Causes, Pathogenesis and Biomarkers of Bipolar Disorder

Zhiyou Guan *

Tianjin University of Commerce, Tianjin, China

* Corresponding Author Email: guanzhiyou86@gmail.com

Abstract. Bipolar disorder (BD) is a serious psychiatric disease marked by recurring episodes of mania and depression. BD is often misdiagnosed as depression because the disease recurs and the manic phase is not easy to detect, which delays subsequent treatment. Since the diagnosis of BD is currently mainly through subjective forms such as clinical interviews and is relatively difficult, exploring its biopathological mechanisms as deeply as possible will help better diagnosis and treatment. This essay will concentrate on the biological factors that may contribute to BD. This article will summarize the existing identified or possible causes of BD from five aspects: genetic factors, molecular neurobiological clue, sun radiation changes, insights from neuroimaging and biomarkers. To begin with, BD is a highly heritable psychiatric disorder, and multiple genetic loci have been identified. Furthermore, advances in understanding the ZNF04A molecular foundations of the genetic associations in BD. What's more, sun radiation changes affect serotonin changes, which in turn affect mood changes, ultimately leading to mood disorders. Moreover, changes in brain volume and cortical thickness are a key feature of patients with BD. Last but not least, Abnormal changes in uric acid-related factors and the gut microbiota may lead to BD. These causes deepen our understanding of the biological etiology of BD, find new treatment candidates, and prioritize functional follow-up research techniques.

Keywords: Bipolar disorder (BD); Mania; Depression; Pathogenesis.

1. Introduction

The mental illness known as bipolar disorder (BD) is typified by recurrent episodes of depression followed by either mania or hypomania. The mania is Bipolar I, and the hypomania is Bipolar II. The hallmarks of manic and hypomanic parts are heightened activity, greater energy, and an elevated or irritated mood that deviates noticeably from typical behavior. Unless otherwise specified, the term "BD" refers to both types I and II in this article.

About 8 million adults in the US and about 40 million people all over the world suffer from BD, a seriously debilitating mental illness [1]. The global prevalence of BD is estimated at 2% [2]. Individuals with BD are more likely to undergo accidents, substance abuse and physical illness, but the highest mortality rate is from suicide. The suicide rate for men and women with BD averages 0.4% per year, more than 20 times higher than the general population [3].

Contemporary viewpoints regard the manifestation of bipolar symptoms as the outcome of an ongoing interplay among genetic predisposition, neurobiological dysfunction, and environmental factors. BD, like other common psychiatric diseases, is attributable to a multifaceted interaction of various causes at both the population and individual levels [4], which has numerous etiological variables, encompassing biological, psychological, social, and familial influences. This article will focus on the biological variables that may cause BD and organize existing information about pathogenesis and biomarkers of BD to provide a preliminary summary.

BD, like other common psychiatric disorders, can be most effectively understood through various analytical frameworks, encompassing genetics, neural networks, psychological functioning, social support, additional biological and environmental influences [5]. Biological factors provide a vital function in the development of BD and primarily influence the course of this disease, so I want to focus this entire article on biological factors. This article will delineate the recognized or potential causes of BD from five perspectives: genetic factors, molecular neurobiological indicators, sun radiation changes, discoveries from neuroimaging and biomarkers.

2. Genetic Factors and Molecular Neurobiological Clue

One of the direct causes of BD is related to genetic inheritance. Evidence from twin studies reflects a high heritability rate, with an estimate of 80%, emphasizing the strong genetic component underlying the illness [6].

BD has a complicated etiology and is a heritable mental condition. 64 related genomic locations were found [7]. So far, the most widely replicated and studied common genetic variation associated with BD is the SNP rs1006737 in the gene CACNA1C [8]. The risk-associated SNP in CACNA1C is located within pathways linked to genetic susceptibility for bipolar illness. The impacts on human brain expression suggest a biological and neural system mechanism behind the clinical genetic connection [9]. Postmortem brain investigations revealed reduced or increased CACNA1C gene expression in persons possessing the A allele, notably in the cerebellum, while other brain areas shown no such reduction [9, 10]. Additional research is essential to elucidate these inconsistencies prior to drawing definitive findings. It has been demonstrated that risk alleles for BD are enriched in genes involved in synaptic signaling pathways and brain-expressed genes, particularly those with high specificity of expression in prefrontal cortex and hippocampus neurons [7]. 15 genes that encode druggable targets, including HTR6, MCHR1, DCLK3, and FURIN, were shown to be strongly associated with bipolar disorder through the integration of expression quantitative trait locus data [7].

