Since the early 1990s, developmental neurobiology has made important strides towards elucidating the pathophysiology of psychiatric disorders. Nowhere has this link between basic science and clinical insights become more evident than in the field of schizophrenia research. In this volume, the editors bring together some of the most active investigators in this field. Each contributor provides an up-to-date overview of the relevant research, including directions for further investigation.

The book begins with a section on advances in developmental neurobiology. This is followed by sections on etiological and pathophysiological developments, and models that integrate this knowledge. The final section addresses the clinical insights that emerge from the developmental models and sets the scene for future efforts at early detection and prevention of schizophrenia.

This book will be valuable to researchers in psychiatry and neurobiology, students in medicine and psychology, and all mental health practitioners.
Neurodevelopment and Schizophrenia

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Foreword

Although both Kraepelin and Bleuler noted that premorbid abnormalities in childhood could be present many years before a schizophrenic psychosis developed (Marenco and Weinberger, 2000), until the late 1980s and 1990s, most people viewed schizophrenia as an adult-onset mental illness. As a result, most biological studies focused on a search for possible neurodegenerative changes that might account for the onset of the condition. During the 1960s and 1970s (see Garmezy, 1974; Offord and Cross, 1969), evidence began to accumulate from developmentally oriented follow-up and follow-back studies that abnormalities in interpersonal relationships, neurodevelopmental immaturities, and attentional deficits in childhood all predicted the later onset of schizophrenia (see Rutter and Garmezy, 1983). However, it was not until 1987 (Murray and Lewis, 1987; Weinberger, 1987) that psychiatrists concerned with adult patients firmly took on board the notion that schizophrenia might be a neurodevelopmental disorder. Since then, there has been a veritable explosion of research tackling this proposition using a variety of research strategies. In parallel, there has been an upsurge in studies of brain development and function, giving rise to a much better understanding of brain plasticity and of the role of neurotransmitters in both normal functioning and disease states. Clearly, the time is ripe for a book that brings together the findings and concepts deriving from both basic and clinic neuroscience, in order to examine the neurodevelopmental hypothesis in a critical but constructive fashion and then to consider the implications for clinical practice. This book does just that, and does it extremely well.

There is abundant consistent evidence that there are strong genetic influences on the underlying liability to develop schizophrenia. Accordingly, one key challenge for the neurodevelopmental hypothesis is to make explicit how neurodevelopmental risk factors relate to genetic risk for schizophrenia. It is appropriate, therefore, that the book begins with an account of what is known about genetic influences on brain development, followed by reviews of what has been learned about normal brain development from structural and functional magnetic resonance imaging studies. Contrary to some people’s view that brain development is confined to infancy, it is evident that there are important neural changes that extend into late adolescence.
and early adult life. It remains the case that we have much to learn still about how these changes relate to both normal and abnormal development, but they provide a possible basis for the transition from the premorbid features of childhood to the overt psychosis seen in adult life. This transition is also discussed with respect to the evidence that there may be new abnormal brain changes that occur at this time.

The velo–cardio–facial syndrome is put forward as a possible model for the interplay between genes, brain, behavior, and cognition, and it is also suggested that structural magnetic resonance imaging could provide a useful endophenotype for genetic studies. This reflects the growing awareness that susceptibility genes probably do not act directly on mental disorders and that, therefore, it may be useful to examine genetic effects on neurobiological abnormalities representing more proximal effects of genes.

The neurodevelopmental hypothesis has been accompanied by indications of the possible contributory causal role of epigenetic factors, malnutrition, pre- and perinatal risk factors (including infection), minor physical anomalies, and adverse rearing environment. The evidence on all of these is succinctly reviewed, with the conclusion that the risk effects are probably real even though their effect size is small.

Initially, with the advent of persuasive findings in genetics and in biological psychiatry more generally, it became unfashionable to consider either social risk factors or the effects of drug abuse: both of which had constituted a major focus of interest in the 1960s and 1970s. However, animal studies and migration studies of humans have shown that there is now reasonable evidence that social factors are influential, even though we do not understand how they operate. What is quite different from the 1960s and 1970s is the appreciation that it is necessary to understand how social factors may impact on brain development and that there may well be a synergistic interplay between environmental risk and genetic vulnerability, with the risks largely dependent on the presence of genetic susceptibility. Much the same message derives from the study of recreational drugs, with the specific suggestion that the drug effects associated with heavy early usage affect neurotransmitters in ways that may precipitate the onset of psychosis when combined with genetic susceptibility.

Further chapters provide a more detailed consideration of the possible role of the dopamine system, of mis-wired limbic lobe or thalamocortical circuitry, of estrogen and X-chromosome effects on brain development, of premorbid structural brain abnormalities, and of neurodegenerative models.

From a clinical perspective, it is crucial to know whether the neurodevelopmental features are specific to schizophrenia or apply to a broader range of psychiatric conditions. In frustrating fashion, the evidence suggests both substantial commonalities and important specificities. A key chapter considers whether the extensive
Foreword

evidence of premorbid abnormalities means that it should now be possible to identify children who are likely to develop schizophrenia. It is concluded that this is not yet possible, yet combining risk factors from different functional domains can usefully enhance the accuracy of predictive models. The final chapter discusses how it may be possible for the pathophysiology to be explained by an integrative neurochemical model and how there is now the beginning of a basis for possible preventive interventions.

