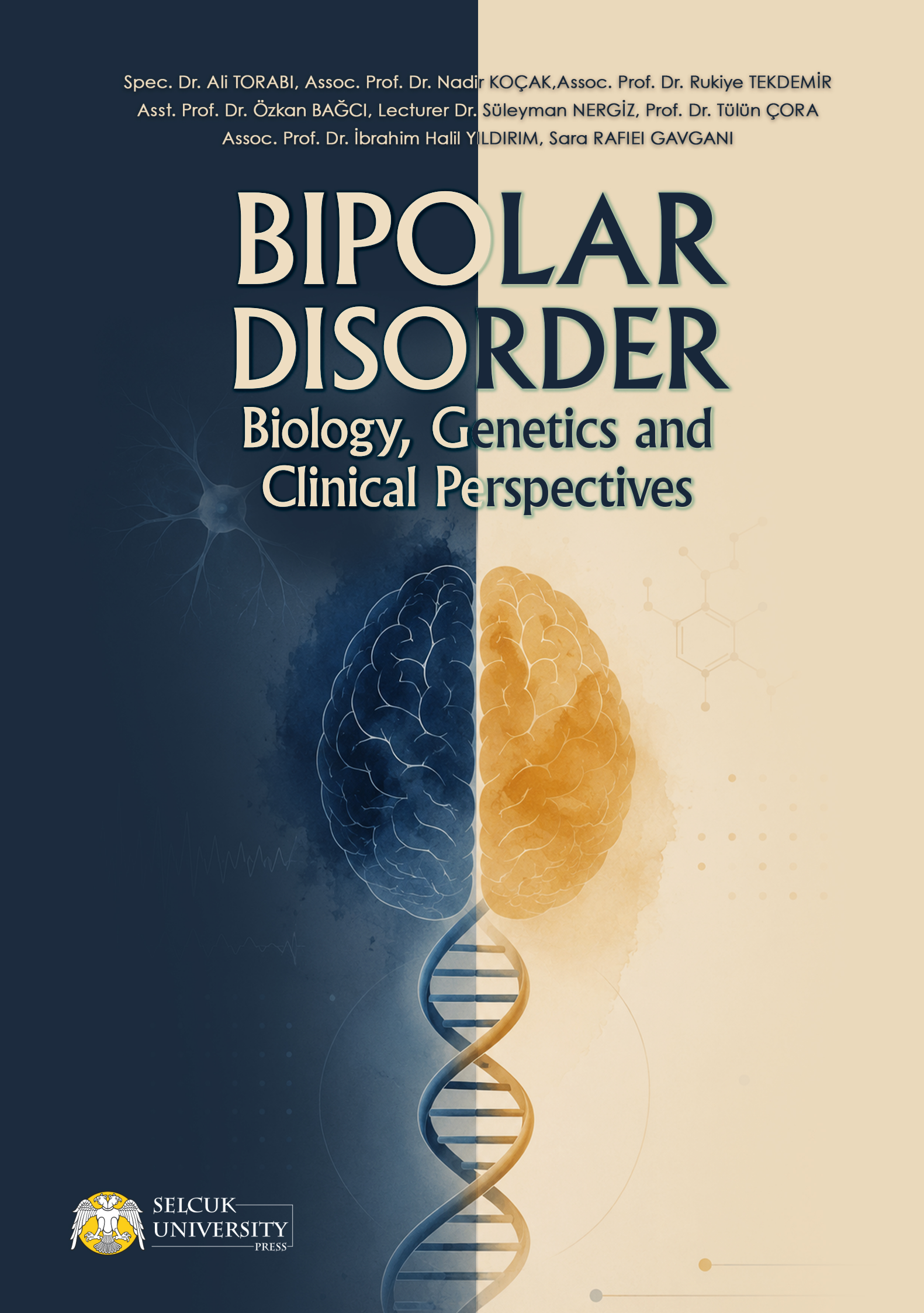
Spec. Dr. Ali TORABI, Assoc. Prof. Dr. Nadir KOÇAK,Assoc. Prof. Dr. Rukiye TEKDEMİR
Asst. Prof. Dr. Özkan BAĞCI, Lecturer Dr. Süleyman NERGİZ, Prof. Dr. Tülün ÇORA
Assoc. Prof. Dr. İbrahim Halil YILDIRIM, Sara RAFIEI GAVGANI

