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Bipolar disorder: An evolutionary psychoneuroimmunological approach

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A B S T R A C T

Bipolar disorder is a mental health disorder characterized by extreme shifts in mood, high suicide rate, sleep problems, and dysfunction of psychological traits like self-esteem (feeling inferior when depressed and superior when manic). Bipolar disorder is rare among populations that have not adopted contemporary Western lifestyles, which supports the hypothesis that bipolar disorder results from a mismatch between *Homo sapiens*'s evolutionary and current environments. Recent studies have connected bipolar disorder with low-grade inflammation, the malfunctioning of the internal clock, and the resulting sleep disturbances. Stress is often a triggering factor for mania and sleep problems, but stress also causes low-grade inflammation. Since inflammation desynchronizes the internal clock, chronic stress and inflammation are the primary biological mechanisms behind bipolar disorder. Chronic stress and inflammation are driven by contemporary Western lifestyles, including stressful social environments, unhealthy dietary patterns, limited physical activity, and obesity. The treatment of bipolar disorder should focus on reducing stress, stress sensitivity, and inflammation by lifestyle changes rather than just temporarily alleviating symptoms with psychopharmacological interventions.

1. Introduction

Bipolar disorder is a mental health condition that causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). Bipolar disorder is costly for societies: in the US, for example, the total costs of bipolar I disorder were estimated at $202.1 billion in 2015, corresponding to an average of $81,559 per individual (Cloutier et al., 2018). Globally, bipolar disorders are the 17th leading source of disability among all diseases (Vigo et al., 2016).

The Diagnostic and Statistical Manual of Mental Disorders (DSM) classifies bipolar disorder into four main subtypes: bipolar I disorder, bipolar II disorder, cyclothymia, and bipolar disorder not otherwise specified (American Psychiatric Association, 2013). These four subtypes of bipolar disorder are estimated to affect a total of 4.4 % of the population of the United States. The lifetime prevalence estimate of bipolar disorders is 2.4 %, though prevalence rates vary by country (Carvalho et al., 2020; Merikangas et al., 2011b). Bipolar I disorder is defined by manic episodes which may manifest as delusions, hallucinations, overconfidence, grandiosity, talkativeness, extreme disinhibition,

irritability, decreased need for sleep, and highly elevated mood (Carvalho et al., 2020). Type I diagnosis requires at least one manic episode with or without episodes of depression. Manic episodes may compromise psychosocial functioning to an extent that requires hospitalization (Carvalho et al., 2020). Bipolar II disorder requires at least one hypomanic episode and one depressive episode, and as such is characterized primarily by depressive episodes which alternate with hypomania rather than with mania (Carvalho et al., 2020). Cyclothymic disorder is milder than bipolar disorder, and is characterized by mood swings between mild depressive and hypomanic states, lasting for at least two years (Carvalho et al., 2020). Bipolar disorder not otherwise specified (BP-NOS) includes bipolar features that do not meet the criteria for a specific bipolar disorder (Towbin et al., 2013).

In mania, a person has abnormal mood that is either euphoric, expansive and elevated, or irritable with increased energy (American Psychiatric Association, 2013). In addition, in mania, a person has a group of class B signs and symptoms, like decreased need for sleep, inflated self-esteem or grandiosity, flight of ideas and racing thoughts, unusual talkativeness, distractibility, psychomotor agitation, poor

decision making, increase in goal-directed activity, excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments), and possibly psychotic features (American Psychiatric Association, 2013). Hypomania (literally: below mania) is a milder condition: people with hypomania are often fully functioning (unlike individuals suffering from a full manic episode) and they lack psychotic symptoms. For many individuals, hypomania is a positive state to be in if not followed by depression or mania itself (Goodwin, 2018).

Bipolar disorder is often life-threatening, with 15–20 % of those diagnosed committing suicide, and one-third to half attempting suicide (Dong et al., 2019; Schaffer et al., 2015). Life expectancy of individuals with bipolar disorder is shortened by 10–15 years, not just because of an increased suicide rate, but also because of an elevated prevalence of such medical comorbidities as cardiovascular disease, diabetes, and other metabolic conditions (Schaffer et al., 2015). The diagnosis of bipolar disorder is challenging because signs and symptoms of the disorder are so wide-ranging that they can be seen, in part, in just about every major psychiatric disorder (Gordovez and McMahon, 2020).

In this article, we review existing evolutionary explanations for bipolar disorder (section 2), and present the environmental mismatch hypothesis of bipolar disorder as a new hypothesis in section 3. This hypothesis is able to explain why comorbidities occur so often with bipolar disorder and why natural selection has not eliminated the genetic variants (alleles) that expose to bipolar disorder. The hypothesis is also able to explain why there are sleeping problems in bipolar disorder and why many behavioral traits mentioned above become dysfunctional. We highlight the role of neuroinflammation as a plausible proximate mechanism in bipolar disorder, seeking to integrate the proximate level of analysis—i.e. what biopsychosocial mechanisms cause bipolar disorder—with the ultimate level of analysis—i.e. what evolutionary fitness benefit, if any, does it provide for the organism (cf. Luoto et al., 2019; Rantala et al., 2018). We conclude by reviewing medical treatments (section 8) and lifestyle changes (section 9) that decrease low-grade inflammation and that may prove effective in the context of bipolar disorder.