Similar to other psychiatric disorders, BD exhibits a polygenic inheritance pattern, with genome-wide association studies (GWAS) indicating that its heritability arises from the cumulative effect of numerous single nucleotide polymorphisms (SNPs), each exerting a small individual influence. There are two primary approaches that are employed to elucidate the neurobiological consequences of genes associated with BD, which are bioinformatics-based gene network to pathway discover and empirical research on how certain genes are expressed and function. The molecular underpinnings of the genetic connections are being investigated in the latest research [11]. Initially discovered to be a gene linked to schizophrenia risk, ZNF04A (zinc finger protein 804A) has since been linked to a wider range of psychotic symptoms, including BD [12]. A transcription factor that controls the expression of different genes in vitro is thought to be encoded by it [12].

BD is a highly heritable psychiatric disorder, and multiple genetic loci have been identified. Although many gene loci have been identified, they have not been directly proven to be associated with the onset of BD, but they play a role in the pathophysiology of BD. More and better treatments can be investigated as the nature of the disease's etiology is thoroughly investigated.

3. Sun Radiation Fluctuations and Endocrine System

BD is closely related to the seasonal fluctuations in solar radiation. Changeable or continuous lack of sunshine weather affects mood and behavior through the endocrine system, leading to psychological disorders.

Variations in sun radiation influence alterations in mood, which subsequently impact endocrine changes, finally resulting in mood disorders. Initial research indicates that significant seasonal variations in sun radiation, possibly influencing circadian rhythms, may correlate with an earlier onset of BD and an increased probability of experiencing a depressive episode at onset [13]. Furthermore, the relationship between BD and seasonal changes can be more intuitively seen through the rating scale. Significant seasonal variation was observed in the Young Mania Rating Scale (YMRS) and Beck Depression Inventory (BDI) scores, with the lowest values in the spring and the highest scores in the summer for two clinical groups [14]. The positive effects of modest sunshine exposure on serotonin modulation are the cause of the mania increased rates seen in the spring [14]. It has been proposed that a key element in the pathophysiology of mania is the central nervous system's increased serotonin (5-hydroxytryptamine or 5-HT) availability [15]. These results emphasize the necessity of tailored strategies to mitigate climate-induced anxiety in individuals with mental disorders and the significance of taking seasonal elements into account when creating a treatment plan.

Understanding mental health effects of climate change, especially for vulnerable populations like those with BD, is crucial for creating focused interventions and support networks. The relationship between climate change and BD is likely multifactorial and complex, which needs more research.

4. Insights from Neuroimaging

The pathophysiology of BD involves complex interactions between genetic vulnerability and environmental exposures, leading to epigenetic, endocrine, and inflammatory changes. Neural changes brought on by these changes facilitate the development and progression of BD [16].

Advances in neuroimaging, The ENIGMA consortium, through large-scale collaborative efforts, is volumetric assessments of subcortical regions derived from MRI of BD patients revealed some slight decreases in the volume of the hippocampus (-0.23), amygdala (-0.11), and thalamus (Cohen's d -0.15), while only the lateral ventricles showed an increase in volume (+0.26) [17]. The parietal, temporal, and frontal cortices all showed slight decreases in cortical thickness, but meta-analyses of cortical areas similarly revealed no changes in cortical surface area [18]. White matter tracts by the more recent meta-analyses employing diffuse tension imaging revealed that BD is associated with broad but mild reductions in white matter integrity across the brain, particularly in the bilateral cinguli and corpus callosum [19]. This indicates that BD is intricately associated with alterations in brain anatomy.

The relationship between alterations in brain volume and cortical thickness and BD remains ambiguous, raising the question of whether these changes are causative factors of BD or if the disorder itself induces structural brain modifications. The causal relationship requires additional and further research.

5. Biomarkers

The identification of reliable biomarkers remains an important part of BD research. The two main biomarkers, uric acid-related and intestinal flora, will be elucidated in the following article.

