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Edited by Judith M. Rumsey and Monique Ernst

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Neuroimaging in Developmental Clinical Neuroscience

Edited by

Judith M. Rumsey

Neurodevelopmental Disorders Branch
Division of Developmental Translational Research
National Institute of Mental Health, Rockville, MD, USA

Monique Ernst

Neurodevelopment of Reward Systems, Mood and Anxiety
Disorders Program
Emotional Development and Affective Neuroscience Branch
National Institute of Mental Health, Bethesda, MD, USA

With a Foreword by

Husseini K. Manji

Chief, Laboratory of Molecular Pathophysiology
Director for the Mood and Anxiety Disorders Program
National Institute of Mental Health, Bethesda, MD, USA



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Contributors

James M. Bjork, Ph.D.

Laboratory of Clinical and Translational Studies
National Institute of Alcohol Abuse and Alcoholism
National Institutes of Health
Bethesda, MD, USA

Hilary P. Blumberg, M.D.

Associate Professor of Psychiatry and Diagnostic
Radiology
Director, Mood Disorders Research Program
Yale University School of Medicine
New Haven, CT, USA

Nathalie Boddaert, M.D.

Necker Hospital
Paris V University
Paris, France

Susan Bookheimer, Ph.D.

Professor, Psychiatry and Biobehavioral Sciences
UCLA School of Medicine
Ahmanson-Lovelace Brain Mapping Center
University of California, Los Angeles
Los Angeles, CA, USA

Silvia A. Bunge, Ph.D.

Assistant Professor
Psychology Department
Center for Mind and Brain
University of California
Davis, CA, USA

Beata Buzas, Ph.D.

National Institute of Alcohol Abuse and Alcoholism
 Rockville, MD, USA

B. J. Casey, Ph.D.

Director of the Sackler Institute for Developmental Psychobiology
 Sackler Professor of Developmental Psychobiology
 Departments of Psychiatry, Neurology and Neuroscience
 Weill Cornell Medical College
 New York, NY, USA

Nadia Chabane, M.D., Ph.D.

Robert Debre Hospital
 Paris VII University
 Paris, France

Eveline A. Crone, Ph.D.

Brain and Development Laboratory
 Department of Developmental Psychology
 Leiden University
 Leiden, The Netherlands

Mirella Dapretto, Ph.D.

Associate Professor
 Department of Psychiatry and Biobehavioral Sciences
 Ahmanson-Lovelace Brain Mapping Center
 University of California, Los Angeles
 Los Angeles, CA, USA

John A. Detre, M.D.

Associate Professor
 Departments of Neurology and Radiology
 University of Pennsylvania
 Philadelphia, PA, USA

Vaibhav A. Diwadkar, Ph.D.

Department of Psychiatry and Behavioral Neuroscience
 Wayne State University School of Medicine
 Detroit, MI, USA

Jeffery N. Epstein, Ph.D.

Associate Professor
 Department of Pediatrics
 Cincinnati Children's Hospital Medical Center
 Cincinnati, OH, USA

Monique Ernst, M.D., Ph.D.

Head, Neurodevelopment of Reward Systems
 Emotional Development and Affective Neuroscience Branch
 Mood and Anxiety Disorders Program
 National Institute of Mental Health
 Bethesda, MD, USA

Guido K. W. Frank, M.D.

University of Colorado at Denver and Health Sciences Center
 Department of Psychiatry
 The Children's Hospital (Pavilion)
 Denver, CO, USA

David C. Glahn, Ph.D.

Director of Neuroimaging Core in Psychiatry
 Associate Professor
 Department of Psychiatry and Research Imaging Center
 University of Texas Health Science Center at San Antonio
 San Antonio, TX, USA

David Goldman, M.D.

Chief, Laboratory of Neurogenetics
 National Institute on Alcohol Abuse and Alcoholism
 Bethesda, MD, USA

Daniel A. Gorman

Department of Psychiatry
 Hospital for Sick Children and
 University of Toronto
 Toronto, Ontario, Canada

Ian H. Gotlib, Ph.D.

Psychology Department
 Stanford University
 Stanford, CA, USA

Michael G. Hardin, M.S.

