

*Studying the effects of bipolar disorder on the microenvironment of
different areas in the brain*

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Introduction

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Bipolar disorder (BD) is a multicomponent genetic illness that involves severe mood disturbance, neuropsychological deficits, and physiological changes and it is one of the leading causes of disability globally (Rowland and Marwaha, 2018). Patients often experience extreme mood swings from manias to depressions and vice versa. In fact, the name "bipolar disorder" was adopted by the DSM (Diagnostic and Statistical Manual for Mental Disorders) in 1980 to replace the term "manic depression" (Phillips and Kupfer, 2013). The mood swings are different in different individuals and ranges from mild hypomania or depression to severe manias or depressions, sometimes accompanied by psychosis (Miklowitz, 2008; Müller-Oerlinghausen et al., 2002). We tend to classify BD into 3 subtypes: BD I which includes manic episodes, BD II which includes only hypomanic episodes and major depressive episodes and Cyclothymia which is consistent of hypomanias and minor depressions (Cerimele et al., 2014).

BD affects both young and adult people: recently, there have been some evidence that indicates an increase in the prevalence of BD in young people (Moreno et al., 2007). In addition, in the United States, BD patients make up 10% to 25% of all the geriatric patients with mood disorders (Aziz et al., 2006). When it comes to biological sex, men are affected slightly more than women in a ratio of 1.1:1 (Miller and Black, 2020). It is unclear what is the lifetime prevalence of people who are on the bipolar spectrum (suffer from one of the 3 BD subtypes mentioned before) because different studies have come to very different results. In any case, all the studies have found that the patients' lifetime prevalence decreases significantly (Cerimele et al., 2014).

The mortality rate of people with BD is quite high – around 10% to 20% of individuals with this illness has committed suicide and more than a third have attempted suicide at least once (Müller-Oerlinghausen et al., 2002).

As we have established before, the BD portrays a threat on a variety of people in different ages, hence, it is of great importance for us to develop new ways of identifying patients before they experience an outbreak.

In the research literature, it is apparent that diagnosing BD is quite challenging because the diagnosis is made exclusively based on clinical information which is not objective: BD I is diagnosed based on one manic episode, BD II is diagnosed based on depressive and

hypomanic episodes and Cyclothymia is diagnosed based on hypomanic and depressive symptoms that do not count as depressive episodes. In addition, some other psychiatric illnesses resemble the BD's symptoms, especially recurring unipolar depressive disorder (a disorder which is characterized by recurrent depressive episodes). The misdiagnosis between unipolar disorder and BD is made the most when differentiating unipolar disorder and BD II, that's because patients who suffer from BD II do not experience manic episodes. However, it is difficult to differentiate BD patients in general because manic episodes are rarer than the depressive ones (Phillips and Kupfer, 2013). Furthermore, it is also extremely challenging to come to proper findings because of the insufficient sample sizes of the current studies (Medeiros and Goes, 2022).

There are a lot of things which are still unknown about the BD's diagnosis, nature and treatment: first of all, it is unknown how to diagnose patients with BD based on biological methods besides tracking down their family history in order to identify potential risks of having BD which is a tedious and inaccurate method. In addition, there are no known specific biomarkers (biological measures that could indicate about the presence or the severity of the illness) for BD (Frey et al., 2013; Salagre and Vieta, 2022). It is neither known how differentiate BD patients from people who suffer from similar psychiatric illnesses such as recurring unipolar depressive disorder and schizophrenia (Salagre and Vieta, 2022).

Clearly, our limited knowledge about BD and lack of understanding of the biological mechanisms that are underlying it, combined with the insufficiency of proper sized samples, are the main reasons for the challenges we have been facing in regard to BD.

In the last decade, various studies have focused on the genetics of bipolar disorder and the various risk factors that can affect its development (Rowland and Marwaha, 2018). It is found that bipolar disorder has a major genetic component and it seems to be very heritable (Kim et al., 2021). The new findings shows that there are some genes that seem to be associated with bipolar disorder. Those include: SERINC2 (increases the risk of bipolar disorder in Asian population), SLC6A2 (affects the likelihood of having bipolar disorder I and its severity) (Kim et al., 2021; Yang et al., 2021).

One of the popular approaches in order to better understand the genetics of bipolar disorder, is to perform GWAS (Genome-Wide Association Study) which helps identifying

significant SNPs (Single Nucleotide Polymorphisms) that are associated with this illness. It is also common to use PRS (polygenic risk scores) – in general, those scores are the summation of all the individual's alleles which are associated with the phenotype (in this context, the phenotype is bipolar disorder) weighted by the size of their effect on it – which provides a way to approximate how well a patient will respond to a clinical treatment. Another useful method is WES (whole-exome sequencing) which helps identifying rare variants in genes and brain-related pathways. Finally, there is WGS (whole-genome sequencing) which is the most extensive yet most expensive and technically challenging method (Oraki Kohshour et al., 2022).

We believe that the brain's microenvironment withholds the potential to uncovering ways of identifying BD based on biological measures. In this study, we used the data collected in the experiments of ... in order to try and check if the machine learning algorithms available to us today could shed some light on the biological mechanisms underlying BD and identify some significant biological differences between BD patients and healthy individuals and perhaps even between BD patients and people who suffer from similar illnesses.

If we will identify some kind of biomarkers for BD it could enable us to diagnose BD patients earlier – even before they experience an outbreak. In addition, if the said biomarkers would be specific for BD, it could help differentiating it from other psychiatric illnesses and enable many patients get their appropriate medicine and treatments.

Unfortunately, it is very plausible that we won't be able to detect any biomarkers. The reason for this would probably be our limited data.

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