

SPECIAL ARTICLE

Multidisciplinary contributions towards an evolutive interpretation of bipolar disorders: could it be the pathological drift of a potentially adaptive condition?

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This paper tries to summarize the results of studies from different areas of knowledge supporting the idea that temperamental traits, such as “reckless/hyper-exploratory” attitudes, commonly believed to be associated with psychopathology, surprisingly turn out as adaptive under specific stress conditions. In particular, this paper analyzes an ethologic line of research on primates suggesting models for a sociobiological interpretation of mood disorders in humans; a study that found high frequencies of a genetic variance associated with bipolar disorder in people without bipolar disorder but with hyperactivity/novelty-seeking traits; the outcomes of socio-anthropological-historical surveys on the evolution of mood disorders in Western countries in the last centuries; surveys on changing societies in Africa and African migrants in Sardinia; and studies that found higher frequencies of mania and subthreshold mania among Sardinian immigrants in Latin American megacities. Although it is not unequivocally accepted that the prevalence of mood disorders has increased, it would be logical to suppose that a nonadaptive condition should have disappeared over time; mood disorders, on the contrary, persist and their prevalence might have even increased. This new interpretation could lead to counter discrimination and stigma towards people suffering from the disorder and would be a central point in psychosocial treatments in addition to pharmacological therapy. Our aim is to hypothesize that bipolar disorder, strongly characterized by these traits, may be the result of the interaction between genetic characteristics, not necessarily pathological, and specific environmental conditions rather than a mere product of an aberrant genetic profile. If mood disorders were mere nonadaptive conditions, they would have disappeared over time; however, their prevalence paradoxically persists if not even increases over time. The hypothesis that bipolar disorder may result from the interaction between genetic characteristics, not necessarily pathological, and specific environmental factors seems more credible than considering bipolar disorder as a mere product of an aberrant genetic profile.

Keywords: Bipolar; genetics; environmental; adaptation

Introduction

This opinion paper examines some contributions from historical-anthropological, ethological, and biomedical disciplines dealing with the hypothesis that temperamental traits such as reckless or hyper-exploratory attitudes and “compulsive hyper-responsibility,” commonly believed to be associated with psychopathological risk, could produce adaptive behaviors in particular circumstances characterized by stress conditions caused by social, economic, or conflict crises.¹⁻⁴ Some evidence seems to indicate that traits related to novelty seeking, reduced risk perception, proneness to compete, search for high social status, and emotional instability (well known as typical in people with a diagnosis of bipolar spectrum disorders)⁵⁻⁹ may provide adaptive advantages, perhaps as nuanced

traits.⁵ It must be highlighted that evolution selects for DNA survival by various aspects, not necessarily for individual, kin, or group functioning and happiness.^{3,5,6}

However, if mood disorders were merely a product of a genetic aberration, this condition, which affects people who live shorter lives and give birth to fewer children^{10,11} and is likely to lead to poverty and social defeat,¹² would have disappeared over time. Paradoxically, some relevant epidemiological studies repeated over time in the United States,¹³ New South Wales,¹⁴ and Korea¹⁵ have found an increase in the prevalence of mood disorders, at least over the past three decades. Although it is not unequivocally accepted that an increase in the prevalence of mood disorders has occurred,¹⁶ it would be logical to suppose that a mere nonadaptive condition should have disappeared over time, but it hasn't; on the contrary,

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mood disorders certainly persist if their prevalence is not even increased. It is therefore legitimate to assume that, at least in subclinical conditions, some features of mood disorders may produce adaptive aptitudes and specific environmental and historical contexts or cultural conditions can foster these kinds of temperamental aspects.

