

Evolutionary aspects of bipolar affective illness

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Summary

Bipolar affective illness (bipolar disorder – BD), also known as manic-depressive illness, is characterized by periodic opposite states of mood, activity, and motivation (mania and depression), sometimes of extreme intensity. The development and maintenance of such states in evolution can betoken a possibility of their adaptive character, enabling adaptation to an unfavorable external situation (depression) and a mobilization to using resources when available (mania). In the article, the main focus is put on the evolutionary aspect of “bipolarity” and manic/hypomanic states. Molecular-genetic studies show that in evolution, the genes connected with a predisposition to BD have been conserved. In the paper, the evolutionary adaptive concepts connected with the functioning of *Homo sapiens* during the middle and late Pleistocene periods were discussed as well as the “mismatch” theories associated with not befitting brain functioning to contemporary conditions. The benefits of mania and hypomania, also in the context of their link to depression were delineated, indicating their relationship to the increase in reproductive success. They result from such features of mania/ hypomania as increased exploratory, psychomotor and sexual activity, and prompt risk-taking. The reproductive success can be connected with hyperthymic and cyclothymic temperaments, most frequently occurring in subjects with BD. The hyperthymic temperament often leads to increased social status and a tendency to leadership, and the cyclothymic temperament can increase creativity. Examples of the relationship between manic/hypomanic states and the phenomenon of emigration as well as the advancement of American society are provided.

Key words: bipolar affective illness, evolution

Introduction

The great American geneticist, Theodosius Dobzhansky (1900-1975), born in Nemyriv, Ukraine, Vinnytsia region, is the author of the saying: Nothing in biology makes sense except in the light of evolution [1]. Psychiatry, similarly to other medical fields, is entrenched in biology. Therefore, according to Dobzhansky, the explanations about the causes of mental illnesses and their treatment should be compatible with the theory

of evolution. The concepts of William Hamilton and George Williams popularized by Richard Dawkins made the majority of evolutionary biologists assume that the target of natural selection is individual genes, and the organism containing them constitutes only a vehicle for their proliferation [2]. On the other hand, medicine, including psychiatry, aims to restore and maintain the health of the organism, where the genes are considered substantial albeit secondary carriers of information about the structure and function of the organism. This tension between the evolutionary-biological and medical perspectives may be overlooked because frequently the interests of the organism and its genes are convergent and the genes of a healthy organism have a good chance for proliferation. However, it sometimes happens otherwise. A genetic variant can rapidly proliferate in the next generations and exert an adverse effect on health. For example, a gene increasing the level of impulsivity can promote sexual contact and the number of offspring, while at the same time increasing the risk of addiction. For evolution, the effect of a gene on health is not relevant, provided that its copy numbers increase in the next generations.

The attempts to reconcile the medical and evolutionary paradigms inspired the creation of a branch of psychiatry called evolutionary psychiatry in the 1990s. It has been assumed that this event was a consequence of two books. The first one is "Evolutionary psychiatry: A new beginning" authored by Anthony Stevens and John Price, published in 1996 [3], and the second "Darwinian psychiatry", with authors Michael McGuire and Alfonso Troisi, issued in 1998 [4]. The subject of both publications is pointing to an evolutionary aspect of mental disorders, the main assumption being an adaptive approach. It states that the contemporary symptoms of mental disorders, at a specific stage of *Homo sapiens*' evolution could have served an adaptive function and increased the reproductive success of some representatives of our species. Genetic variants connected with mental disorders could proliferate faster in the past, and therefore they have been maintained in the population to this day. The evolutionary usefulness of most physical and psychological features was formed during the period of the environment of evolutionary adaptedness (EEA), between 100-10 thousand years ago, in the era of the late Pleistocene. At that time, the human species was at the hunter-gatherer stage, functioning in groups of about 50 individuals. There is also a possibility that some mental disorders were formed during the period of the Anthropocene which began 10 thousand years ago, as a collateral product of *Homo sapiens*' brain evolution. Also, they may have appeared or increased in number as late as during recent centuries resulting from non-befitting contemporary conditions to the previous periods of evolutionary adaptation (so-called "mismatch" hypothesis). During the Anthropocene, evolution has been influenced by cultural factors which are conceptualized as the gene-culture coevolution [5].

