Introduction

Bipolar disorder (BD) is a complex and mostly genetic illness that involves severe mood disturbances, 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 major subtypes based on the way they affect the patients: BD I patients experience manic episodes, BD II patients experience only hypomanic episodes and major depressive episodes and Cyclothymia patients experience hypomanias and minor depressions (Cerimele et al., 2014).

Recently, some new evidence indicating an increase in the prevalence of BD in young people was found which means that BD affects both young and adult people alike (Moreno et al., 2007). In addition for that, 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 any of the BD subtypes known to date) 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 bipolar disorder portrays a real and severe threat on a wide variety of people of all ages and sexes, hence, it is of great importance to develop new ways of identifying patients before they experience an outbreak.

In the research literature, it is apparent that diagnosing BD is a challenge all of itself since the diagnosis is made exclusively based on non-objective clinical information which mainly

consists of behavioral habits: 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). As a result, a misdiagnosis between BD and other illnesses is not uncommon. The misdiagnosis between unipolar disorder and BD is most apparent when differentiating unipolar disorder and BD II, that's because patients who suffer from BD II do not experience manic episodes but rather only hypomanic and depressive episodes as mentioned before. However, it is difficult to differentiate BD I patients from unipolar ones as well because manic episodes are rarer than the depressive ones in both BD I and BD II (Phillips and Kupfer, 2013). Furthermore, it is extremely challenging to come to proper findings in researches regarding the BD because of the insufficient sample sizes of the current studies in the field (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. This problem stems from that 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 to 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 to be used in researches, are the main reasons for the challenges we have been facing regarding 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, for example, the genes SERINC2 (increases the risk of bipolar disorder in Asian population) and 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 to better understand the genetics of bipolar disorder, is to perform GWAS (Genome-Wide Association Study) which is a useful method for identifying significant SNPs (Single Nucleotide Polymorphisms) that are associated with a certain illness or disease. It is also common to use PRS (polygenic risk scores) – which, in general, are the weighted amounts of all the individual's alleles that are associated with a certain phenotype, weighted by the size of their effect on it (which is derived from preliminary GWASs) – which provides a way to approximate how likely is a patient to develop a certain illness or disease and also to approximate his respondence to a certain treatment. Another useful method is WES (whole-exome sequencing) which is great at identifying rare variants that are likely to affect a certain illness or disease but it is lacking in extensivity since it sequences about 1% of the whole genome and can only analyze protein-encoding regions on the genome. Finally, there is WGS (whole-genome sequencing) which is simply a full scan of the genome. This is the most extensive and thorough yet most expensive and technically challenging method so although this is probably the best way to understand the BD to its fullest it is not possible to use it as frequently and easily in researches as the previous ones (Oraki Kohshour et al., 2022).

We believe that the brain's microenvironment withholds the potential for uncovering new ways of identifying and diagnosing BD based on biological measures. In this study, we used the data collected in previous studies (Akula et al., 2014; Hu et al., 2016) in order to try and shed some light, using the technology and algorithms that are available for us today, on the biological mechanisms underlying BD and identify some significant biological differences between BD patients and healthy individuals; perhaps even between BD patients and people who suffer from similar illnesses such as schizophrenia.

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