Gene-environment interaction modulates aggressive and novelty-seeking behavior in primates

A sociobiological interpretation of mood disorders in humans could come from ethology and genetic surveys on primates. A line of research conducted by the Suomi group¹⁷ explained the differences in rhesus monkeys' biobehavioral responses to social conflicts through an elaborate gene/environment interaction model. Around 5-10% of young rhesus monkeys observed in nature growing in herds exhibit hyperactive and inappropriately aggressive responses even in play situations or due to mild stress; this feature is associated with impairment of central serotonin metabolism. The hyperactive/aggressive behavior patterns emerge early in life and lead to substantial adaptive disadvantages. Young monkeys with these characteristics are often isolated from the herd and have little chance of survival. Consequently, the persistence of these behaviors in many individuals is paradoxical. However, although these characteristics are heritable, their expression is subject to modification by early experiences, particularly early social attachment with caregivers and especially with the mother. Monkeys with hyperactive and inappropriately aggressive responses and associated central impaired serotonin metabolism but with secure attachment relationships with their mothers (or an adoptive mother) during infancy had similar aggression patterns but modulated to the point where they could use these behaviors with advantages for themselves and the herd. These monkeys showed a high probability of becoming the head of the herd.¹⁷

The first question that arises from reading Suomi's work is whether something like the rhesus monkey dynamic, the species with the highest similarity in genetic heritage to humans, can also occur in *Homo sapiens*.

Suomi's model can apply to something that seems to be the apparent opposite of depression: an overactivity/over-exploration behavior. However, according to the neo-Kraepelinian interpretation, there is a continuum between bipolar disorders and depression.¹⁸ From this point of view, mania would be like fire before the ashes (depression), an antecedent, though often unidentified, of many cases of depression.¹⁹ Furthermore, even according to Bowlby's hypotheses, people at risk of developing a depressive disorder would have personality characteristics of "compulsive hyper-responsibility," or an aptitude for taking charge of the needs of the closest people with basic hyperactivity.²⁰ Assuming this perspective, it should be considered that people with a bipolar spectrum diagnosis experience more and longer periods of depressed mood and shorter manic/hypomanic periods.²¹⁻²⁴

A genetic variant associated with bipolar disorder was found in people without bipolar disorder but with hyperactivity/novelty-seeking traits

A recent study found a genetic variant associated with bipolar disorder in people without bipolar disorder but with hyperactivity/novelty-seeking traits.²⁵ A sample of old adults without lifetime mood disorders living in the community was recruited from the overall sample of a previous study of active aging and exercise.²⁶ They were subdivided using a previously validated tool²⁷ into those with or without hyperactivity/exploration traits. The two samples were compared with a group of old adults with bipolar disorder of the same age. The frequency of the genetic variant RS1006737 of *CACNA1C*, one of the most well-known genetic variants associated with bipolar disorder,²⁵ was measured in the three groups. The results highlight that people with hyperactivity/novelty-seeking traits but without lifetime bipolar disorder showed the same frequency of RS1006737 in the *CACNA1C* locus as the sample of old adults with bipolar disorder (OR = 0.79, 95%CI 0.21-2.95). Furthermore, people with hyperactivity/novelty-seeking traits but without lifetime bipolar disorder had a higher frequency of this specific genetic variant than people without both hyperactivity/novelty-seeking traits and bipolar disorder (OR = 4.75, 95%CI 1.19-18.91).

People with hyperactivity/novelty-seeking traits are "challengers" with hyperthymic temperaments/personalities that could have adaptive resources in a new contemporary lifestyle, especially in high-density urban environments. In fact, if the life framework requires adaptation to fast and changing rhythms, it could favor people with a basic predisposition to it, i.e., people who can mobilize their energy for limited periods and with less need for sleep.²⁸

It could be hypothesized that when the challenges exceed the ability to adapt and the demand is too stressful, mood disorders can emerge with features of broken biological/social rhythms.

Suggestions from a socio-anthropological-historical reading of the evolution of mood disorders

In the last decades, human beings have chosen to live in a few cities with millions of inhabitants where life runs 24 hours a day every day.²⁹ The impact of the daily lifestyle, determined by social changes, business travel, changes in eating habits, noise, and light pollution on the social and circadian rhythms has consequences for several metabolic pathways in the human organism.³⁰

Light pollution, which decreases melatonin secretion at night and unbalances (neuro) steroids in favor of testosterone and estrogen, was found to be the cause of an increased prevalence of prostate³¹ and breast³² cancer in megacities and was also identified as a determinant of the risk of bipolar disorder.³³⁻³⁵ Analogously, some studies have shown that, in the springtime, a large increase in sunlight due to climate change in

specific locations can be a strong predictor of an early onset of bipolar disorder.^{36,37}

Paradoxically, the environment of megacities may be somewhat adaptive for people with a hyperthymic and explorative “pathologic subthreshold” temperament since they may be more prone to responding to challenges as they can handle energy peaks and dips by accelerating their performance in specific circumstances or adapting to a constantly changing world with new solutions.³⁰

The social transformations related first to industrialization and then to globalization may have created adaptive hyperactive behaviors and exploratory attitudes. Could they have caused an increase in mood disorders or, at least, a transformation of psychopathology?