2. Previous evolutionary explanations for bipolar disorder

In comparison to the extensive research that has been done to explain the origin and prevalence of schizophrenia and depression (Rantala et al., 2018) from an evolutionary point of view, very little evolutionary work has been done on the bipolar spectrum (Del Giudice, 2018). In general, the evolutionary explanations for bipolar disorder have proposed some adaptive advantages for hypomanic and bipolar symptoms (Sherman, 2001). This idea is based on the fact that bipolar disorder patients have a wider range of functionality and self-sufficiency in comparison to schizophrenic patients, and also on data showing that bipolar disorder patients have a small fertility reduction in comparison to that observed in schizophrenic patients. The relative reproductive success in bipolar disorder patients is about 85 % in females and 75 % in males, whereas reproductive success of about 50 % in females and 20 % in males has been reported in schizophrenic patients (Jacobson, 2016; Power et al., 2013). Since bipolar disorder reduces reproductive success relative to unaffected individuals, the crucial question is why have the genetic variants (alleles) that make individuals vulnerable to bipolar disorder been retained by natural selection?

The adaptive advantages that have been suggested for bipolar disorder traits include search for high social status, proneness to compete, parental effort, and access to mates (Akiskal and Akiskal, 2005; Del Giudice, 2018; Gilbert et al., 2007; Stevens and Price, 2000). Gardner (1982) pointed out that manic and depressive episodes of bipolar disorder could be seen as an analogy to the behavior that non-human and human animals use to communicate their social status. For instance, the manic episodes—characterized by high energy, fast and assertive

speech, and expansive body posture—could be a reflection of the behavior that is triggered by winning dominance contests, whereas the depressive episodes characterized by low motivation, lack of energy, and melancholic states could be interpreted as a reflection of submissive behaviors observed in low-ranking individuals (Annen et al., 2012; Johnson et al., 2012).

Following this hypothesis, it has been suggested that those individuals who have a genetic predisposition towards bipolar disorder could have a failure in emotion regulation systems, being very sensitive to triggers (e.g., adverse or stressful situations) and very insensitive to stop signals (Del Giudice, 2018). Nevertheless, this hypothesis does not specify the genes and alleles that are associated with the development of bipolar disorder which would, at the same time, be also related to the regulation of behaviors associated with dominance–submissiveness dynamics in nature. Besides, there is evidence that shows an overlap in some genes that are related to the development of schizophrenia, major depression, and bipolar disorder (Becker, 2004; Gordovez and McMahon, 2020; Moskvina et al., 2009), making the idea that there could be some evolutionary advantages for those individuals with a genetic predisposition to bipolar disorder less plausible.

Another hypothesis suggests that bipolarity lies along a continuum from extreme temperament to full-blown affective illness (Akiskal and Akiskal, 2005). Thus, although full-blown mania may not be adaptive as such, hypomania and traits like creativity, inventiveness, cheerfulness, competitiveness, stimulus-seeking, and promiscuousness might have provided a reproductive advantage in our evolutionary history (Akiskal and Akiskal, 2005; Luoto, 2019; Luoto et al., 2019). It has also been argued that mild versions of manic syndromes reflect fast life history strategies (Del Giudice, 2018). However, the life history hypothesis fails to explain why mood swings occur in bipolar disorder and why sometimes manic and depressive symptoms exist as a mixed state. Moreover, most of the literature on the potential advantages of bipolar disorder (e.g., Akiskal and Akiskal, 2005; Kyaga et al., 2015) are mainly focused on the manic episodes whilst overlooking depressive symptoms.

One of the few evolutionary explanations for the depressive episodes in bipolar disorder (Sherman, 2001, 2006, 2012) has proposed that depression (as a part of bipolar disorder spectrum) could have evolved as an adaptation (see Bourrat, 2019, for a discussion on adaptations) to the selective pressures of climate, helping to save energy resources in winter, whereas manic episodes are an adaptation to increase activities and mating during spring and summer (Sherman, 2012). According to Sherman (2006), these adaptive strategies evolved in Neanderthal populations during the Pleistocene, a period characterized by long and severe winters and short summers in Northern Europe, approximately between 3000 and 30,000 years ago. However, nowadays these adaptations are seen as disorders because we live in a very different kind of environment than those that our ancestors inhabited; therefore, because of a mismatch between *Homo sapiens*'s environment of evolutionary adaptedness and current environments, the behaviors associated with bipolar disorder that are assumed to be evolutionarily adaptive are adaptive no longer (Sherman, 2012). Empirical evidence does not support this hypothesis because bipolar disorder occurs also in African people (Esan and Esan, 2016) despite the fact that their ancestors did not adapt to northern winters nor crossbred with Neanderthals like Europeans did (Vernot and Akey, 2014).

Assuming an oligogenic etiology, Wilson (1998) suggested that the genes that cause bipolar disorder were adaptive in the human evolutionary environment by enhancing social competition, but pathogenic in current environments. Neither of these hypotheses explains why genes that are associated with bipolar disorder are also associated with other mental disorders. All adaptive explanations for bipolar disorder have this same shortcoming. Furthermore, genetic vulnerability to bipolar disorder is not caused by just a few genes (as Wilson, 1998, suggested), but at least tens of different genes and alleles which most of us carry, though only relatively few individuals will develop the disorder (Gordovez and McMahon, 2020). For this reason, bipolar disorder onset

cannot be predicted based on certain GWAS-significant risk-factor alleles (Zhang et al., 2020). All these previous evolutionary hypotheses also fail to explain why most patients with bipolar disorder have at least one comorbidity. Likewise, they have not been able to explain why stress triggers the disorder.