Several evolutionary concepts have been developed, in particular of "major" mental disorders such as schizophrenia, bipolar mood disorder, and depression. In the 21st century, also such books appeared as "Textbook of evolutionary psychiatry and psychosomatic medicine: The origins of psychopathology" authored by Martin Brüne,

Professor of Psychiatry at the Bochum University [6], and “Evolutionary psychopathology”, by Marco Del Giudice, Professor of Psychology at the University of New Mexico [7]. The recent review in “*Psychiatria Polska*” on the evolutionary concepts of mood disorders was published in 2006 [8].

Bipolar affective illness

Bipolar affective illness (bipolar disorder – BD), also known as manic-depressive illness, is characterized by the periodic occurrence of opposite changes in mood, activity and motivation (mania and depression), sometimes of extreme intensity. For a diagnosis of BD, the ascertainment of manic or hypomanic symptoms at any point in life is required, whereas depression is an element of both unipolar mood disorder (recurrent depression) as well as BD.

Depression probably constitutes the most universal reaction of the organism to an adverse external situation, mediated by the central nervous system. The evolutionary aspect of the depressive response of the organism has been the subject of many hypotheses. Depression also makes an important component of BD, frequently dominant as far as the number of affective episodes is concerned, and usually is the main cause of disability of BD patients.

In bipolar affective illness, there is a state opposite to depression, with elevated mood and activity, which is mania or a phenomenon of lesser intensity – hypomania. In some patients with periodic depression, there is a conversion during their lifetime into bipolar disorder. Therefore, a genetic relationship could be suspected between these two illnesses, where the state of mania or hypomania would be determined by the expression of an additional genetic predisposition. However, in a study by Merikangas et al. [9], the independent genetic transmission of BD type I (with manic states) and depression was demonstrated.

Some researchers think that in BD, mania makes the primary phenomenon (primacy of mania). The advocate of this concept was Athanasios Koukopoulos (1931-2013), the eminent Italian specialist on bipolar illness, of Greek origin. He thought that the illness is connected with excessive brain excitation (mania). Because such an excitation can be harmful to the brain, depression makes a protective reaction. This is reflected in his saying: “Mania is fire, depression its ashes” [10]. The issue of primacy or “independence” of mania can correspond with the results of a recent genetic study showing a separate inheritance of mania and depression [9]. The outstanding BD expert, Jules Angst, postulates that unipolar mania, the illness running without depressive episodes should constitute a distinct diagnostic entity [11].

Epidemiological studies show that BD with mania occurs in at least 1% of the population. A manic state, sometimes with great agitation and psychotic symptoms usually causes extreme behavioral disorganization and requires intensive treatment, mainly in a psychiatric hospital. Hypomania occurs in several percent of the population. In most patients, it does not result in significant disturbance of functioning and some

patients even think that their performance is improved. In BD, the main disability is connected with depressive states, bearing also a suicidal risk. Therapeutic management includes both the treatment of acute episodes as well as the prevention of mania and depression which is connected with the long-term application of mood-stabilizing drugs.

Taking into account the significant health and social consequences of BD, the illness constitutes an important psychiatric issue. Evolutionary interpretation asks for the ultimate causes of the illness, i.e., how a given feature of brain function determining a given behavior could be under some circumstances connected with better adaptation to environmental conditions. The consequence of this could lead to increased chances for reproductive success resulting in the preservation and maintenance of this phenomenon up to the present time. In this article discussing the evolutionary aspects of BD, attention will be paid mainly to the bipolarity phenomenon and its decisive component, i.e., mania or hypomania.