Some studies have analyzed the evolution of depressive symptoms in the last centuries following a socio-anthropological interpretation.³⁸ According to these surveys, depression, as described in modern psychiatric handbooks and characterized by low self-esteem, feelings of guilt and helplessness, “epidemicly” grew in the 17th century in England.³⁹ Before this time, the rare descriptions of “melancholia” were centered on psychosomatic symptoms.³⁹

According to some sociological theories, the economic change affects psychopathology at two interactive levels³⁹:

1. The decline of the extended family model, typical of the agricultural culture and led by industrial work, affected identification processes from group to individualism and had an impact on the concept of affective relationships traditionally associated with larger families.
2. The enhancement of individual responsibility by the new social models represented a cornerstone of change. In fact, according to the “new common sense” of the bourgeois society, the attainment of personal goals was considered the result of individual efforts, while defeats and failures were the sole responsibility of the person concerned, with a more and more marginal role played by “medieval providence.”

A new malaise started to be associated with guilt; hence, the new “English disease” appeared.

As these theories were developed within socio-anthropological research, possible gene-environment interactions were not considered.

The transformation of African psychopathology related to social and economic changes

From a cultural anthropological perspective, it is incorrect to view the development of other cultures as a “late” achievement of Western cultural structures.⁴⁰ However, the rapid social changes introduced by globalization have, elsewhere too, led to changes in the ways of adaptation and communication.⁴¹ Psychopathological manifestations and the expression of mood disorders have also changed in non-Western cultures.⁴² Although probably not identical to those found in Europe by the studies cited, these changes currently occurring in other cultures are nonetheless of extreme interest from our point of view.

In contrast with the “Western” pathology, depressive symptoms in sub-Saharan Africa were described in the 1950s and 1960s as consisting of ideas of reference, delusions of persecution, and psychosomatic symptoms.⁴³ The hypothesis advanced by the “Dakar school” was that this expression of mood disease depended on whether, in West Africa, mother-child and then community-individual relationships created a sort of symbiotic personality.⁴⁴ In this cultural ground, being sad means being separated from the group to which the person belonged and feeling threatened and persecuted.⁴³

A subsequent modification of depressive psychopathology in sub-Saharan Africa has been described by several observers.⁴⁵⁻⁴⁸ Morton Baiser, a relevant trans-cultural psychiatry researcher, when attempting to repeat an epidemiological survey years after the first one among the Serers of Senegal, recounted that his previous interviewers report that “those strange diseases that you used to ask if there were any have now arrived.”⁴⁹

From our point of view, the studies that have been able to photograph this change are, therefore, exciting.

An epidemiological community survey carried out in the late 1980s captured the change of African psychopathology on the ground of significant social changes in the Dogon plateau in Mali.⁵⁰ It concerned a population, predominantly illiterate, who lived in nomadic camps (Peul ethnicity) or villages (Dogon ethnicity).⁵⁰ Rates of depressive disorders were firmly lower than in studies conducted in Europe with similar tools.⁵¹ Depressive disorders without predominant somatic symptoms were rare among illiterate people.⁵⁰ In contrast, in the few literate people, a “classic western-like” depressive syndrome was found, with typical symptoms such as sadness, negative cognitive polarity, feelings of guilt, and loss of hope and interest.³⁹ In the principal component analysis of depressive symptoms, a trend of inverse correlation was found between the two different traditional/Western “pictures.”⁵² Even with the limitations of a cross-sectional investigation, the study seemed to suggest that the cultural change was associated not only with the “transformation” of symptoms but also with an increase in the rate of depressive disorders, at least when described according to DSM criteria (these were, in fact, infrequent in illiterate and non-“Westernized” people). Anyway, although some researchers have shown an increase in the incidence of mood disorders, bipolar disorder is much less prevalent than major depressive disorder in all populational studies.^{9,23,30}