It is important to note that sometimes adaptations can become dysfunctional (Nesse, 2019). Diarrhoea, for instance, is an adaption to expel pathogens in the intestines. However, if the adaptation is poorly regulated, it can be lethal: in the case of diarrhoea, the resulting dehydration can lead to a worse outcome than the pathogen. In a scenario such as this, a person can die from a dysregulated defence mechanism, not the disease itself (Nesse and Williams, 1994). Likewise, stress arises from the fight or flight response, which can be life-saving in a dangerous situation because of its performance-enhancing effects, but if stress becomes chronic, it interferes with the immune system and causes health problems (Cohen et al., 2012). Besides extreme variation in mood, traits like creativity, optimism, competitiveness, liveliness, self-esteem, and self-confidence can become dysfunctional in bipolar disorder, being either too high (in mania) or too low (in depression). In addition, sleep can become either inadequate (in mania) or excessive (in depression). The central question is: why do all of these traits become dysfunctional in patients with bipolar disorder?

3. A disease of modern lifestyle

The prevalence of bipolar disorder varies greatly between different countries. For example, in China, India, and Nigeria, only about 0.1 % of the population suffer from it (Gureje et al., 2010; Merikangas et al., 2011a; Zhang et al., 2017). The highest prevalence of bipolar disorder has been reported in a Brazilian town in São Paulo, where the prevalence of bipolar disorder was 8.3 % (Moreno and Andrade, 2005). In another study done in the harbor town of Pelotas in Brazil on 1560 adolescents aged 18–24, 7.5 % had experienced a manic period and 5.3 % a hypomanic one (Jansen et al., 2011). Because the participants were from several different ethnic groups, the prevalence of the disorder does not seem to be explained by ethnic factors but rather with factors connected to the environment. The differences between the countries studied seem too large to be explained only by differences in research methods. Interestingly, major depressive disorder is also most commonly found in Brazil (Bromet et al., 2011), suggesting that the same factors that increase the cross-national prevalence of bipolar disorder might also increase the cross-national prevalence of major depressive disorder.

There is no scientific evidence on the existence of bipolar disorder in the evolutionary history of our species. In studies where the prevalence of mood disorders has been examined among hunter-gatherers, the disorder is not reported at all (Hollan and Wellenkamp, 1994, 1996; Keyes, 1986; Schieffelin, 1986). Thus, it is very unlikely that bipolar disorder has been prevalent in hunter-gatherers. Separating a depressive episode connected to bipolar disorder from that of a clinical depressive state is extremely difficult especially in short-term interviews on which hunter-gatherer interviews are based. Because unipolar clinical depressive state is known to be extremely rare among hunter-gatherers (Rantala et al., 2018), bipolar disorder cannot be very common either; otherwise the depressive episodes connected to it would have been reported in existing studies. However, some caution is needed when interpeting such null findings about the mental health problems of hunter-gatherers, because individuals with bipolar disorder might not have been tolerated, particularly if manic or hypomanic behavior became dysfunctional within the group. One of the reasons that contributed to hunter-gatherer survival may have been that they expunged or even killed individuals who disrupted group harmony (Boehm, 1999, 2000).

Studies on populations with a traditional lifestyle can help assess the extent to which contemporary Western lifestyles may contribute to the disorder. The Amish are known to lead a lifestyle characteristic of the 18th century. A mental health study on 12,500 Amish people found that only 28 of them suffered from bipolar disorder (Egeland and Hostetter, 1983). This means that the likelihood of an Amish person having bipolar disorder is 0.22 %. Instead, 4.4 % of Americans experience this disorder (Gureje et al., 2010; Merikangas et al., 2011a). The difference between the Amish people and other Americans is therefore over 18-fold.

As with major depressive disorder (Rantala et al., 2018) and eating disorders (Rantala et al., 2019), contemporary Western lifestyles seem to constitute a risk factor for bipolar disorder. The crucial question is: why?

4. Inflammation and bipolar disorder

Recent evidence has indicated that major depressive disorder arises from a state of neuroinflammation (Miller and Raison, 2016; Setiawan et al., 2015). Factors related to contemporary Western lifestyles, such as unhealthy diet and low physical activity, increase susceptibility to inflammatory dysregulation and chronic stress, both of which increase the amount of proinflammatory cytokines in peripheral blood, leading to low mood and sickness behavior (Rantala et al., 2018). Proinflammatory cytokines may aggravate short-term mood changes to a chronic maladaptive depressive state by preventing the normalization of mood after adverse life events (Rantala et al., 2018), which explains why the prevalence of depression increases with contemporary lifestyles (cf. Hidaka, 2012).

Bipolar disorder is also associated with neuroinflammation. For example, postmortem evidence from brain tissues (Sayana et al., 2019) and biomarkers in plasma and cerebrospinal fluid (CSF) (Isgren et al., 2017) indicate neuroinflammation in patients with bipolar disorder. However, how neuroinflammation causes the symptoms of bipolar disorder like mania is not properly understood, nor are the reasons why bipolar disorder patients have neuroinflammation in the first place. In this article, we will provide answers to these two question.