Abnormal changes in uric acid-related biomarkers may cause BD. These contain the uric acid-to-creatinine (UCR), uric acid-to-albumin (UAR), uric acid-to-lymphocyte (ULR) ratios and uric acid-to-high-density lipoprotein (UHR), which are notable ratios [20]. Compared with healthy controls and bipolar depression patients, patients with bipolar mania had higher ULR, UHR, UCR, and UAR, while patients with bipolar depression had lower ULR and UCR [20]. A risk factor for bipolar mania is a high UAR, and patients with bipolar mania have a more robust inflammatory response than those with bipolar depression [20].

According to current research, BD may have non-brain origins as well. An increasing number of studies have shown that mental disorders are also significantly affected by changes in the gut microbiota. Investigating the gut microbiota in BD reveal underlying causes that have not yet been found and provide fresh insights and treatment options for mood disorders [21]. While the microbial colonization resistance was much lower in BD, the populations of Faecalibacterium prausnitzii, Clostridium Cluster IV, the Bacteroides-Prevotella group, Enterobacter spp. and Atopobium Cluster were notably greater than in healthy controls [22]. Immunological alterations and the severity of the disease were associated with the gut microbiota composition of BD patients, which was different from that of healthy controls. The growth of Enterobacter species and the Bacteroides-Prevotella group suggests that the gut microbiota is dysbiotic [22]. This study discovered that BD participants had changed gut microbiota makeup [22].

Despite extensive research, several biomarkers have not yet proven to be clinically useful [23]. These indicators might not be unique to BD because they often show up in other inflammatory or mental illnesses. Biomarkers can help with early diagnosis, treatment response prediction, and illness progression tracking as the field shifts to a precision psychiatry paradigm. Moving past the paradigm of identifying individual biomarkers is the trend of the future.

6. Conclusion

Bipolar disorder (BD) is acknowledged as a serious mental illness. The five causes of BD are summarized and sorted out in this article. Clarifying and refining the causes of BD can lead to better understanding and treatment of this disease. Initially, BD is a highly heritable psychiatric condition, with numerous genetic loci identified. Moreover, progress has been made in comprehending the ZNF04A biological basis of the hereditary correlations in BD. Furthermore, alterations in solar radiation influence endocrine changes, which then impact mood fluctuations, finally resulting in mood disorders. Furthermore, alterations in brain volume and cortical thickness are a significant characteristic of individuals with BD. Finally, abnormal alterations in uric acid-related variables and the gut flora may contribute to BD. Understanding the pathophysiology, pathogenesis, and genetic basis of BD is still difficult, even when compared to other mental diseases. This is partly due to the disease's intrinsic complexity, the relative lack of research on it, and the challenge of simulating it in cells or animals. Fortunately, Substantial progress has been achieved in comprehending the neurobiology of affective disorders, leading to the identification of novel targets and biomarkers. Many areas of clinical and research psychiatry have seen tremendous advancements in recent years on a global scale.

Future management of bipolar illnesses will emphasize not only diagnosis and therapy but also ongoing monitoring. At the same time, more diverse and convenient early detection and screening methods for physiological abnormalities related to BD will be discovered and studied, so that earlier detection and earlier intervention can be achieved, thereby reducing the incidence and lifetime prevalence.

References

[1] Nierenberg, A. A. , Agustini, B. , & Ole Kohler-ForsbergCristina CusinDouglas KatzLouisa G. SylviaAmy PetersMichael Berk. (2023). Diagnosis and treatment of bipolar disorder-a review. the Journal of the American Medical Association, 330(14), 1370-1380.

[2] Merikangas KR, Jin R, He JP. (2011). Prevalence and correlations of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry, 68(3), 241-251.

[3] Tondo, L. , Isacsson, G. , & Baldessarini, R. J. . (2003). Suicidal behaviour in bipolar disorder. CNS Drugs, 17(7), 491-511.

[4] Kendler, K. S. , & Kendler, K. S. . (2019). From many to one to many—the search for causes of psychiatric illness. JAMA Psychiatry, 76(10), 1085-.

[5] Goes, F. S. . (2023). Diagnosis and management of bipolar disorders. The BMJ, 381(8380), 17.