Graduate Research Fellow
 Emotional Development and Affective Neuroscience
 Branch
 Mood and Anxiety Program
 National Institute of Mental Health
 Bethesda, MD, USA

Clinton D. Hermes, J.D.

Senior Vice President and General Counsel
 St. Jude Children's Research Hospital
 Memphis, TN, USA

Rebecca M. Jones, M.Phil.

Sackler Institute for Developmental Psychobiology
 Weill Medical College of Cornell University
 New York, NY, USA

Jutta Joormann, Ph.D.

Assistant Professor
 Department of Psychology
 University of Miami
 Coral Gables, FL, USA

Jessica H. Kalmar, Ph.D.

Associate Research Scientist
 Yale University School of Medicine
 New Haven, CT, USA

Walter H. Kaye, M.D.

Professor of Psychiatry
 University of Pittsburgh Medical Center
 Western Psychiatric Institute and Clinic
 Pittsburgh, PA, USA

Matcheri S. Keshavan, M.D.

Professor and Associate Chair
 Department of Psychiatry and Behavioral
 Neuroscience
 Wayne State University School of Medicine
 Detroit, MI, USA

Dae-Shik Kim, Ph.D.

Associate Professor
 Boston University School of Medicine
 Boston, MA, USA

Liat Levita, Ph.D.

Instructor of Psychology in Psychiatry
 Sackler Institute for Developmental Psychobiology
 Weill Medical College of Cornell University
 New York, NY, USA

Lisa H. Lu, Ph.D.

Postdoctoral Fellow
 Laboratory of Neuro Imaging
 David Geffen School of Medicine
 University of California
 Los Angeles, CA, USA

Rachel Marsh, Ph.D.

Division of Child Psychiatry
 Department of Psychiatry
 Columbia University
 New York State Psychiatric Institute
 New York, NY, USA

Kristin McNealy

Doctoral Student in Neuroscience
 Neuroscience Interdepartmental Program
 Center for Culture, Brain and Development
 Ahmanson-Lovelace Brain Mapping Center
 University of California, Los Angeles
 Los Angeles, CA, USA

Kevin A. Pelphrey, Ph.D.

Associate Professor
 Department of Psychology
 Carnegie Mellon University
 Pittsburgh, PA, USA

Susan B. Perlman, M.A.

Doctoral Student
 Department of Psychology
 Carnegie Mellon University
 Pittsburgh, PA, USA

Bradley S. Peterson, M.D.

Professor
 Department of Psychiatry
 Columbia College of Physicians and Surgeons
 Somers, NY, USA

x **List of contributors**

Daniel S. Pine, M.D.

Chief, Emotional Development and Affective
 Neuroscience Branch
 National Institute of Mental Health
 Bethesda, MD, USA

Steven R. Pliszka, M.D.

Professor and Vice Chair
 Chief, Division of Child and Adolescent Psychiatry
 Department of Psychiatry
 University of Texas Health Sciences Center at
 San Antonio
 San Antonio, TX, USA

Konasale Prasad, M.D.

Department of Psychiatry
 University of Pittsburgh School of Medicine
 Pittsburgh, PA, USA

Hengyi Rao, Ph.D.

Department of Psychiatry and Neurology
 Center for Functional Neuroimaging
 University of Pennsylvania
 Philadelphia, PA, USA

Allan L. Reiss, M.D.

Howard C. Robbins Professor
 Department of Psychiatry and Behavioral Sciences
 Director of the Center for Interdisciplinary Brain
 Sciences Research
 Stanford University School of Medicine
 Stanford, CA, USA

Perry Renshaw, M.D., Ph.D.

Department of Psychiatry
 McLean Brain Imaging Center
 McLean Hospital
 Harvard University Medical School
 Belmont, MA, USA

Susan M. Rivera, Ph.D.

Assistant Professor
 Department of Psychology
 M.I.N.D. Institute

Center for Mind and Brain
 University of California, Davis
 Davis, CA, USA

Jason Royal, Ph.D.

Division of Child and Adolescent Psychiatry
 Columbia University
 New York State Psychiatric Institute
 New York, NY, USA

Judith M. Rumsey, Ph.D.