Conservation of genes for “major” psychiatric disorders – how adaptive genes produce an illness phenotype

Molecular-genetic studies show that prototypes of genes connected with mental disorders can be found in the ancient past. In recent years, researchers from the Louisiana State University in Shreveport analyzed genes identified as essential for schizophrenia, depression, and bipolar disorder in such lower organisms as worm *Caenorhabditis elegans*, fruit fly *Drosophila melanogaster*, and zebrafish. As to schizophrenia, they studied 344 genes identified by the Psychiatric Genomics Consortium. Comparing *Drosophila* and zebrafish it was found that these schizophrenia risk genes were conserved at significantly higher rates than genes in general for these two species. These genes also frequently showed a phenomenon of synteny, which means the presence of at least two genetic loci on one chromosome. Schizophrenia risk genes affected different stages of development allowing differential modulation by the environment [12]. As to depression, 336 genes identified by the genome-wide association studies (GWAS) were investigated. Likewise, as in schizophrenia, depression risk genes in *C. elegans* and zebrafish showed significantly higher similarity, participated in more interactions with each other, and had more frequent synteny than other genes [13].

In the study of bipolar affective illness, Franklin and Dwyer [14] first determined the risk genes for BD. Based on the analyses of Nurnberger et al. [15] and Stahl et al. [16] they recognized 230 such genes. Next, they identified their homologous equivalents in *C. elegans*, zebrafish, and *Drosophila*. Further analysis showed that BD risk genes are highly conserved across species and are significantly more interactive with each other in comparison to random genes. It was also found that these genes are associated with lethality and altered life span. In addition, syntenic blocks of genes were identified associated with BD comorbidity such as coronary disease and obesity.

According to these authors from Louisiana, the genes connected with mental disorders influence many significant processes for the development and functioning of the

brain. The majority of them present a variability that is maintained in the population because in some environmental conditions brings reproductive advantage. However, in relatively rare cases, a combination of several variants eventually disturbs brain functioning and may be harmful. The authors show that despite the possibility of improving reproductive success by individual or combination of the variants, some of their constellations may lead to the illness phenotype which is described as the “inevitable bad luck”. Therefore, the genes for bipolarity and manic states played a significant role in the evolutionary development of humans, whereas their rare combinations interacting with environmental factors can lead to the illness. Goto et al. [17] think that the main effect of the genotype of “major” psychiatric illnesses was due to a selection of the alleles of genes for the dopaminergic and serotonergic systems.

Adaptive concepts

The origin of “bipolarity” in humans can be traced back to even half a million years ago. The evolutionary concept of BD proposed by Sherman [18] postulates that “bipolar” behavior was formed in the period of the middle Pleistocene, as a seasonal adaptation to the winter period in a moderate climate zone. This pertained to human ancestors living during this time in a moderate climate, namely *Homo neanderthalensis*. Such adaptation could correspond with an association of BD with the pyknic type of human body build postulated by Kretschmer [19], conserving warmth and cold-adapted, occurring in Neanderthals. Recently, Spanish researchers showed that Neanderthals had the ability to hibernate, reflected by the findings in the Spanish caves of Atapuerca. In the skeletal collection from half a million years ago, the features of disturbances of bones and kidneys resulting from hibernation were found [20].

Thus, the climate adaptation of *Homo neanderthalensis* could make a forefather of seasonal affective disorder, first described in the 1980s [21]. In this illness, “winter depression” occurs as well as an intensification of mood and activity (hypomania) in the summer months. It can be mentioned that already in the late 1980s, Whybrow and Bahr [22] depicted winter depression as the hibernation response. Therefore, among many features inherited by *Homo sapiens* from *Homo neanderthalensis* one of these can be a tendency to seasonal changes in functioning. This can contribute to the issue of possible introgression of the Neanderthal genes into the *Homo sapiens* genome [23]. For the exploration of this subject, the Swedish researcher, Svante Pääbo received the 2022 Nobel Prize in Physiology or Medicine. The development of manic and depressive features as an adaptation to changing environmental conditions took place in the period of the late Pleistocene, also known as the environment of evolutionary adaptedness (EEA), when the human species was functioning at the hunter-gatherer stage with groups of about 50 individuals. This pertains to *Homo sapiens* functioning on various continents, including Africa. The EEA is assumed as the period between 100-10 thousand years ago, although in some populations it could have lasted longer or shorter. During this time, the expression of mania with increased life activity was

connected with better utilization of available resources, while depression with decreased activity allowed one to better make it through the environmental shortages. Both mania and depression had a distinct adaptive aspect here.