[6] Craddock N, Sklar P: Genetics of bipolar disorder. Lancet 2013, 381:1654-1662.

[7] Mullins, N. , Forstner, A. J. , O'Connell, K. S. , Coombes, B. , & Andreassen, O. A. . Genome-wide association study of over 40,000 bipolar disorder cases provides novel biological insights. Nature Genetics.

[8] Kerner, B. (2014). Genetics of bipolar disorder. The Application of Clinical Genetics, 7, 33–42.

[9] Bigos KL, Mattay VS, Callicott JH, et al. Genetic Variation in CACNA1C Affects Brain Circuitries Related to Mental Illness. Arch Gen Psychiatry. 2010;67(9):939–945.

[10] Gershon, E. S. , Grennan, K. , Busnello, J. , Badner, J. A. , Ovsiew, F. , & Memon, S. , et al. (2014). A rare mutation of cacna1c in a patient with bipolar disorder, and decreased gene expression associated with a bipolar-associated common snp of cacna1c in brain. Molecular Psychiatry, 19(8), 890-894.

[11] Harrison, & Paul, J. . (2016). Molecular neurobiological clues to the pathogenesis of bipolar disorder. Current Opinion in Neurobiology, 36, 1-6.

[12] Quinn, Thomas, P., Akbarian, Schahram, & Glatt, et al. (2015). Bioinformatic analyses and conceptual synthesis of evidence linking znf804a to risk for schizophrenia and bipolar disorder. American journal of medical genetics, Part B. Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics, 168B(1), 14-35.

[13] Bauer M, Glenn T, Achtyes ED, et al. Association between polarity of first episode and solar insolation in bipolar I disorder. J Psychosom Res 2022;160:110982.

[14] Mohamed, S. M. , Elbeh, K. , Mohammed, N. A. E. , El-Hameed, E. G. A. , & Ahmed, G. K. . (2025). Seasonal patterns and climate change anxiety in mood disorders: a comparative study of bipolar disorder and depression. Middle East Current Psychiatry, 32(1).

[15] Poletti, S. , Myint, A. M. , Schüetze, Gregor, Bollettini, I. , Mazza, E. , & Grillitsch, D. , et al. (2016). Kynurenine pathway and white matter microstructure in bipolar disorder. European Archives of Psychiatry & Clinical Neuroscience.

[16] Oliva, V. , Fico, G. , Prisco, M. D. , Gonda, X. , Rosa, A. R. , & Vieta, E. . (2025). Bipolar disorders: an update on critical aspects. The Lancet Regional Health - Europe, 48(000).

[17] Hibar DP, Westlye LT, van Erp TGM, et al, Costa Rica/Colombia Consortium for Genetic Investigation of Bipolar Endophenotypes. Subcortical volumetric abnormalities in bipolar disorder. Mol Psychiatry 2016;21:1710 6.

[18] Hibar DP, Westlye LT, Doan NT, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry 2018;23:932 42.

[19] Favre P, Pauling M, Stout J, et al, ENIGMA Bipolar Disorder Working Group. Widespread white matter microstructural abnormalities in bipolar disorder: evidence from mega and meta analyses across 3033 individuals. Neuropsychopharmacology 2019;44:2285 93.

[20] Gao, H., Zhang, C., Feng, J., Luo, Y., Wang, T., Wei, Y., & Chen, J. (2024). A large-scale study on uric acid-related biomarkers in patients with bipolar disorder. Psychiatry Research, 339, 116089.

[21] Painold, A. , Mrkl, S. , Kashofer, K. , Halwachs, B. , Dalkner, N. , & Bengesser, S. , et al. (2019). A step ahead: exploring the gut microbiota in inpatients with bipolar disorder during a depressive episode. Bipolar disorders, 21(1), 40-49.

[22] Lu, Q. , Lai, J. , Lu, H. , Ng, C. , & Hu, S. . (2019). Gut microbiota in bipolar depression and its relationship to brain function: an advanced exploration. Frontiers in Psychiatry, 10, 784.

[23] Lorenzon, N. , & Dierssen, M. . (2024). Diving into the precision psychiatry debate: how deep can we go?. European Neuropsychopharmacology, 84(000), 2.