# BIPOLAR DISORDER

## Biology, Genetics and Clinical Perspectives



SELCUK UNIVERSITY PRESS

# BIPOLAR DISORDER
## BIOLOGY, GENETICS AND CLINICAL PERSPECTIVES

AUTHORS
SPEC. DR. ALİ TORABI
ASSOC. PROF. DR. NADİR KOÇAK
ASSOC. PROF. DR. RUKİYE TEKDEMİR
ASST. PROF. DR. ÖZKAN BAĞCI
LECTURER DR. SÜLEYMAN NERGİZ
PROF. DR. TÜLÜN ÇORA
ASSOC. PROF. DR. İBRAHİM HALİL YILDIRIM
SARA RAFIEI GAVGANI

SELCUK UNIVERSITY PRESS

**BIPOLAR DISORDER: BIOLOGY, GENETICS AND CLINICAL PERSPECTIVES**

**Authors:**
Spec. Dr. Ali TORABI (ORCID: 0000-0002-1843-1592)
Assoc. Prof. Dr. Nadir KOÇAK (ORCID: 0000-0002-1104-1292)
Assoc. Prof. Dr. Rukiye TEKDEMİR (ORCID: 0000-0001-7912-5727)
Asst. Prof. Dr. Özkan BAĞCI (ORCID: 0000-0002-9896-6764)
Lecturer Dr. Süleyman NERGİZ (ORCID: 0000-0001-6979-3713)
Prof. Dr. Tülün ÇORA (ORCID: 0000-0001-9787-7519)
Assoc. Prof. Dr. İbrahim Halil YILDIRIM (ORCID: 0000-0001-5518-5004)
Sara RAFIEI GAVGANI (ORCID: 0009-0001-8258-4817)
**Cover Design:** Tuğçe DELEN
**Selcuk University Press:** June, 2026
**ISBN:** 978-975-448-264-5
**DOI:** https://doi.org/10.59726/SUPress/9789754482645
**Keywords:** 1. Bipolar disorder, 2. Molecular genetics, 3. Neurobiology, 4. Clinical phenomenology, 5. Biomarkers.
**Cite This:** Torabı, A., Koçak, N., Tekdemir, R., Bağcı, Ö., Nergiz, S., Çora, T., Yıldırım, İ. H., Gavgani, S. R., (2026), Bipolar Disorder: Biology, Genetics and Clinical Perspectives, Selcuk University Press.

Selcuk University Press in under the body of Scientific Publications Coordinatorship.
**Publisher:** Selcuk University Press
**Publisher Certification Number:** 43463
**Scientific Publications Coordinator:** Prof. Dr. Tuncer ACAR

**Addres:** Selçuk Üniversitesi Yayınları, Alaeddin Keykubat Yerleşkesi, Akademi mah. Yeni İstanbul Cad. No:369
Posta Kodu: 42130, Selçuklu-Konya/Türkiye
**Web:** yayinevi.selcuk.edu.tr
**E-posta:** yayinevi@selcuk.edu.tr
**Phone:** 0 (332) 241 00 41

# Bipolar Disorder

## Biology, Genetics, and Clinical Perspectives

*A Comprehensive Psychogenetic Review*

**NeuroPsyBiT Research Group**

RTSGD NeuroPsychogenetic Bipolar Türkiye

*in collaboration with*

Research and Treatment Society of Genetic Disorders (RTSGD)

*Dedicated to all individuals and families living with bipolar disorder,*

*and to the researchers and clinicians who devote their careers*

*to understanding and treating this complex condition.*

*"In the middle of difficulty lies opportunity."*

*— Albert Einstein*

# Table of Contents

# Preface

Bipolar disorder is one of the most complex and debilitating psychiatric conditions known to humankind. Affecting approximately 1–2% of the global population, it is characterized by extreme oscillations in mood, energy, and cognition that profoundly disrupt the lives of those affected and their families. Despite centuries of clinical observation and decades of intense research, the precise pathophysiology of bipolar disorder remains an open question, a testament to the staggering complexity of the human brain and genome.

This book was conceived from a desire to bridge the ever-widening gap between clinical psychiatry and molecular genetics. In our experience as clinicians and researchers associated with NeuroPsyBiT (RTSGD NeuroPsychogenetic Bipolar Türkiye) and the Research and Treatment Society of Genetic Disorders (RTSGD), we have observed that while remarkable progress has been made in understanding the genetic architecture of bipolar disorder, much of this knowledge remains siloed within specialized journals and inaccessible to clinicians, trainees, and researchers in adjacent fields.