Chief, Neurodevelopment and Neuroimaging
 Program and
 Executive Function and Attention Deficit
 Hyperactivity Disorder Program
 Neurodevelopmental Disorders Branch
 Division of Developmental Translational Research
 National Institute of Mental Health
 Bethesda, MD, USA

Maulik P. Shah, B.A.

Medical student
 Mood Disorders Research Program
 Yale University School of Medicine
 New Haven, CT, USA

Marisa M. Silveri, Ph.D.

Department of Psychiatry
 Harvard Medical School
 Cognitive Neuroimaging and Neuropsychology
 Laboratory
 Brain Imaging Center
 McLean Hospital
 Belmont, MA, USA

Elizabeth R. Sowell, Ph.D.

Associate Professor of Neurology
 David Geffen School of Medicine
 Laboratory of Neuro Imaging
 University of California, Los Angeles
 Los Angeles, CA, USA

Jeffrey A. Stanley, Ph.D.

Department of Psychiatry and Behavioral
 Neuroscience

Wayne State University School of Medicine
Detroit, MI, USA

Henning U. Voss, Ph.D.

Assistant Professor of Physics in Radiology
Citigroup Biomedical Imaging Center
Weill Cornell Medical College
New York, NY, USA

Jiong-jiong Wang, Ph.D.

Research Assistant Professor
Departments of Radiology and Neurology
Center for Functional Neuroimaging
University of Pennsylvania
Philadelphia, PA, USA

Ke Xu, M.D., Ph.D.

Department of Psychiatry
School of Medicine

Yale University
New Haven, CT, USA

Deborah Yurgelun-Todd, Ph.D.

Cognitive Neuroimaging/Neuropsychology
Laboratory
Brain Imaging Center
McLean Hospital
Harvard Medical School
Belmont, MA, USA

Monica Zilbovicius, M.D.

Unité INSERM-CEA
Service Hospitalier Frederic Joliot
Orsay, France

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Foreword

Neuroimaging has in many ways revolutionized the field of psychiatry, and its ability to help clinicians and researchers understand the mechanisms of childhood psychiatric disorders should not be underestimated. This volume reviews recent developments in neuroimaging techniques and their implications for child psychiatry. It is a unique book in that it focuses on children and integrates brain mapping with genetics and behavioral testing. What is truly astounding is the rapid evolution of this field since the seminal first edition of this book appeared in 2000.

In the past decade, one of the enormous shifts in our thinking about psychiatry has been the growing appreciation that many, if not all, major psychiatric disorders have their antecedents in childhood. It is now clear that the major psychiatric disorders are serious, debilitating, life-shortening illnesses that affect millions of people worldwide. The major psychiatric disorders are clearly “chronic illnesses of the young,” characterized by multiple episodes of symptom exacerbation, residual symptoms between episodes, and functional impairment. These illnesses arise from the complex, developmentally determined interaction of multiple genes and environmental factors, and the phenotypic expression of the disease includes not only affective disturbance, but also a constellation of cognitive, motor, autonomic, endocrine, and sleep/wake abnormalities. Research on the biological underpinnings of the major psychiatric disorders has therefore begun to focus less on absolute changes in individual neurotransmitters, and more on the

role of neural circuits and synapses, and the processes controlling their function.

Revolutionary techniques in neuroimaging and genetics, combined with epidemiological and longitudinal research, have now firmly established that psychiatric disorders are developmental disorders. They emerge while the brain is still developing and evolve into the more easily recognized chronic and disabling course. The field of childhood neuroimaging has played a key role in redefining this thinking. As Section 2 of this book so thoroughly describes, neuroimaging has helped identify atypical brain developmental processes associated with a variety of disorders. These include: attention deficit/hyperactivity disorder (ADHD) (Chapter 7); autism and autism spectrum disorders (Chapter 8); schizophrenia (Chapter 9); bipolar disorder (Chapter 10); anxiety and depressive disorders (Chapter 11); Tourette syndrome and obsessive-compulsive disorder (OCD) (Chapter 12); fragile X syndrome (Chapter 13); alcohol-related disorders (Chapter 14); and eating disorders (Chapter 15). The work outlined in these chapters clarifies the notion that studying these disorders early in life is most likely to eventually allow us to make a major impact on their course. The neuroimaging of normally developing children provides investigators with the unparalleled opportunity to assess human structural brain development and the key domains of normal developmental processes underlying cognitive and regulatory aspects of human behavior. With regards to psychopathology, neuroimaging provides investigators with the opportunity to study and identify risk factors that may appear before the symptoms of any illness and which are therefore unconfounded by treatment. Among its many valuable advantages, neuroimaging also provides investigators with the tools to track the longitudinal course of an illness, to determine correlates of symptom reduction, and to directly assess the effects of medications or other interventions.