5. Proximate mechanisms for mania/hypomania

Bipolar disorder is connected to the malfunctioning of the internal clock and sleep disturbances caused by it. For example, jet lag caused by flying across multiple time zones reportedly induces episodes of bipolar disorder in susceptible people. West-to-east travellers experience a phase advance in their circadian rhythms, while east-to-west travellers experience a phase delay: those who travel from west to east are more likely to develop mania, while those travelling from east to west are more likely to develop depression (Walker et al., 2020). Likewise, 'social jet lag' that disrupts circadian rhytms, such as partying late, may also induce mania (Walker et al., 2020). It is well documented that patients with bipolar disorder have an irregular sleep–wake rhythm, eveningness chronotype, abnormality in melatonin secretion, and irregularity of social time cues (reviewed in Takaesu, 2018). Studies have shown that individuals with bipolar disorder have disruptions in circadian rhythm even when they are symptom-free (Rosenthal et al., 2020). Previous research has not, however, been able to explain why people with bipolar disorder have a malfunctioning internal clock. Generally, it is clear that the widespread adoption of electric light over the past century has created an artificial, evolutionarily novel factor that blurs the boundary between the natural day–night cycle and can therefore cause the circadian rhythm anomalies that occur frequently in bipolar disorder (Walker et al., 2020), therefore contributing to the mismatch between our evolutionary and current environments.

Studies on nonhuman animals have shown that the activation of the immune system desynchronizes the internal clock of test animals (Mavroudis et al., 2013). The injection of proinflammatory cytokines into the bloodstream has also been proven to disrupt and desynchronize the functioning of the internal clock (Cermakian et al., 2014). It may not, then, come as a surprise that even in humans, the activation of the immune system causes irregular functioning of the internal clock (Mavroudis et al., 2013). The amount of proinflammatory cytokines informing the person of the body's low-grade inflammatory state is

considerably higher among people suffering from bipolar disorder compared with controls (Muneer, 2016). Since peripheral low-grade inflammation can cause neuroinflammation (Huang et al., 2018), the elevated low-grade inflammation observed in patients with bipolar disorder (Muneer, 2016) can be assumed to disrupt the functioning of the internal clock by causing neuroinflammation. Psychological stress leads to increased levels of proinflammatory cytokines both in humans and in laboratory animals (Cheng et al., 2015; Maes et al., 1998). Stress has also been shown to disturb the functioning of the internal clock (Landgraf et al., 2014). Stressful life events trigger mania (Proudfoot et al., 2012) and higher stress is associated with more severe symptoms of mania (Kim et al., 2007). These findings indicate how stress contributes to inflammation and how stress and inflammation lead to circadian clock dysfunction and disturbed sleep, which in turn result in mania (Fig. 1).

The dyssynchrony of the internal clock causes symptoms of bipolar disorder because it disrupts the sleep–wake system. Internal clock dyssynchrony makes the pineal gland secrete the so-called ''night hormone,'' i.e. melatonin, during the wrong time of the day, and/or in excessive quantities. Possibly for this reason, the melatonin concentration of the pineal gland is reportedly lower than normal in people suffering from bipolar disorder (Dallaspezia and Benedetti, 2009). In a study in which bipolar disorder patients going through the manic phase were given 3 mg of melatonin before going to sleep, the amount of sleep of the patients doubled and the symptoms of mania decreased (Bersani and Garavini, 2000). In a randomized-controlled trial with bipolar patients in an euthymic (stable) state, it was found that adjunctive Ramelteon, which is a melatonin receptor agonist, was effective in relapse prevention during a 24-week study period (Norris et al., 2013).

In mania, it is typical to experience less sleep which is also of lower quality. A diminished need for sleep usually precedes the manic episode. It seems that the decrease of sleep is not a symptom of mania, but rather its cause. There is empirical evidence for this argument: in test animals, the hyperactive (i.e. manic) phase is triggered by forcing the animals to stay awake for long periods of time (Kato et al., 2007). In humans, staying up for a long time or trying to avoid sleeping can trigger mania in those having a genetic predisposition for it (Lewis et al., 2020; Wehr et al., 1987). Decreased sleep maintains and accelerates mania, and this is why its treatment focuses on normalizing the sleep–wake rhythm with sleeping medicine. The symptoms of mania can also be effectively alleviated by placing the person in a dark room during the night for 14 h. This way of treatment is called ''dark therapy,'' and it has been proven to stabilize the functioning of the internal clock (Abreu and Braganca, 2015). Relatedly, lithium and valproic acid, which are used to treat bipolar disorder, have a stabilizing effect on the functioning of the internal clock (Dallaspezia and Benedetti, 2009).

The manic episodes of bipolar disorder seem to be caused by the malfunctioning of the internal clock induced by low-grade inflammation. Patients suffering from bipolar disorder are known to be sensitive to changes in circadian rhythm. For example, both the increase of natural light and the use of light therapy treatment can trigger a manic episode in people suffering from bipolar disorder (Simonsen et al., 2011). Because of the malfunctioning of the internal clock, people suffering from bipolar disorder do not get enough good-quality sleep. Stress, which is often a trigger of mania (Kim et al., 2007), is known to reduce sleep quality and quantity (Kalmbach et al., 2018). Stress levels also become elevated if sleep time shortens and the quality of sleep decreases (Wolkow et al., 2015). This may lead to a vicious cycle that may cause mania or hypomania (Fig. 1).

6. Proximate mechanism behind depressive episodes in bipolar disorder

If mania is triggered by stressful life events that cause overactivity in the stress system and reduced sleep, which in turn leads to a vicious cycle that escalates stress levels even further, it is possible that when the stress continues for a long time, it eventually causes underactivity in the stress system because of HPA-negative feedback (Fig. 1) (cf. Miller et al., 2007). Indeed, both hypercortisolism and hypocortisolism have been observed in patients with bipolar disorder—and almost at equal rates (Maripuu et al., 2017). Unfortunately, longitudinal studies on the stress system both during mania and during depression are lacking. Nevertheless, in absence of direct evidence from individuals with bipolar disorder, it may be useful to note that hypocortisolism has been associated with atypical depression (Juruena et al., 2018), which has similar symptoms as are commonly observed during the depressive phase of bipolar disorder (Robertson et al., 1996).