Our approach in this volume is deliberately pedagogical. We begin with the clinical foundations — the historical evolution of the bipolar concept, the modern diagnostic criteria, the rich phenomenology of manic and depressive episodes, and the nuanced sub-phenotypic features that make each patient's presentation unique. We believe that a firm grounding in clinical reality is essential before venturing into the molecular realm, for it is the clinical phenotype that ultimately defines the target of genetic investigation.

From this clinical base, we build upward through the neurobiology of bipolar disorder — examining the neuroanatomical circuits, neurotransmitter systems, neuroendocrine axes, neuroimaging findings, circadian biology, and the rapidly expanding field of neuroinflammation. Each of these domains provides critical clues about the biological substrates that genetic variants must ultimately influence.

We then turn to the genetic and molecular biology of bipolar disorder. Beginning with the foundational evidence from family, twin, and adoption studies, we trace the evolution of genetic approaches from linkage analysis through the genome-wide association study (GWAS) era and into the current landscape of whole-exome and whole-genome sequencing. We examine in detail the candidate genes that have emerged from decades of investigation, the common and rare variant architectures, and the increasingly important roles of epigenetics and gene-environment interactions.

In the final section, we attempt what we consider the most important and challenging task: integrating these disparate streams of evidence into coherent molecular clustering models. We propose hypothetical frameworks that link specific genetic variants to neurobiological pathways and, ultimately, to clinical phenotypes. These hypotheses are offered not as definitive conclusions but as starting points for future investigation, and we fully expect that many will be refined, revised, or replaced as the field advances.

Throughout this book, we have strived to present the current literature fairly and accurately, acknowledging areas of consensus and controversy with equal honesty. Each

chapter concludes with key learning points designed to consolidate the reader's understanding and facilitate review.

We hope this volume serves as a useful companion for psychiatrists, geneticists, neuroscientists, trainees, and all who seek to understand the biological foundations of bipolar disorder. The journey from bedside to bench and back again is long and winding, but it is a journey that holds the promise of transforming the lives of millions.

NeuroPsyBiT Research Group March 2026

# PART I
# CLINICAL FOUNDATIONS

CHAPTER 1

# Historical Perspectives and the Evolution of the Bipolar Concept

## 1.1 Ancient Descriptions of Mania and Melancholia

The recognition that extreme states of elation and profound sadness represent distinct yet related conditions extends back to the earliest written records of medical thought. Ancient Greek physicians, most notably Hippocrates (c. 460–370 BCE), described mania and melancholia as two fundamental disturbances of temperament. Hippocrates attributed these states to imbalances in the four humors — specifically, an excess of yellow bile producing mania and an excess of black bile (melas kholé) producing melancholia. While these humoral theories have long since been superseded, the clinical observations underlying them were remarkably astute.

Aretaeus of Cappadocia, writing in the first century CE, is widely credited as the first physician to explicitly link mania and melancholia as manifestations of a single disease process. In his treatise "On the Causes and Signs of Chronic Diseases," Aretaeus observed that melancholia could transform into mania and that both conditions shared a common underlying etiology. This insight, revolutionary for its time, would not be fully elaborated upon for nearly two millennia.

The Roman physician Galen (129–216 CE) further refined humoral theory and distinguished several subtypes of melancholia, including forms associated with fear, despondency, and misanthropy. Throughout the medieval period, however, these observations were largely subsumed into religious and supernatural explanations of mental disturbance, with conditions we would now recognize as bipolar disorder attributed to demonic possession, moral failing, or divine punishment.

The Renaissance and early modern period saw a gradual return to naturalistic explanations of mental illness. Robert Burton's monumental work "The Anatomy of Melancholy" (1621) provided an encyclopedic account of depressive states, though it did not clearly distinguish melancholia as a phase within a cyclical illness. Théophile Bonet, in the seventeenth century, made an important contribution by linking mania and melancholia under the term "manico-melancolicus," recognizing their alternation within the same patient.