“Mismatch” concepts

In recent years, the concepts appeared to postulate that bipolar disorder can be a “mismatch” to changing environmental conditions in recent centuries. This may reflect the effect of cultural factors on the course of evolutionary processes [5]. The increasing risk of developing BD is to a great extent due to environmental changes influencing the biological clock. Carta et al. [24, 25] indicate that such factors as noise and artificial light connected with life in big cities can contribute to a disruption of biohythms and sleep disturbances. This may result in the adverse effects on the hormonal system, mainly melatonin and neurosteroids. Consequently, persons possessing the genes predisposing to BD can have a higher risk of developing the illness. However, persons with a hyperthymic temperament can take advantage of increased stimulation connected with living in big cities, which may increase their reproductive potential.

Recently, Rantala et al. [26] theorized an increased incidence rate for BD caused by many contemporary factors influencing pathogenic processes of the illness, such as low-grade inflammation, disruption of biological rhythms, and sleep disturbances. These are social stress factors, unhealthy dietary patterns, limited physical activity, and obesity. Stress can be a precipitating factor for mania and sleep disturbances but can also cause low-grade inflammation, connected with the desynchronization of the internal clock. The authors hypothesize that a genetic predisposition to BD may not emerge, providing more intense modification of these environmental factors, especially those producing low-grade inflammation.

“Parasitic” concept

There are also evolutionary concepts of mood disorders suggesting that they may be due to infection with microorganisms, especially viral ones. In such a situation, the behavior of the host changed by the parasite’s genes favors proliferation of these genes and natural selection can maintain this. The behavior of the host (human) furthering the proliferation of a virus to other persons relies on increased motor and sexual activity. A classic example is the rabies virus. Following the infection with this pathogen, information enrolled in some viral genes transforms a complex homeothermic organism into a machine facilitating the proliferation of the parasite’s genes. A similar mechanism can be found in humans after infection with viruses such as HIV and recently, with SARS-CoV-2. There is evidence for a more frequent incidence of mania in patients infected with HIV than in the general population [27]. Also, in BD patients with COVID-19, manic episodes occur more frequently [28]. Many cases of

the first manic episode in patients with no previous psychiatric disturbances have been described, including one patient from our center [29].

Evolutionary advantages of mania/hypomania

Evolutionary conservation of genes for mania of various intensities, also in the context of its relationship with depression can indicate an association with reproductive success. Such features of manic/hypomanic states as increased exploratory, psychomotor and sexual activity as well as prompt risk-taking can be adaptationally advantageous in many situations. They bring about a significant improvement in functioning in the face of challenges concerning the availability of resources and thus increase reproductive abilities.

This concept was formulated in a slightly different form by a recently deceased eminent researcher of BD, Hagop Akiskal (1944-2021). Among the numerous achievements of this great scientist, the elaboration of the Temperament Scale of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A) should be mentioned. The TEMPS-A distinguishes hyperthymic, cyclothymic, depressive, anxious and irritable temperaments [30]. This questionnaire has Polish validation [31]. According to Akiskal's point of view, affective temperaments constitute the most frequent phenotypic expression of the genes associated with predisposition to BD, most often hyperthymic and cyclothymic temperaments. Kelsoe [32] thinks that genes connected with bipolarity are pretty frequent in the population. When, during the process of inheritance, some threshold value for the number of genes determining the risk of illness is exceeded, the illness phenotype appears, in line with the concept of "inevitable bad luck" described earlier [14]. On the other hand, in the case of a limited number of "bipolarity" genes", an individual can display the features of an affective temperament (hyperthymic or cyclothymic). Contrary to full-blown mood disorders, various affective temperaments can be associated with better psychosocial functioning and higher social and economic status.