The book provides a rich intellectual meal of great interest and importance. Nevertheless, we have to ask where all these creative ideas and empirical findings get us. The book has two main achievements. First, it provides an excellent compilation of what is known about the neurodevelopmental origins of schizophrenia, what the findings explain, and what research challenges remain (together with invaluable suggestions on how these challenges might be met). The evidence is compelling that, in crucial ways, schizophrenia is a neurodevelopmental disorder and that research using this concept has been immensely productive. There is the promise of a better understanding of how neurodevelopmental features relate to genetic risk, but that understanding has not yet been achieved. Similarly, although the onset in late adolescence/adult life, long after premorbid manifestations have been evident in childhood, is no longer quite the mystery that it was, the causal pathways have still to be delineated. Nevertheless, the book clearly documents that neurodevelopmental approaches are now mainstream in the study of schizophrenia and that much has been learned in the last decade or so.

The second achievement is that the consideration of neurodevelopmental origins of schizophrenia has thrown invaluable light on the broader issues involved in normal and abnormal brain development. This gives the book an interest that extends well beyond the world of schizophrenia clinicians and researchers. It is not light bedtime reading, but the book does provide an engrossing read that is richly rewarding.

Michael Rutter

REFERENCES


Foreword


Preface

This volume arises out of a widely perceived need to take stock of our new knowledge about the developmental pathophysiology of schizophrenia. In 1997, we published our first book on this topic, entitled *Neurodevelopment and Psychopathology*. That volume, which was surprisingly well received, covered neurodevelopmental approaches to adult psychopathology, though many of the chapters concerned schizophrenia. The enormous progress made in the subsequent years, particularly on schizophrenia, has led us to focus the current volume exclusively on this disorder, arguably the most debilitating of all psychiatric illnesses.

Since the early 1990s, our understanding of the developmental origins of schizophrenia has “come of age,” with impressive advances emerging from both the basic sciences and clinical studies. In retrospect, it is clear that the early neurodevelopmental models that emerged in the mid-1980s were extremely simplistic and too often relied on speculations about cellular and molecular mechanisms that were not subsequently confirmed. Furthermore, to a large extent, they ignored the contribution of psychology and certainly they included no mention of the role of the social environment. We believe that the recent explosion of knowledge in both neuroscience and cognitive science, as well as in imaging and epidemiology, has allowed us to begin to remedy such deficiencies. Therefore, this new book brings together many of the most productive and admired investigators in those areas of research, individuals who we believe have contributed most to contemporary developmental models of schizophrenia. Each of the chapters provides a state-of-the-art overview of the authors’ area of expertise, including directions for the future.

We start with a section on recent advances in developmental neurobiology. The current state of our knowledge of genetics is reviewed, including the recent identification and apparent replication of susceptibility genes for schizophrenia (Ch. 1). The latter is no small cause for rejoicing as claims for the identification of genes had previously materialized and dematerialized with disturbing regularity, rather like the sightings of alien spacecraft. Then, progress in our understanding of the normal development of the human brain and its structural (Ch. 2), functional (Ch. 3), and cognitive (Ch. 4) properties is successively outlined. Such a perspective is vital since schizophrenia researchers have all too often attempted to outline the abnormal
psychology and physiology underlying the condition before the normal had been charted. The important field of brain plasticity and its limits is then discussed in Ch. 5 with its implications for long-term functioning and psychopathology.

The next section contains overviews of pathophysiology and etiology of schizophrenia. The lessons for schizophrenia from the study of unusual genetic disorders such as the velo-cardio-facial syndrome are discussed, as is the impact of genetic loading for schizophrenia on brain structure (Chs. 7 and 8). The important and now well-documented effects of early environmental factors such as perinatal complications (Ch. 11) and nutritional anomalies (Ch. 9) on risk of schizophrenia are reviewed. Then the newer field of the effects of risk factors nearer to the onset of psychosis is considered, such as psychosocial adversity (Ch. 13) and drug abuse (Ch. 14) in pathogenetics, their epigenetic interaction (Ch. 10), and their impact on gene expression (Ch. 12). Chapter 6 outlines a novel theory on the etiological role of stress on schizophrenia and how its effects may be mediated by glucocorticoids. At a pathophysiological level, the developmental dysregulation of the neurotransmitter systems such as dopamine (Ch. 15), and the limbic (Ch. 16) and thalamocortical (Ch. 17) circuitry are critically reviewed. The important role of X chromosome and estrogens in brain development and its relevance for schizophrenia are discussed in Ch. 18. The possible premorbid neurodegenerative changes in the schizophrenic illness (Ch. 20) and the commonalities versus differences between developmental/degenerative changes in common neuropsychiatric disorders beginning in childhood/adolescence (Ch. 21) are discussed.

In the final section, some of the important clinical questions that drive pathophysiological research are considered. Can we identify preschizophrenia children? What do studies of those at high genetic risk of the disorder teach us? Does understanding of pathophysiology lead to specific predictions for preventive and therapeutic approaches?

For too long, the origins of schizophrenia have been considered to be shrouded in mystery. However, the exciting advances that have been made in schizophrenia research in the past decades, captured in this volume, have made the disease more comprehensible, even though the puzzle continues to unravel. We also hope that this volume will be of value for both researchers and practicing clinicians. Throughout this volume, the implications of research findings for clinical practice are discussed. The book will have served its purpose if the topics discussed herein provided stimulation and new learning for a new generation of researchers and clinicians in their efforts to inch toward better scientific knowledge and therapeutic possibilities as applied to the patient with schizophrenia.

We wish to express our sincere gratitude to Drs Vaibhav Diwadkar, Debra Montrose, Raj Rajarethinam, and Vandana Shashi for providing peer reviews of the chapters in this book. We are in particular grateful to Karol L. Rosengarth for her painstaking efforts in formatting and proofreading this work.