By the 1980s, a strong migration from sub-Saharan Africa and North Africa to Sardinia had begun. Unlike people that stay in their country of origin, migrants (at least voluntary migrants) show an aptitude for exploring and finding “new solutions.” The importance of social cohesion (mediated by Islamic brotherhoods) as a protective element against the stress of uprooting and the impact of the new reality was evident among Senegalese migrants in Sardinia.⁵³ Unlike other groups of migrants, the strongly cohesive context in which they lived protected them against the risk of psychopathology.⁵³ Furthermore, the social cohesion mediated by syncretic rituals represented a sort of social mediation

with the evolving reality,⁵⁴ but it also prevented them from integrating into the new society individually. In the small group of Senegalese migrants that had abandoned these close community ties and had “established themselves” individually in the new social reality, a very high risk of depressive episodes emerged.⁵³ On the contrary, the rare psychopathological episodes among migrants “belonging to the group” were characterized by persecutory symptoms associated with the impression of having lost their commitments with the community of origin (linked to the rituals of “Wotal,” which in fact sanctioned the close ties, including economic ones with the family of origin).^{53,55}

However, what are the mechanisms through which the transformation of psychopathology takes place? Do social changes trigger equal responses in all individuals, or do some individuals have specific characteristics that allow them to adapt their behaviors to address specific needs?

Finding solutions in an evolving society in Malawi: daredevil behavior can be advantageous, but it could be risky

In the village of Namwera, in Malawi, the Italian cooperation system promoted a project that contributed to the creation of an industrial tailoring workshop in the late 1980s, when the country was affected by profound changes.⁵⁶ After an initial training period, the project expected women working in the tailoring workshop to buy a sufficient amount of machines to set up their own tailoring businesses in their villages of origin. This path would have not only implied the abrupt transition from the role of traditional women to that of businesswomen but also the temporary departure from their villages to work with “white Catholics” (which was not well perceived among the Muslim majority living in traditional villages).⁵⁶ The well-being of three samples of women (seamstresses, women with conventional jobs/peasant women/homemakers, nurses, or midwives) was assessed by a survey.⁵⁶ It found that women who had chosen innovative jobs had specific personal backgrounds. In fact, 80% of the women covering innovative roles (seamstresses and nurses) were abandoned by their fathers at a young age⁵⁶ and faced serious economic issues. Although father abandonment was not rare in that culture, these women, owing to their “exploratory features” and their sense of “super-responsibility” (which recalls Bowlby’s “depressive style”⁴), used their cultural leap to take charge of the financial and nutritional problems of a whole family.

Although the number of people suffering from psychopathologies was high both among seamstresses and women with “traditional” roles, the symptomatic expression was basically different: in fact, the seamstresses presented a “classical Western-like” depressive symptomatology whereas the women with “traditional” roles presented ideas of persecution and psychosomatic symptoms.⁵⁶

By breaking with tradition, the seamstresses were exposed to more risks than the women who had remained tied to a traditional work model, as the latter were not subject to societal conflicts. However, the seamstresses

benefited from greater financial comfort and many of them even managed to become leaders in their contexts, whereas women with “traditional” roles were more likely to be unable to respond to the new economic needs that emerged in the changing society.⁵⁴

Women working as nurses, on the contrary, could maintain a more acceptable social role and, at the same time, enjoy a satisfactory economic situation. Not surprisingly, they were the most emotionally stable group.

In conclusion, economic changes, particularly crisis conditions, selected individuals who were more prone to a break with tradition and to a cultural “leap” and who followed paths leading to individualization. In fact, these people could get ahead of those who were not prone to a leap and established new social ranks, but at the same time they were also at increased risk of stress and thus of mental health problems with “new” clinical presentations.

Considering these interpretations, cultural change provides opportunities for “desperate, exploratory, super-responsible” individuals who would suffer social defeat otherwise.⁵⁴

The question that emerges is: does social change “create” the new pathology as traditionally believed, or does the interaction between individual predisposition and social change lead to “new pictures”?

Studying exploratory and hyper-responsibility people: volunteer migrants departing from an island

An island halfway between Africa and Europe is a crossroads where people arrive and leave.

