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# HANDBOOK OF CLINICAL NEUROLOGY

Series Editors:

MICHAEL J. AMINOFF, FRANÇOIS BOLLER,  
DICK F. SWAAB

106

3rd Series

## NEUROBIOLOGY OF PSYCHIATRIC DISORDERS

Edited by:

THOMAS E. SCHLAEPFER  
CHARLES B. NEMEROFF

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# NEUROBIOLOGY OF PSYCHIATRIC DISORDERS

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*Series Editors*

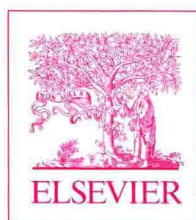
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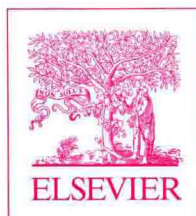
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## Foreword

We are pleased to present, for the first time, a volume in the *Handbook of Clinical Neurology* series devoted exclusively to psychiatric disorders. It is true that Volumes 45 and 46 of the second series – on Clinical Neuropsychology and Neurobehavioral Disorders – had a few chapters that dealt with aspects of the major psychiatric disorders, but these were limited in scope and number. The volumes were published in 1985, when there was still a strict separation and even animosity between the fields of neurology and psychiatry. George W. Bruyn, one of the founders of the HCN series, however, was not convinced of any fundamental difference between these two disciplines and stated boldly that, “psychiatry is nothing but unexplained neurology.”

Many neurologists of the late nineteenth and early twentieth century felt quite at home with psychiatry, which was then considered to be a special branch of neurology, a point of view shared by such luminaries as Charcot, Meynert, Von Monakow, Edinger, Wernicke, Spielmeier, Pick, and Von Gudden. In those days, most mental hospitals had a laboratory for anatomy and pathology. Many of the famous university professors held chairs in both neurology and psychiatry, as they were interested in both the clinical and the fundamental aspects of the central nervous system. For a long time formalized residency training included both psychiatry and neurology, and the term “neuropsychiatry” was coined, to illustrate the integration of the two fields.

Psychotherapy, developed by Sigmund Freud in the early 1900s, was the principal method of treatment for mental disorders throughout the 1950s. The emergence of analytical psychiatry gradually led to a schism between neurology and psychiatry. For instance, in the Netherlands this resulted in a complete separation between the two when, in 1974, the Dutch Society for Neurology and Psychiatry was split into two separate societies.

In the meantime, in the late 1950s, the first antipsychotic and antidepressant drugs came into widespread use and their clinical effects resulted in “chemical imbalance” hypotheses of mental disorders. This formed the conceptual basis for the development of “biological psychiatry”: research now focused on the brain itself and on the neurobiological mechanisms that caused disorders such as depression and schizophrenia. We have thus, in a sense, come full circle to a situation where the differences and borders between psychiatry and neurology are once again blurred. Mental illnesses are now considered to be genetically and environmentally influenced disorders of brain chemistry. The emergence and development of imaging techniques have contributed tremendously to the shift of attention to the neurosciences in psychiatry. The structural and molecular basis of neuropsychiatric disorders is becoming clearer, making the present volume an extremely timely one.

We congratulate the two volume editors, Thomas Schlaepfer and Charles Nemeroff, for putting together this outstanding volume, which will appeal to psychiatrists, neurologists and neuroscientists alike. Clinical, genetic, molecular, imaging, neuropathological, immunological, epidemiological, metabolic, therapeutic and historical aspects of the major psychiatric disorders are reviewed in a thoughtful and scholarly manner. In addition, the potential and limitations of animal experimental models for these disorders are extensively discussed.

As always we are very grateful to the team at Elsevier, and especially to Mr. Michael Parkinson, for expert assistance in the development and production of this volume.

Michael J. Aminoff  
François Boller  
Dick F. Swaab



# Preface

*"I don't consider this my science. This is my avocation. But that avocation has been completely influenced by my science."*

Eric Kandel in a 1996 lecture commemorating the 100th anniversary of the New York State Psychiatric Institute, Columbia University College of Physicians and Surgeons.