The chapters included in Sections 3 and 4 of this book describe many of the most recent advances in neuroimaging with respect to ethical considerations, and technology, experimental design, and

data analysis. They also address which neuroimaging techniques can safely be used to study children – an issue of enormous importance. The most striking thing about these sections of the book is how much the field has expanded – both in scope and volume – since 2000. Because neuroimaging affords us the possibility of directly studying the organ of interest, it has significantly altered how we conceptualize, diagnose, understand, and treat psychiatric disorders. Our expanded understanding, in turn, has led us to refine and improve neuroimaging techniques. There have been advances not only in neuroimaging technology (and particularly in temporal and spatial resolution), but also the adaptation and development of novel cognitive neuroscience techniques. This integrated circle of growth has allowed investigators to conduct innovative translational research directly with children.

The National Institutes of Health (NIH) broadly defines translational research as “the process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease.” True translational research takes this idea a step further and encompasses the bidirectional interplay between clinical and laboratory research – from bench to bedside and back again. Toward that end, neuroimaging has allowed investigators to use methods in children derived directly from cognitive neuroscience approaches used in various settings. These approaches create a basis for improving our understanding, assessment, and treatment of psychiatric disorders in children and adults; these approaches also aid the investigation of mechanisms of treatment response and provide imaging phenotypes for understanding genetic effects on brain and behavior. Ultimately, there is potential for the interventional application of the techniques themselves.

Much has been written lately about the future of predictive and, ultimately, preemptive tools in psychiatry. Part of the rationale for such thinking is the knowledge gleaned from neuroimaging and other studies showing that structural and other changes precede the development of psychiatric disorders in asymptomatic children and adolescents.

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This knowledge has worked synergistically with that derived from the growing field of early intervention in psychiatric disorders to change our thinking from palliative to predictive to preventive care in psychiatry. There is thus a clear need to refine these multifactorial diseases into mechanism-based subcategories so that particular target-based therapies can be matched to particular markers in subgroups of patients. Biological markers or biomarkers are quantitative measurements that provide information about biological processes, a disease state, or response to treatment. The neuroimaging biomarkers discussed in this volume thus hold the potential to provide a better understanding of the etiology and pathophysiology of the complex and heterogeneous psychiatric disorders. Moreover, biomarkers hold considerable potential to identify patients who are likely to respond to a particular treatment modality. Indeed, the Food and Drug Administration has recently changed its definitions and requirements of biomarkers to include broader categories, and to encourage submissions of putative biomarkers.

Since the first edition of this book was published in 2000, an extraordinary number of articles have been published regarding the ability of early intervention to delay the onset or positively influence the course of many psychopathological conditions. Neuroimaging – both of children and adults – has been an integral part of this evolving field. However, more research is certainly needed to further elucidate this topic, to identify and refine the prodromal manifestations of each psychopathological condition, to introduce and use appropriate measuring instruments, and to apply validated interventions, particularly in children. Neuroimaging is one of the most powerful tools in our armament to predict psychopathology. Finally, and as Chapter 16 of this book so excellently points out, there are multiple ethical issues concerning neuroimaging in children, and these must be examined very carefully.

Given the varied nature of presentation and variability in course of many of the major psychiatric

illnesses, separating and appropriately treating at-risk individuals constitutes a serious challenge. Careful selection of the subjects who might benefit from an early intervention and appropriate study designs to correctly evaluate outcome, though ongoing, are still needed. Prospective large-scale studies from high-risk populations with appropriate biological markers, likely neuroimaging in nature, could help identify “real” high-risk subjects and develop new treatment algorithms. Moreover, the primary outcome measure of randomized controlled trials should be not only syndromic resolution, but also functional and psychosocial recovery, along with cognitive improvement. The results from studies conducted with high-risk subjects will eventually help identify clinical prodromes and biological markers in subjects from the general population as well.