An important point to note is that bipolar patients may be biologically susceptible to experiencing depressive episodes because of hypocortisolism. However, even outside of biologically driven depressive episodes, patients with bipolar disorder may also experience adverse life events that sometimes occur as a part of anyone's life. Such adverse life events as unemployment, romantic rejection, or the death of a loved one can activate different types of low mood states that are adaptations to specific adverse life events, concomitant with specific depressive symptoms and the possibility that adaptive short-term mood changes become prolonged into long-term depressive episodes (Luoto et al., 2018; Rantala et al., 2018). This can partially explain why not all patients with bipolar disorder have similar symptoms during the depressive phase. Low-grade inflammation in patients with bipolar disorder can make them more vulnerable than neurotypical controls for previously adaptive short-term mood changes to turn into longer maladaptive depressive episodes (cf. Rantala et al., 2018; Luoto et al., 2018), while hypocortisolism can also make them susceptible to experiencing periods
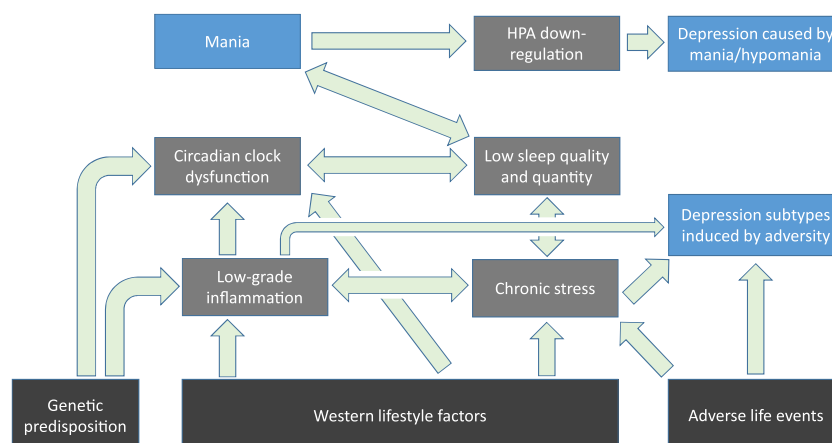

Fig. 1. The environmental mismatch model for bipolar disorder, including low-grade inflammation and chronic stress as proximate mechanisms.

of depression.

Hypersomnia is a common depressive phase symptom in bipolar disorder, and the dyssynchrony of the internal clock present in manic episodes can also be observed during depressive episodes. Even outside of depressive episodes, roughly 25 % of euthymic bipolar patients experience hypersomnia (Kaplan et al., 2011), suggesting dyssynchrony of the internal clock in individuals with bipolar disorder. Light therapy has been proven to alleviate the depressive state of bipolar disorder patients as it synchronizes the functioning of the internal clock (Tseng et al., 2016).

Staying up late is able to trigger mania, but staying up late can also elevate mood during a depressive episode. Healthy individuals feel grumpy, unpleasant, and nauseous after having stayed up late, but people suffering from bipolar disorder seem to react to it in exactly the opposite way (Bunney and Bunney, 2013). This is why bipolar disorder treatment developed in the 1970s focuses on making the patient stay up as much as possible (Wirz-Justice et al., 2005; Wu et al., 2009). Its efficacy has been examined in various studies, and meta-analyses based on these studies have proven the method to be an effective way of treating bipolar disorder (Wirz-Justice et al., 2013). Making the patient stay up late from 24 to 48 h is known to alleviate the symptoms of depression significantly for 40 % to 60 % of the patients (Wirz-Justice et al., 2013). The only downside of this is the fact that for a small percentage of people this procedure can trigger mania or hypomania. Medical treatment of the depressive phase starts functioning only after two to eight weeks of starting it, but making the patients stay up late alleviates the symptoms right away. Unfortunately this effect does not last for a long time. According to fMRI studies, the efficacy of making patients stay up late is based on the dopamine rise caused by staying awake (Wu et al. 2009).

If the inflammatory hypothesis of bipolar disorder is correct, the most important thing in the long run is to reduce chronic stress and low-grade inflammation in the body, as they disrupt the functioning of the internal clock and cause neuroinflammation. Light therapy and making the patient stay up may enable only a temporary alleviation of the symptoms during the depressive phase (Lam et al., 2020). In addition to these, it has been proven that a therapy form based on creating a regular daily social rhythm, including regular sleep and eating times, helps stabilize the functioning of the internal clock (Abreu and Braganca, 2015).