## 1.2 The Nineteenth Century: Falret, Baillarger, and the Birth of Circular Insanity

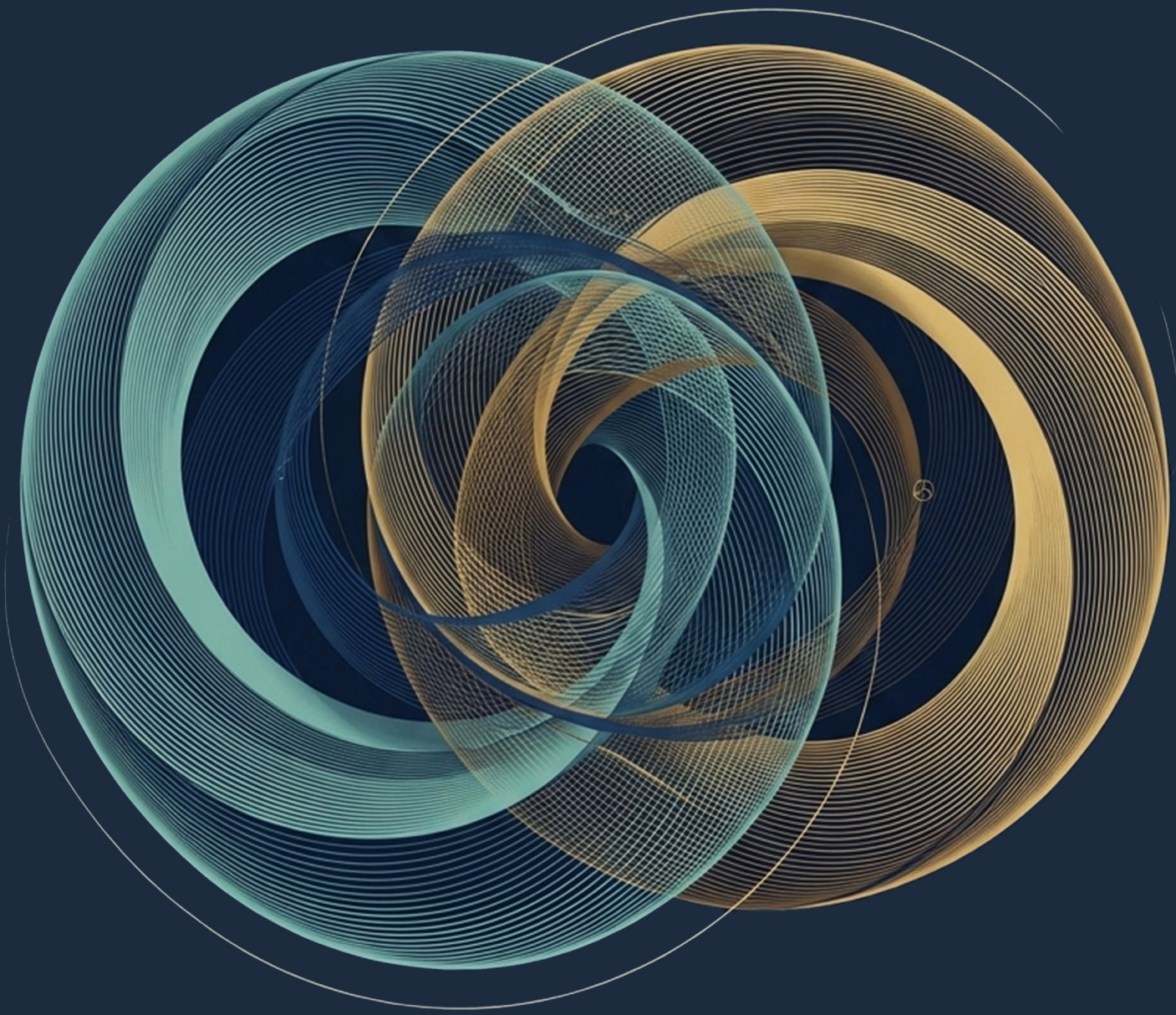
The modern conceptualization of bipolar disorder as a distinct nosological entity began to crystallize in mid-nineteenth century France. In 1851, Jean-Pierre Falret described "la folie circulaire" (circular insanity), a condition characterized by the regular alternation of mania and melancholia with intervening periods of lucidity. Falret's contribution was