As the outstanding chapters in this volume have highlighted, the future of early intervention depends on our ability to identify individuals at risk for developing major psychiatric illnesses, and the capacity to provide targeted treatment that specifically prevents onset or recurrence of episodes. Though such work will not easily be put into practice, we now have significant clues about not only disease onset and progression, but also about the tools that are needed to help implement successful early intervention.

The back cover of the previous 2000 edition of this book noted that the book's focus on children and on integrating brain mapping with genetics and behavioral testing was “an interface *that is likely to become* fundamental to functional neuroimaging” (italics mine). Eight years later, these prescient words reflect how quickly extraordinary innovations can be adopted in medicine when they truly advance our understanding. The excellent chapters contained in this book highlight how far the field of neuroimaging in childhood has brought us but, more importantly, how far it can yet take us.

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Preface

Neuroimaging in Developmental Clinical Neuroscience provides a broad review of the use of neuroimaging in the emerging field of developmental clinical neuroscience. This volume updates and expands the earlier *Functional Neuroimaging in Child Psychiatry*, edited by Monique Ernst and Judith Rumsey and published in 2000. Since the publication of the earlier volume, there has been an exponential surge in the number of neuroimaging publications addressing the development of the pediatric brain. Paralleling this growing literature is a widening of the scope and diversity of the studies, with respect to both scientific focus and the methods applied.

A heightened focus has been directed onto normative development in a variety of domains, including cognitive control, emotion regulation, goal-directed behavior, social cognition, and language. Recent advances in imaging technologies, such as blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), perfusion imaging using arterial spin labeling (ASL), and magnetic resonance spectroscopy (MRS) now provide a rich armamentarium of techniques whose integration with one another and with other neuroscience approaches offers unprecedented opportunities for elucidating human neurodevelopment. Structural magnetic resonance imaging, one of the oldest of the techniques included in this volume, has likewise advanced, as new analytic techniques have enhanced our ability to derive meaningful information from anatomical images.

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These approaches are increasingly being applied to delineate neurocircuitry involved in developmental neuropsychiatric disorders and have begun to provide a basis for advancing assessment and treatment. Beyond this, these approaches are being expanded to investigate mechanisms of treatment response and to provide imaging phenotypes for understanding genetic effects on brain and behavior. And finally, there are hints of potential for interventional applications of these techniques themselves.

This book is organized into five sections. Section 1 is dedicated to the understanding of normative pediatric brain-behavior development. This section describes our knowledge of human structural brain development from a neuroimaging perspective. Key domains of normal developmental processes underlying cognitive and regulatory aspects of human behavior are addressed in six chapters that focus primarily on functional brain measures, including fMRI and electrophysiology. Section 2 considers atypical developmental processes associated with a variety of disorders, including attention deficit/hyperactivity disorder (ADHD), autism spectrum disorders, schizophrenia, bipolar disorder, anxiety and depressive disorders, Tourette syndrome and obsessive-compulsive disorder (OCD), fragile X syndrome, alcohol-related disorders, and

eating disorders. Section 3 will provide the reader with essential knowledge of legal, regulatory, and ethical guidelines and considerations governing research involving children. Section 4 addresses neuroimaging techniques that can safely be used to study children. Also included are two special topics that integrate neuroimaging with other neuroscience approaches – the study of responses to pharmacological and other interventions and imaging genetics, an emerging approach that shows promise for deconstructing complex behavioral phenotypes. Finally, in Section 5 we highlight the value of a developmental perspective and the progress achieved in understanding human brain maturation and developmental neuropsychiatric disorders using these approaches. Finally, we outline some critical needs and challenges and consider directions for future research.

The authors wish to thank David Shore, M.D., Associate Director for Clinical Research, National Institute of Mental Health (NIMH) and Benedetto Vitiello, M.D., Chief, Child and Adolescent Treatment and Preventive Intervention Research Branch, NIMH for their helpful review of selected material. We also wish to thank our families for their patience and support while we dedicated so much of our energy toward this unique volume.