Neuroinflammation and sleep problems provide a proximate-level explanation for why psychological traits like creativity, optimism, competitiveness, self-esteem, and self-confidence become dysfunctional, being either too high or too low in bipolar disorder. These psychological traits are known to be regulated by neurotransmitters like dopamine and serotonine (Ben Zion et al., 2006; Sharot et al., 2012; Takeuchi et al., 2010; Watanabe and Yamamoto, 2015). Their synthesis is interfered by neuroinflammation and lack of sleep. For example, stress is known to upregulate the immune system (Slavich and Irwin, 2014), but it is known to also upregulate the serotonergic system (Kawahara et al., 1993; Keeney et al., 2006; Leite-Panissi et al., 2006; Midzyanovskaya et al., 2006; Racca et al., 2005; Singewald et al., 1997; Vindas et al., 2016). In mania, lack of sleep increases dopamine levels (cf. (Wu et al., 2009). Therefore, the psychological trais that are regulated by these neurobiological mechanisms may become overexpressed and, ultimately, dysfunctional. In contrast, in the depressive phase, dopamine and serotonine levels drop (Ashok et al., 2017; Salvadore et al., 2010), which explains reduced self-esteem, pessimism, loss of creativity and loss of self-confidence in the depressive phase.

7. What triggers and maintains neuroinflammation in patients with bipolar disorder

Bipolar disorder is typically triggered by stressful life events (Lex et al., 2017; Proudfoot et al., 2012). Stress is known to trigger neuroinflammation (Rantala et al., 2019) and to influence sleep quality and quantity (Kalmbach et al., 2018). Thus, the mechanism of how stress triggers bipolar disorder seems clear (Fig. 1).

Childhood traumas and early-life stress have been linked with an increased risk for bipolar disorder (Aas et al., 2016; Farias et al., 2019; Watson et al., 2014). Studies have connected them also to increased sensitivity to social threat and adversity later in life, which lead to a state of chronic stress more easily in modern societies (Agorastos et al., 2019; Fogelman and Canli, 2019). Experiences of social threat and adversity are known to upregulate components of the immune system involved in inflammation (Slavich and Irwin, 2014), which may provide another mechanism for how childhood traumas and early-life stress increase risk for bipolar disorder. It is possible that one reason why bipolar disorder is so rare among hunter-gatherers is because they are very child-centric as a group and children are unlikely to be subjected to the kind of neglect and abuse as they are today (see Hewlett and Lamb, 2017). There are also many social stressors unique to contemporary urban environments, which increase social stress in those with contemporary urban Western lifestyles (Lederbogen et al., 2011; Willie et al., 2016).

However, many people have experienced childhood traumas, early-life stress, and severe chronic stress without developing bipolar disorder. Genetic factors can explain some of the variance in why chronic stress may in some individuals cause bipolar disorder, while in others it may cause major depressive disorder, schizophrenia, or eating disorders (Rantala et al., 2019). However, genetic risk factors for bipolar disorder overlap with those for schizophrenia, major depression, and other disorders (Gordovez and McMahon, 2020; Smelan et al., 2020). Genetic factors may also explain some of the variance in stress sensitivity and inflammation (Arnau-Soler et al., 2018; Ottesen et al., 2020). Yet the heritability of bipolar disorder in people with a Western lifestyle is approximately 60 % (Johansson et al., 2019). Thus, much of the variance remains unexplained by genetic factors.

One possible explanation for why chronic stress causes bipolar disorder in some individuals while in others it may cause major depressive disorder, schizophrenia, or eating disorders may be related to individual differences in gut microbiota. Recent studies have associated many mental disorders with aberrant gut microbiota (reviewed in Gondalia et al., 2019). Dysbiosis can cause inflammation in the gut (Lobionda et al., 2019), which can increase production of proinflammatiory cytokines that are able to pass the blood–brain barrier and cause neuroinflammation. Gut microbiota is also known to influence stress sensitivity (Sudo, 2019), which might explain how gut microbiota is associated with bipolar disorder.

In addition to problems with gut microbiota, some food sensitivities seem to be more common in patients with bipolar disorder than in healthy controls. For example, Dickerson et al. (2011) found that patients with bipolar disorder had increased antigliadin IgG levels and increased levels of antibodies against deamidated gliadin compared to controls. However, antibodies that would have predicted celiac disease were not elevated (Dickerson et al., 2011). Another study reported elevated antigliadin IgG antibody levels during the acute manic phase compared to controls, but no differences from controls after a 6-month follow-up (Dickerson et al., 2012). In manic individuals, elevated IgG levels were associated with re-hospitalization during the follow-up, suggesting a correlation between glutein sensitivity and the clinical course of manic symptoms (Dickerson et al., 2012). Correspondingly, a study on 103 Tunisian psychiatric inpatients reported three times higher prevalence of increased antigliadin IgG levels in inpatients than in controls (Sidhom et al., 2012).

In addition to wheat glutein sensitivity, sensitivity to bovine milk casein seems to be more common among bipolar disorder patients than in healthy controls. Severance et al. (2010) measured anti-bovine casein immunoglobulin levels in 75 individuals with bipolar disorder and 65 controls, finding that 27 % of patients with bipolar disorder type I had casein antibodies in their blood, but none of the patients with bipolar disorder type II had antibodies. Among healthy controls, 11 % had casein antibodies (Severance et al., 2010). The amount of casein antibodies in blood correlated positively with the severity of manic

symptoms, but not with depressive symptoms (Severance et al., 2010). The anti-casein IgG levels of those bipolar disorder patients with recent onset of psychosis were much higher than in controls (OR 15.19 for disease association) (Severance et al., 2010).

There is some evidence that inflammation in the gastrointestinal tract might accelerate spread of food antigens to systemic circulation, which could explain elevated glutein and casein antibody levels in patients with bipolar disorder. For example, patients with bipolar disorder have elevated levels of anti-*Saccharomyces cerevisiae* antibodies, resulting in 3.4–4.4 higher odds ratio of disease association (Severance et al., 2014). This suggests that a leaky gut syndrome (Camilleri, 2019) might be more common in patients with bipolar disorder than in healthy controls. Stress increases permeability of the gut (Camilleri, 2019), which may explain the connection between stress, inflammation, and bipolar disorder onset. Since stressful life events often trigger mania (Proudfoot et al., 2012), they may accelerate spread of food antigens to systemic circulation in patients with bipolar disorder.

