## Contents

<table>
<thead>
<tr>
<th>List of Contributors</th>
<th>page vii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>xiii</td>
</tr>
<tr>
<td>Preface</td>
<td>xvii</td>
</tr>
</tbody>
</table>

### Section 1 Normal developmental processes 1

1. Introduction to Section 1 3

2. Morphological development of the brain: what has imaging told us? 5
   Lisa H. Lu and Elizabeth R. Sowell

3. Neural correlates of the development of cognitive control 22
   Silvia A. Bunge and Eveline A. Crone

4. Neurobiology of emotion regulation in children and adults 38
   Ian H. Gotlib and Jutta Joormann

5. Goal-directed behavior: evolution and ontogeny 53
   Monique Ernst and Michael G. Hardin

6. Charting brain mechanisms for the development of social cognition 73
   Kevin A. Pelphrey and Susan B. Pearlman

7. Language and the developing brain: insights from neuroimaging 91
   Kristin McNealy, Mirella Dapretto and Susan Bookheimer

### Section 2 Atypical processes in developmental neuropsychiatric disorders 109

8. Introduction to Section 2 111
7 A pathophysiology of attention deficit/hyperactivity disorder: clues from neuroimaging
Jeffery N. Epstein

8 Brain imaging of autism spectrum disorders
Monica Zilbovicius, Nathalie Boddaert and Nadia Chabane

9 Neuroimaging of schizophrenia and its development
Matcheri S. Keshavan, Vaibhav A. Diwadkar, Konasale Prasad and Jeffrey A. Stanley

10 Cortico-limbic development in bipolar disorder: a neuroimaging view
Jessica H. Kalmar, Maulik P. Shah and Hilary P. Blumberg

11 Anxiety and depressive disorders
Daniel S. Pine

12 Disturbances of fronto-striatal circuits in Tourette syndrome and obsessive-compulsive disorder
Rachel Marsh, Daniel A. Gorman, Jason Royal and Bradley S. Peterson

13 From genes to brain to behavior: the case of fragile X syndrome
Susan M. Rivera and Allan L. Reiss

14 Alcohol exposure and the developing human brain
James M. Bjork

15 Neuroimaging as a tool for unlocking developmental pathophysiology in anorexia and bulimia nervosa
Guido K. W. Frank and Walter H. Kaye

Section 3 Ethical issues
Introduction to Section 3

16 Legal and ethical considerations in pediatric neuroimaging research
Clinton D. Hermes

Section 4 Techniques and integration with other research approaches
Introduction to Section 4

17 BOLD fMRI: an update with emphasis on pediatric applications
Liat Levita, Rebecca M. Jones and B. J. Casey

18 Magnetic resonance spectroscopy: methods and applications in developmental clinical neuroscience
Marisa M. Silveri, Deborah Yurgelun-Todd and Perry Renshaw

19 Diffusion tensor imaging in developmental clinical neuroscience
Dae-Shik Kim

20 Arterial spin labeling perfusion magnetic resonance imaging in developmental neuroscience
Jiong-Jiong Wang, Hengyi Rao and John A. Detre

21 Neuroimaging of treatment effects in developmental neuropsychiatric disorders
Steven R. Pliszka and David C. Glahn

22 Functional alleles, neuroimaging and intermediate phenotypes in the deconstruction of complex behavioral variation
David Goldman, Beata Buzas and Ke Xu

Section 5 Progress and future directions
Introduction to Section 5

23 Neuroimaging in developmental clinical neuroscience today
Judith M. Rumsey and Monique Ernst

Appendix A: Functional MRI educational resources and software
Appendix B: Neuroinformatics and neuroethics resources
Glossary
Index
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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.
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.

Husseini K. Manji, M.D.
Preface

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.
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.