Akiskal thought that the temperaments connected with a higher risk for BD can provide in some situations evolutionary benefits [33]. From an evolutionary point of view, the advantageous consequences of hyperthymic temperament can be easily explained. Persons with such a temperament can have leadership features, tend to gather other people around them, and are characterized by a great level of energy and expansivity. Tendency to leadership and defense of own territory could in the past, but probably also in the present time, be related to a higher probability of proliferating one's genes. Corresponding with this are numerous studies showing an association between a manic state and a sense of higher social rank [34, 35]. Akiskal's group postulated a connection between hyperthymic temperament and playing executive roles in various professions [36]. In a paper by Scandinavian authors it was shown that genetic predisposition to BD is linked to leadership features [37]. In turn, in a Polish study, higher indexes of hyperthymic temperament measured by TEMPS-A were found in both male and female subjects engaging in extreme and high-risk sports [38].

According to Akiskal [31], cyclothymic temperament is connected with frequent falling in and out of love, which in consequence may lead to many relationships. This likely resulted in having numerous offspring in the evolutionary past [31]. The most frequent feature in people with cyclothymic temperament is a tendency to rapid changes in mood and energy levels, probably connected with higher emotional reactivity. It was also found that cyclothymic temperament can be associated with creativity and artistic abilities [39]. A connection between bipolarity/bipolar disorder and creativity/artistic abilities was found in numerous Polish studies performed, among others, in Poznań and Kraków. Rybakowski and Klonowska [40] found higher creativity scores in patients with BD compared with the control group. Siwek et al. [41] demonstrated higher indexes of bipolarity in students of art schools. Special attention should be given to the exploration of the association between bipolar illness and creativity performed by the American researcher, Tiffany Greenwood [42], from the University of California at San Diego. In her recent review paper, she presents evidence of the genetic connection between creativity and bipolar illness and suggests that creativity, mainly in the context of mild and moderate forms of BD, can increase reproductive ability. A similar view on artistic activity and its relationship with reproductive success is presented by English psychologist, Geoffrey Miller [43], currently working at the University of New Mexico in Albuquerque.

The connection between elevated mood and activity, explicitly termed “hypomania”, with success in America is presented in the book “The hypomanic edge. The link between (a little) craziness and (a lot) of success in America” issued in 2005 [44]. Its author is a psychologist, John Gartner, working at the Johns Hopkins University in Baltimore. The main message of the author is to reveal the relation between the state of hypomania and the shaping impact on America made by those with a tendency to such behavior. Gartner thinks that immigrants coming to America were in the majority people with high energy levels and a significant risk-taking tendency, i.e., behavior characteristic for a state of hypomania which allowed them to achieve unusual goals. Genes connected with a predisposition to hypomania might have been “favored” in the specific conditions of American society. Several years ago, researchers from Sardinia attempted to experimentally verify this issue. They compared the immigrants from Sardinia living in Argentina with sex- and age-matched people in the domestic country. It was found that Sardinian immigrants in Argentina had a significantly higher frequency of manic/hypomanic episodes than Sardinian residents [45].

In his book, Gartner also presents biographies of people for whom the states of mania/hypomania, being undoubtedly an element of bipolar mood disorder, enabled them to accomplish remarkable achievements. Among such persons the discoverer of America, Christopher Columbus, appears; also Alexander Hamilton, one of the commanders of the American Revolutionary War, and later a father of the American financial system; and Andrew Carnegie, who helped bring about the industrial boom of America. The power of one of the American icons, Hollywood, was built up at the beginning of the 20th century through the actions of the Mayer and Selznick families,

Jewish emigrants from Eastern Europe. David O. Selznick thanks to his manic motivation to act brought to completion his great work "Gone with the wind" in 1939. In a state of depression that soon followed, he gave up his rights to the film. One of the last examples described in Gartner's book is the researcher of molecular genetics, Craig Venter, talented and having an unusually strong motivation to act. In 1997 he established the private company Celera (from the Latin word *celer* – quick), which soon raised a challenge to researchers of the international Human Genome Project. Competition between the two teams contributed to an unusual acceleration of performance of the whole undertaking, and Venter can be considered to have made a great contribution to this work. Probably, Venter has been the first representative of *Homo sapiens* to have their complete genome identified [44].