The mechanisms of how food sensitivities may increase the risk of bipolar disorder may include the activation of the vagus nerve, the production of proinflammatory cytokines, or metabolites like beta-casomorphins (cf. Pal et al., 2015). Thus, a small subgroup of bipolar disorder patients might benefit from eliminating dairy products or gluten from their diet. It is important to note that the foods causing food sensitivities are often evolutionarily novel food items for humans (Lindeberg, 2010), providing more support for the hypothesis that bipolar disorder may be caused by the mismatch between evolutionary and current environments.

The modern obesity epidemic is also an evolutionary novelty (Power, 2012). Patients with bipolar disorder are known to have an increased risk for obesity, and obesity is associated with greater bipolar disorder severity (Goldstein et al., 2011). The leading explanation for the association between bipolar disorder and weight gain is treatment with medication, with medication thought to trigger weight gain in bipolar disorder patients (McElroy et al., 2002). However, an increased prevalence of obesity is reported also among patients who have not used medication (Maina et al., 2008). As visceral fat is known to produce proinflammatory cytokines (Krams et al., 2018, 2020), we hypothesize that the reason why obesity is associated with greater bipolar disorder severity is because proinflammatory cytokines produced by visceral fat cause circadian cycle asynchrony. The reason why inflammation and chronic stress trigger bipolar disorder in some patients and why in others they may trigger major depressive disorder can be individual differences in genetic factors influencing neurochemistry, causing elevation of mood with reduction of sleep in individuals with bipolar disorder while reducing mood in others (Fig. 1). Overall, lifestyle factors causing inflammation and chronic stress may explain why the prevalence of bipolar disorder, eating disorders, and major depressive disorder are much higher among people with a Western lifestyle than among Amish or hunter-gatherers (Rantala et al., 2018; Rantala et al., 2019).

It is possible that mood variation was adaptive among people with traditional lifestyles, but because of chronic stress and inflammation mood variation has become potentially dysfunctional (Luoto et al., 2018; Rantala et al., 2018). For example, Nettle (2009) argued that in dire states, individuals should be risk-prone; in poor states, risk-averse; and in good states, risk-prone again. This model suggests that mood states adaptively adjust behavioral risk-taking: depressed states minimize risk-taking until circumstances improve, but when this strategy fails, the individual switches to a high-risk reward–approach strategy that reflects an adaptive tendency to take risks in order to resolve unpropitious circumstances (Nettle, 2009). We suggest that because of the evolutionarily novel conditions imposed by contemporary (urban) Western lifestyles that cause neuroinflammation and chronic stress, this high-risk reward–approach strategy can easily go awry, leading to a dysfunctional manic state. In ancestral environments, the reward–approach strategy may have remained at a hypomanic level as chronic stress and neuroinflammation were absent. Likewise, depressive

episodes might have remained at the level of an adaptive mood change without sickness symptoms that occur in clinical major depressive disorder (Luoto et al., 2018; Rantala et al., 2018).

It is possible that traumatic experiences in childhood trigger epigenetically driven strategies for highly competitive behaviors and search of status that manifest as mania or hypomania, which subsequently become dysfunctional in some people with contemporary (urban) Western lifestyles because of neuroinflammation. This might explain why individuals in mania feel superior whereas in depression, they feel inferior and have a general loss of confidence. Thus, although bipolar disorder can be seen as maladaptive nowadays, it may also reflect an extreme manifestation of a biobehavioral strategy that has been favored by natural selection, expressed pathologically because of the current mismatched environmental conditions (cf. Rantala et al., 2018; 2019).

8. Medical treatment for low-grade inflammation

Lithium has been used as a standard mood-stabilizing drug to treat bipolar disorder since 1949 (Malhi and Gershon, 2009). The effect of lithium was inexplicable for decades. Only in the last few years have there been observations showing that lithium has properties reducing low-grade inflammation in the body (Nassar and Azab, 2014). Lithium inhibits the amount of proinflammatory cytokines and increases the amount of anti-inflammatory cytokines. This may explain the balancing effect of lithium on the functioning of the internal clock (Dallaspezia and Benedetti, 2009). Lithium is the only treatment for bipolar disorder that has shown anti-suicide potential (Plans et al., 2019).

Nonsteroidal anti-inflammatory drugs decrease low-grade inflammation in the body, and this is why it can be assumed that they also reduce the symptoms of clinical depression for patients with low-grade inflammation and/or neuroinflammation (Kappelmann et al., 2017; Kohler et al., 2014). This matter has been extensively examined over the last few years, and a recent meta-analysis found that nonsteroidal anti-inflammatory drugs reduced the symptoms of major depressive disorder substantially more than placebo (Kappelmann et al., 2017; Kohler et al., 2014). Likewise, a meta-analysis found that anti-inflammatory drugs effectively reduced both mania and depression in patients with bipolar disorder (Husain et al., 2017). In addition, a study on 1.6 million subjects reported that low-dose aspirin (which also reduces inflammation) reduced incidence of bipolar disorder (Kessing et al., 2019). However, although anti-inflammatory drugs provide a promising new avenue for developing more effective treatments for bipolar disorder, more studies are needed to confirm what are currently limited findings on the efficacy of anti-inflammatory drugs in treating bipolar disorder (Fries et al., 2020). Overall, we think that the treatment of bipolar disorder should focus on lowering low-grade inflammation (which seems to be an important proximate mechanism underlying bipolar disorder) by implementing lifestyle changes that reduce inflammation, whilst focusing research efforts on finding more effective drugs to reduce inflammation.