A survey conducted in Paris and Sardinia in the late 1990s allowed a comparison between Sardinians living in Sardinia, Sardinians residing in Paris, and Parisians.⁵⁷

Parisians showed more depressive disorders than Sardinians in Sardinia. Second-generation emigrants frequently had depressive symptoms like the non-Sardinian Parisians.⁵⁷ A surprisingly similar result was found when studying Greek Cypriots who migrated to London.⁵⁸

Older Sardinian emigrants in Paris were less at risk of depressive episodes. In young Sardinian emigrants, depressive episodes were associated with anxiety disorders and with substance-related disorders (in men) or eating disorders (in women). We hypothesized that a new stimulating situation offering life opportunities like that of Paris could paradoxically increase the risk of depression in young people exposed to frustration than in older ones with less ambitious goals.⁵⁷ Considering the profile of co-occurrence factors, we also guessed a higher frequency of bipolar depression among young emigrants.⁵⁷

The Paris emigration study did not adopt a methodology focused on bipolar disorder. However, considering the results, we have used tools better adapted to measure the bipolar spectrum⁵⁹ in the following surveys conducted with Sardinian emigrants in the large metropolises of Latin America (Buenos Aires, Rio de Janeiro, and São Paulo).^{30,60} These studies show a significantly higher prevalence of hypomanic episodes, even sub-threshold, in a population of emigrants from rural areas to

metropolitan areas of Latin America compared to the population of origin.^{30,60} Our hypothesis emphasizes that perhaps the manic traits or even mild hypomanic periods could be adaptive, but not bipolar disorder in its severe form.

As previously supposed, megacities, with their frenetic pace, seem to attract (or produce?) people more prone to hyperactivity/hyperthymia. Frenetic social rhythms and noise and light pollution could impact circadian biorhythms and affect mood.²⁸ But a megalopolis can also offer an ideal context for those who love frenzy and are inclined to an accelerated life.⁶¹

From this perspective, the historic sociological dilemma of whether the metropolis could cause the pathology due to the stress of the new life or the increased prevalence of mood disorders in degraded areas of the cities could be due to vulnerable people shifting toward poverty because of mood disorders is not in contradiction or alternative. People with specific characteristics of hyperactivity look for an environment congenial to them, but they also create it. For example, people with manic traits have more possibilities, including being more likely to decide to leave their countries. Previous observations seem to suggest that some basic characteristics linked to specific genetic variants (which predispose to hyperactivity and exploration) may constitute the substrate that responds to social change; the adaptation could succeed, but if it fails, the risk of the “new pathology” increases.

The complex gene-environment interaction on the modulation of aggressive and novelty-seeking behavior

The interaction between genes and the environment is not as simple as we have attempted to summarize through a model in which the exploratory/aggressive trait appears adaptive in highly stressful situations compared to low-stress contexts in which the aggressive trait can be perceived as pathological by the social network. Studies in other social animals have shown the high complexity of gene-environment interactions in the emergence/favoring of exploratory and aggressive behaviors. Stimuli, such as infections, can trigger behavior modifications. Wolves infected by *Toxoplasma gondii* are 11 times more likely than uninfected ones to leave their old pack and build a new one and 46 times more likely to become leaders of the pack.^{62,63} In other mammals, *Toxoplasma* infection increasing testosterone and dopamine levels can induce exploratory behaviors and decrease fear.⁶⁴ The consequences are not univocal: infected hyenas became more likely to be eaten by lions.⁶⁵ Once again, it emerges that a daredevil's behavior can sometimes be advantageous but expose individuals to risks.

A meta-analysis showed that infection by *T. gondii* is associated with bipolar disorder in humans.⁶⁶ Some authors have investigated potential differences in personality traits between humans with latent toxoplasmosis and uninfected controls. Higher protension scores, a higher tendency to disregard rules, and a suspicious attitude are some of the traits most present among men.^{67,68} In an

experimental set of 55 young mothers with latent toxoplasmosis, certain traits such as adventurous, “thick-skinned,” socially bold, enthusiastic, heedless, happy-go-lucky, outgoing behaviors, and again pretension and suspicious attitude correlated with the length of the infection.⁶⁹ Widely considered among rats, the “manipulation hypothesis” speculates that the parasites would benefit from the opportunity of propagation through a modification of host behavior; however, it still seems like a not sufficiently proven guess in humans.⁷⁰

Nevertheless, if it is still a hypothesis, neuromodulation may represent an ideal system by which *T. gondii* could influence the expression of host behaviors. Thymosin beta-4 produced by *T. gondii* vesicles in the brain may unbalance neuro-steroids enhancing estrogen/testosterone against progesterone, thus stimulating aggression, exploration, and shortening the sleep period.⁷¹ On the other hand, evidence has accumulated on a mood stabilizing role of progesterone,^{72,73} which would be lost in case of *Toxoplasma* infection.