Peter Whybrow in his book "American mania – when more is not enough" published in 2005 [46], also issued in Poland, titled "American mania. Ciągłe więcej, ale nigdy dość" [47] thinks that bipolar disorder can make an allegory of contemporary social and cultural phenomena in the USA. The pursuit of material values, stimulated by their unrestricted availability, which is accompanied by excessive optimism can be seen as a metaphor for early periods of mania in the course of BD. Whybrow also refers to genes connected with exploration and pleasure-seeking probably associated with the dopaminergic system, coming mainly from immigrants from the different generations which in this situation may spread more. However, every psychiatrist treating patients with bipolar disorder is aware that a state of elevated mood inevitably evolves into the opposite pole. This is currently reflected in the increase in the USA of indicators of depressive and anxiety disorders which are often accompanied by addiction and self-destructive behaviors.

Concluding remarks

The evolutionary aspect of bipolar affective illness puts a special focus on the development and consequences of mania/hypomania. In the majority of cases, the elevated mood and activity appear in the context of "bipolarity", i.e., when also depressive states occur. In the process of evolution, depression also had many adaptive features. In the case of BD, favorable consequences are mainly associated with hypomania as well as hyperthymic and cyclothymic temperaments, whereas mania is mostly, similar to a malignant tumor, a state "out of control", often leading to dramatic disturbance of functioning in many areas. As an analogy to the development of severe depression termed by Lewis Wolpert "malignant sadness", severe mania could be named "malignant happiness" [48].

Mood regulates the activity of the organism depending on external and internal milieu. In an adverse environment or disease state, the mood worsens so that the organism does not waste the resources. On the other hand, in good health and a propitious environment, the mood improves enabling the use of available resources. Such regulatory function of the mood is adaptational, matching the consumption and accumulation of

energy to current requirements. Diener et al. [49] put forward a hypothesis that people generally tend to a positive mood, which may be called a positive mood offset. During late Pleistocene, such mood increased the probability of such behavior as creativity, planning, interpersonal relations, and social interactions which favored fertility and health and resulted in reproductive success. Therefore, the adaptive role can be played both by mood as a regulator of activity as well as its navigation in a positive direction. One may ask whether extreme and long-term mood changes – mania and depression – had played in the past or present an adaptive role? Seasonal changeability of the mood as well as some features associated with elevated mood – creativity, leadership, social expansiveness, and hypersexuality could contribute to reproductive success in the past and also present. However, their too-great intensity or inappropriate configuration can lead to illness. A similar mechanism has been proposed as to the genes responsible for BD – their limited number improves adaptiveness while an excess or inappropriate configuration brings upon the illness, especially in the context of unfavorable environmental conditions [24-26]. Sexual reproduction inevitably leads to new constellations of the genes and features. Therefore, we cannot avoid bipolar disorder as a consequence. Paraphrasing Timothy Crow, who recognized schizophrenia as the price to pay for the development of language, we can speculate that bipolar disorder is the price for progress paid by those who are excessively optimistic.

A question may be asked whether a better understanding of the evolutionary “ultimate causes” of mania/hypomania and bipolar mood disorder may be useful for a psychiatrist? Undoubtedly, such knowledge can give rise to a wider look at the phenomenon of mood disorders also in the context of symptoms and therapeutic possibilities. The article of Rantala et al. [26] underscoring the effect of contemporary factors on the occurrence of the illness also offers some suggestions for prophylactic management.

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