9. Lifestyle changes that lower inflammation

There are many lifestyle interventions that are known to reduce low-grade inflammation or stress (or both), and they could potentially be used as non-medical treatments for stabilizing the internal clock in patients with bipolar disorder. These lifestyle interventions include adopting a healthy diet (Calder, 2017; Kaulmann and Bohn, 2014; Stachowicz and Lebiedzinska, 2016), avoiding alcohol (Wang et al., 2010) and smoking (Papoutsopoulou et al., 2020), engaging in regular exercise (Kvam et al., 2016; Nabkasorn et al., 2006), mindfulness (Morton et al., 2020), yoga (Pascoe et al., 2017), and increasing contact with nature (Antonelli et al., 2019).

Lifestyle choices such as unhealthy diet, smoking, substance/alcohol misuse, and sedentary life are associated with higher symptom severity in patients with bipolar disorder (Ashton et al., 2020; Kemp et al., 2010;

Sylvia et al., 2011). Thus, lifestyle changes addressing the above factors can be predicted to reduce bipolar disorder symptoms. There is some preliminary evidence to suggest that multimodal lifestyle interventions targeting diet, physical activity, self-motivation, and beliefs surrounding wellbeing are feasible and efficacious in individuals with bipolar disorder (reviewed in Bauer et al., 2016). However, more studies with larger sample sizes and randomized experimental protocol are needed (Bauer et al., 2016).

Since psychosocial stress upregulates the immune system, causing inflammation (Slavich and Irwin, 2014) and sleep problems, reducing and avoiding psychological stress may play an important role in prevention and treatment of bipolar disorder. Achieving this outcome might require downshifting and other changes in a person's social environment. Mindfulness provides another proven method for regulating stress and, in conjunction with pharmacotherapy, has been found to be a promising treatment for bipolar disorder (Bojic and Becerra, 2017).

In addition to lifestyle changes, psychotherapy and cognitive behavioral therapy can be used to decrease chronic stress and inflammation (da Silva et al., 2016; Gazal et al., 2013; Keri et al., 2014). A meta-analysis on the effect of cognitive behavioral therapy on bipolar disorder revealed that it lowers relapse rate and improves depressive symptoms, mania severity, and psychosocial functioning (Chiang et al., 2017).

Patients with bipolar disorder would benefit from having a regular rhythm of life (e.g., going to bed, waking up, and eating at the same time every day). Improved sleep hygiene (e.g., use of blackout curtains and avoiding electronic devices that emit blue light during the evenings) might help to stabilize the circadian rhythm and improve treatment outcomes (Abreu and Braganca, 2015; Palagini et al., 2020; Tahkamo et al., 2019). Not all patients may have the willpower to follow these lifestyle changes rigorously, which is why the most effective approach could be to adopt them as a part of everyday life at clinical settings, after which patients might be better prepared to follow the protocol in their daily lives.

Prevention of bipolar disorder and other mental disorders should be the first duty of healthcare systems and societies, not only because mental disorders cause a substantial economic burden for the society, but also because they cause tremendous suffering for patients and their families. It is well known that societies with high wealth inequality have much higher problems with mental health and criminal behavior than more equal societies (e.g. Byrne and James, 2020; Ribeiro et al., 2014; Wilkinson and Pickett, 2009; Yu, 2018). Greater potential variation in gaining resources in a given society could be expected to increase competition and cause stress in those who are in disadvantaged positions. Thus, a more equal distribution of wealth in a society may help to reduce the prevalence of bipolar disorder and other mental disorders.

10. Conclusion

In light of the evidence presented in this review article, it appears that bipolar disorder results from neuroinflammation caused by unhealthy and evolutionarily novel contemporary Western lifestyles. Instead of scientists and clinicians talking to patients about a strong genetic basis for bipolar disorder, it would be preferable to talk about a genetic *predisposition*: this is because in favorable environmental conditions, even those having a strong genetic predisposition for bipolar disorder never develop the disorder. When scientists and clinicians emphasize that a certain disease is genetic, it creates the idea of inevitability. This does not encourage a person being predisposed to bipolar disorder to shape their lifestyle in such a way as to minimize the likelihood of developing the disorder.

Currently, the medical treatment of bipolar disorder is focused on alleviating mood changes by influencing neurotransmitter levels in the brain. If the inflammation hypothesis of bipolar disorder is correct, then the treatment of bipolar disorder should focus on reducing inflammation. However, it would be important to treat also the root causes of

inflammation rather than just alleviating it with anti-inflammatory drugs. If more support is acquired for the hypothesis that the inflammation driving bipolar disorder is caused by contemporary Western lifestyles, then the treatment of bipolar disorder should focus on lifestyle changes that decrease inflammation. Since there is broad evidence showing that lifestyle influences the risk of developing bipolar disorder, we hope that our evolutionary mismatch approach encourages scientists and clinicians to shift the paradigm of bipolar disorder from the genes' point of view to a more environmental point of view, which is also expected to provide improved treatment outcomes and help societies reduce the substantial disability burden imposed by bipolar disorder.

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