# Word Index

## About NeuroPsyBiT

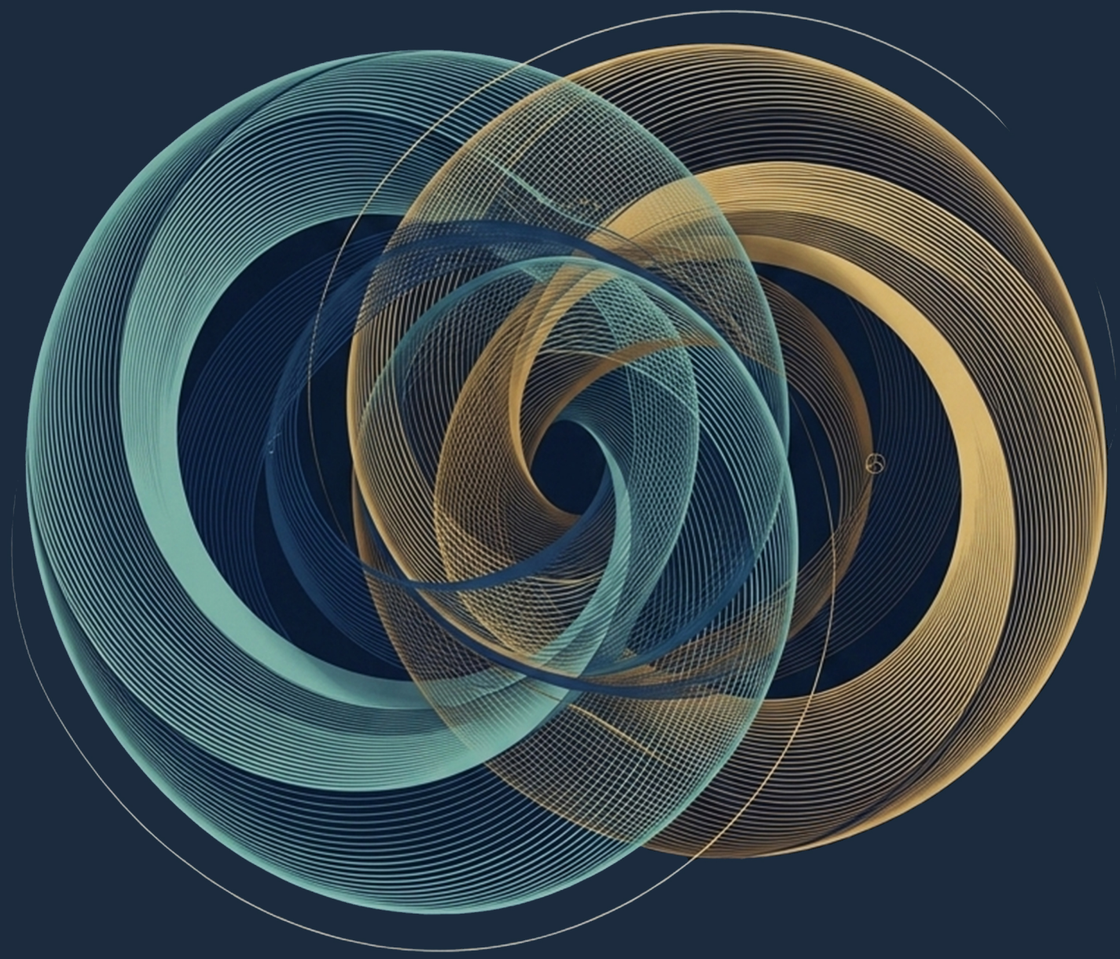
NeuroPsyBiT (RTSGD NeuroPsychogenetic Bipolar Türkiye) is a research initiative dedicated to advancing the understanding of the genetic and neurobiological foundations of bipolar disorder. Operating in collaboration with the Research and Treatment Society of Genetic Disorders (RTSGD), NeuroPsyBiT integrates clinical psychiatry, molecular genetics, and neuroscience to develop integrative models of bipolar disorder pathophysiology and to translate genetic findings into improved clinical practice.

**For more information, visit: neuropsybit.org**



SELÇUK UNIVERSITY PRESS

ISBN: 978-9-75448-264-5



SELCUK UNIVERSITY PRESS

ISBN: 978-9-756449-264-5

9 789754 482645

BIPOLAR DISORDER

BIOLOGY, GENETICS, AND CLINICAL PERSPECTIVES

SELCUK UNIVERSITY PRESS

2026

Spec. Dr. Ali TORABI, Assoc. Prof. Dr. Nadir KOÇAK,Assoc. Prof. Dr. Rukiye TEKDEMİR
Asst. Prof. Dr. Özkan BAĞCI, Lecturer Dr. Süleyman NERGİZ, Prof. Dr. Tülün ÇORA
Assoc. Prof. Dr. İbrahim Halil YILDIRIM, Sara RAFIEI GAVGANI

# BIPOLAR DISORDER

## Biology, Genetics and Clinical Perspectives

SELCUK UNIVERSITY PRESS