R. Szeszkko PhD</td>
<td>Department of Psychiatry&lt;br&gt;The Zucker Hillside Hospital&lt;br&gt;Glen Oaks, NY, USA and&lt;br&gt;Albert Einstein College of Medicine&lt;br&gt;Bronx, NY, USA</td>
</tr>
<tr>
<td>Vanessa Taler PhD</td>
<td>Department of Radiology and Imaging Sciences&lt;br&gt;Indiana University School of Medicine&lt;br&gt;Indianapolis, IN, USA</td>
</tr>
</tbody>
</table>
Historically, the opportunity to examine the inner workings of the human body was limited to the study of cadavers. In the past 30 years, medical imaging technology has provided researchers with a new window into the living human body. Advances in medical imaging technology have, in fact, truly revolutionized nearly every area of medicine. These advances include both dramatic improvements in image resolution and the development of novel imaging techniques, from computed axial tomography (CT), to positron emission tomography (PET), to single photon emission tomography (SPECT), to magnetic resonance imaging (MRI), including fMRI (functional MRI) and diffusion tensor imaging (DTI), to magnetic resonance spectroscopy (MRS), ultrasound, and magnetoencephalography (MEG) – all of which provide an unprecedented view, in exquisite detail, of anatomical structures and/or functions in the living human body.

One medical discipline that has been in the forefront of this revolution is neuropsychiatry (defined here as encompassing both psychiatry and behavioral neurology), where novel neuroimaging tools have been developed and applied to neuropsychiatric disorders in order to understand further the neuroanatomical and neurophysiological bases of mental illnesses and cognitive disorders, including Alzheimer’s and Parkinson’s diseases.

This book reviews important new findings about the role of brain abnormalities in neuropsychiatric disorders based on this new imaging technology. In considering the progress in this area, it is clear that initially the quest was to identify and characterize focal brain abnormalities in an effort to delineate further various psychiatric and neuropsychiatric syndromes. Here, as will be evident from the chapters that follow, much work has already been done to characterize brain pathology in disorders for which the etiologies are unknown, there are often no uniform or pathognomonic clinical symptoms, and there is often extensive overlap in clinical presentation across disorders.

More recently, the focus has shifted from the examination of a single brain region, or multiple discrete brain regions, implicated in a particular syndrome or disorder, to the examination of integrated brain systems. This is a common theme that can be followed throughout the chapters of this book. Specifically, the focus has shifted from investigating only gray matter of the brain to investigating the “other half” of the brain, white matter, and the neural networks involved in the pathophysiology of different neuropsychiatric disorders. Accordingly, we have moved from an appreciation that, for example, schizophrenia is a brain disorder – something that had been debated prior to the late 1980s – to a quest to understand the complex mechanisms underlying the neuropathology of schizophrenia. Thus there has been a shift from the “what” and “where” of brain regions implicated in neuropsychiatric disorders to an effort to understand the neural basis of clinical symptoms, or “how” abnormal brain regions produce the clinical picture of depression, or autism, or schizophrenia. These advances in neuroimaging are moving us towards a new understanding of neuropsychiatric disorders based on their underlying neurobiology. This will likely facilitate the diagnostic reclassification of these complex heterogeneous disorders, improve our ability to predict treatment outcome, and enhance our understanding of the genetic and environmental causes of these disorders.

The change in focus from discrete brain regions and gray matter to white matter and the integrated systems that underlie cognitive, behavioral, and emotional abnormalities has followed, closely, the advances and inroads made in imaging technology. Importantly, none of the insights into the neuropathology of neuropsychiatric disorders, to date, would have been possible without these advances. That is, without the tools to probe the brain, in vivo, we could not even have begun to ask questions about brain structure and function and their perturbations in...
There is now, however, a need to go beyond the technology and shift to more hypothesis- and model-driven approaches. These new approaches must not only elucidate the neural networks involved in complex disorders, but must also examine the inter-relationships among genetic variables, environmental stressors, behavioral, cognitive, social, and emotional factors, and the structural and functional integrity of the neural systems that underlie the symptomatology presently used to classify these disorders.

When we were first approached by Marc Strauss at Cambridge University Press to edit a book on neuroimaging and its contribution to what we know about neuropsychiatric disorders, we thought such a book was very timely, as we believe we are now at a critical juncture in terms of our knowledge of the living brain in both health and illness. Moreover, we believe that the most interesting and important findings are yet to come.

In the chapters that follow, the current status of neuroimaging is reviewed for each of the leading neuropsychiatric disorders. The “maturity” of this research and the breadth and depth of the available data vary considerably across disorders. In some cases, such as schizophrenia or mood disorders, neuroimaging findings are quite extensive, requiring separate chapters to review structural imaging (Proton MR and DTI), functional imaging (fMRI and PET/SPECT blood flow and metabolism studies), and molecular imaging (PET/SPECT receptor studies and MR spectroscopy). In other cases, such as autism spectrum disorders, the data are still relatively sparse and findings across imaging modalities are reviewed in a single chapter. Each disease section ends with a commentary from a luminary in the field, addressing the broad question: “What do we know and where are we going?” This was a feature that we decided to include very early in the editorial process. Given the broad scope of the book, we thought it important for a luminary to review each section, to provide a synthesis, and to comment more generally on the knowledge gleaned from these imaging techniques. The intended audience for this book is also broad and includes the clinical psychiatrist, the general practitioner, the psychiatry or neurology resident, the medical student, the PhD student in psychology or neuroscience, and/or the post-doctoral fellow interested in learning more about how neuroimaging tools lead to new discoveries about brain and behavior associations in neuropsychiatric disorders.

We wish to thank Marc Strauss, Richard Marley, and Nisha Doshi at Cambridge University Press for their assistance on all aspects of this book. We also wish to thank our spouses, George and Nancy, who kindly accepted our taking on, yet again, just one more task. Finally, we give our heartfelt thanks to all of the authors of the chapters in this book. These are leading investigators in their respective fields, who have graciously taken the time to offer their insights into neuropsychiatric disorders based on advances in neuroimaging. It goes without saying that, without them, this book would not exist.

Martha E. Shenton
Bruce I. Turetsky