The ecology of parasites and viruses is affected by economic conditions. The complex interactions between economic and health crises, genetic features, parasitic infections, and aggressive and exploratory behavior may have influenced the evolution of *Homo sapiens*.

In the past, *Toxoplasma* infection was found to be associated with schizophrenia⁷⁴; this apparent conflicting result might be due to changes in new DSM criteria,⁷⁵ in which the diagnosis of schizophrenia has become much more restrictive. It is also possible that manifestations of brain infection may change over time with the evolution from a first phase of stimulation due to thymosin beta-4 (and the increase in aggression/exploration) to the later formation of even extensive areas of sclerosis with calcium deposition. In fact, the co-occurrence of schizophrenia and *T. gondii* infection is characterized by symptomatic specificities such as severe cognitive impairment⁷⁶ and predominance of negative symptoms,⁷⁷ which are associated with brain damage. This interpretation agrees with the cited studies, which found a change over time in the modifications induced by the *Toxoplasma* infection, which evolved from exploration and a hyperactive attitude to suspiciousness and negative symptoms.⁶⁹

Likewise, it is plausible that people with a strong aptitude for exploration and less sensitivity to fear and less inhibition were more exposed to being infected; understandably, the speculations and hypotheses may also have to evaluate the possibility that the association results from reverse causality. An example of social change and illness (from cardiology) is the Roseto study.⁷⁸ Italian immigrants in Roseto, Pennsylvania had much lower rates of heart disease than their neighbors. This was at first attributed to dietary and other differences, as immigrants' dietary and other habits were thought to predict heart disease. The next generation had more “Americanized” social structure and behaviors. Their rate of heart disease matched their neighbors.⁷⁸

Nevertheless, the role of toxoplasmosis in bipolar disorder can be useful as a pathophysiological model showing the complexity of factors that can interact with

the social and genetic aspects, since it is suggestive of the ambivalence of exploratory behaviors, which, on the one hand, expose to risks and on the other, turn out to be adaptive and successful. For example, the important relationship between bipolar disorder and creativity should also be considered.⁷⁹

The new perspective that we propose can open new horizons for understanding psychopathology thanks to a sociobiological reading of the interactions between environment and behavior in the genesis of mood disorders, and it may guide future research.

The research available today does not provide solid pieces of evidence, but, rather substantial clues about a sociobiological genesis of bipolar disorders. In fact, the studies carried out by our group were conducted on small samples and with limited resources, even if they had the merit of photographing very particular and difficult-to-repeat circumstances of transformation, such as those that happened on the Dogon plateau in Mali or the villages of Malawi in the 1980s.

The models extrapolated from ethological studies only have a heuristic value, as they cannot be applied "uncritically" to human studies. We are far from having certainties, and there are also obscure points about gene-environment interaction models.

However, the hypothesis that bipolar disorder may result from the interaction between genetic characteristics (not necessarily pathological in itself) and specific environmental circumstances is undoubtedly more credible and more tenable than that which considers bipolar disorder as the product of an aberrant genetic profile. Even if unproven and, in some respects, absurd, given the supposed increase of the prevalence of the disorder (mainly depression) in our society or at least its stable persistence, the second interpretation was able to strongly influence the stigma towards the disorder and some distorted ways of conceiving therapy. In opposition, according to the new approach, the adaptive potential would be a central point in the psychosocial treatment in addition to pharmacological therapy.⁸⁰ This interpretation could also lead to a decrease in discrimination and stigma towards people suffering from the disorder. Future research is needed to confirm the results of our studies and add new elements that can contribute to the formulation of a new convincing synthesis and model.

Disclosure

The authors report no conflicts of interest.

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