This volume on psychiatric disorders appears for the first time in the prestigious *Handbook of Clinical Neurology* series; an event that affirms our belief of a fundamental conceptual shift in the conceptualization of mental disorders. Psychiatry is the medical discipline diagnostically assessing and treating patients with multifaceted and complex brain disorders that represent the leading causes of disability worldwide. These disorders are highly prevalent; each year over 25% of adult Americans carry the diagnosis of at least one mental disorder and similar data has been reported for Europe. The public health impact of depression is in part due to the fact that available treatments are suboptimal; in the case of major depression, up to 40% of patients responding to antidepressant therapy suffer from clinically relevant residual symptoms despite optimized treatment and a large sequenced treatment (STAR\*D) study, which analyzed outcome following several standardized treatment steps, reported that 33% of patients did not respond despite four evidence-based treatment steps. Historically, brain disorders of unknown etiology fell in the domain of psychiatry and those with known etiology in the domain of neurology.

The quotation above by Eric Kandel was published in 1998. This paper and several others by him and others that predate it had a significant influence on the science of psychiatry, by addressing the conceptual shift from a purely psychoanalytic framework, often conceptualized as the antithesis of biological psychiatry, to the synthesis of psychiatry as a truly comprehensive, behavioral neuroscience. By studying the sea slug *Aplysia* and the fruit fly *Drosophila*, Kandel and his colleagues demonstrated that memory storage depends on the coordinated expression of specific genes that code for proteins that alter structural elements of the brain. This is particularly notable because Kandel, born in Vienna, connected after his immigration to the USA to that city's psychiatric history by training as a psychoanalyst, a profession at that time far removed from the biological sciences. When Sigmund Freud – the founder of psychoanalysis – explored implications of unconscious mental processes for behavior, he tried to adopt a neuroscientific model of behavior in an attempt to develop a scientific psychology. He proposed that the cognitive mechanisms of normal and abnormal mental phenomena could be explained through orderly and rigorous study of brain systems. Given the state of scientific methodology in psychiatry at the time – mainly restricted to histopathology and assessing brain states by verbal reports of patient's subjective experiences – this was a somewhat futile attempt.

During the 20th century, a series of rapidly changing emphases have been prominent within psychiatry, each one dominating a period spanning two or more decades. These developments have contributed to both diffusion and confusion about what psychiatry really is and what it stands for, ultimately affecting the credibility of the profession. The long-standing tradition of moving disorders from the domain of psychiatry to neurology once the pathophysiology was elucidated, as occurred with pellagra and neurosyphilis, has now finally ended with understanding that the major psychiatric disorders are in fact brain diseases. Research on brain disorders has led to novel insights into etiology and pathogenesis using brain imaging techniques and molecular methods. Thus a number of genetic risk factors for psychiatric and neurological disorders have been identified and molecular pathological mechanisms are increasingly being scrutinized in appropriate experimental models. Molecular research has even led to recognition of the biological consequences and transgenerational impacts of violence and abuse. The application of the rapidly increasing knowledge base in molecular and cellular neurobiology into psychiatry presages a new understanding of psychiatric illness and its treatment, thereby overcoming the ideological struggles between



biology and psychodynamics—a confrontation that often was detrimental to patient care. The application of evidence-based medicine to psychotherapeutic treatments has revealed the efficacy of cognitive behavior therapy (CBT), interpersonal psychotherapy (IPT), dialectical behavior therapy (DBT) and most notably in some recent studies, psychodynamic psychotherapy. Molecular biological research has lead to new hypotheses on brain disorders; this research will undoubtedly lead to conceptually new therapeutic strategies and the understanding of the mechanisms of action of effective psychopharmacological and psychotherapeutic treatments. In the future it will be germane to strengthen translational research approaches, a process in which new basic research findings will be translated to clinical application – and from bench to bedside and back – clinical observations are fed back to basic research allowing the generation of new testable hypotheses.

In this volume we sought to provide a comprehensive and integrated view of psychiatric care and its current scientific foundations in 45 chapters. To give a truly international overview – well within the tradition of Sigmund Freud and Eric Kandel – we invited two authors for each chapter, recognized experts in the chapter's subject area, one from the USA and one from elsewhere. In most cases this ambitious goal was achieved, resulting in outstanding reviews of the topics reflecting the international state of the science. Each chapter was reviewed by the editors and the series editors to assure completeness of coverage and quality. We truly believe that the burgeoning body of research on the pathogenesis and pathophysiology of psychiatric illness and the increasing number of treatments available to patients reviewed in this volume is at last beginning to lift the stigma of mental illness and offering hope to those who suffer from it.

Thomas E. Schlaepfer  
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