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REVIEW

Functional Alterations in Patients with Bipolar Disorder and Their Unaffected First-Degree Relatives: Insight from Genetic, Epidemiological, and Neuroimaging Data

Haonan Zhang[1], Jun Chen[1,2], Yiru Fang[1–4]

[1]Clinical Research Center, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [2]Shanghai Key Laboratory of Psychotic Disorders, Shanghai, People's Republic of China; [3]Department of Psychiatry & Affective Disorders Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [4]CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai, People's Republic of China

Correspondence: Jun Chen, Clinical Research Center, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, No. 600 Wanping South Road, Xuhui District, Shanghai, 200030, People's Republic of China, Email doctorcj2010@gmail.com; Yiru Fang, Department of Psychiatry & Affective Disorders Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, No. 197 Ruijin 2nd Road, Huangpu District, Shanghai, 200025, People's Republic of China, Email Yirufang@aliyun.com

Abstract: Bipolar disorder (BD) profoundly affects cognitive and psychosocial functioning, leading to a significant illness burden on patients and their families. Genetic factors are predominant in the onset of bipolar disorder and functional impairments. This disorder exhibits a strong family aggregation, with heritability estimates reaching up to 80%. Individuals with BD often experience impaired functioning, especially in significant areas such as physical performance, sleep, cognition, interpersonal interactions, socioeconomic status, family and marital relationships, work and school performance, well-being, and life expectancy. However, patients with different subtypes exhibit significant heterogeneity in social functioning, cognition, and creativity levels. There are notable differences in psychosocial and cognitive function in their unaffected first-degree relatives (UFR) who do not suffer but may carry susceptibility genes compared to healthy control (HC) without a family history. The observations indicate common genetic structures between BD patients and their UFR, which results in varying degrees of functional abnormalities. Therefore, this article mainly provides evidence on cognition, creativity, and psychosocial functioning in patients with BD and their UFR to provide a more comprehensive understanding of this critical topic in the field of BD. By integrating various findings, including clinical data and neuroimaging studies, our article aims to provide insights and valuable information for a deeper exploration of the pathogenesis of BD and the development of more targeted therapeutic strategies in the future.

Keywords: bipolar disorder, cognition, psychosocial function, creativity, unaffected first-degree relatives, genetics

Introduction

BD is a group of chronic mental illnesses marked by recurrent episodes of mania and depression, which alternate as the primary clinical symptoms. It exhibits a high prevalence, frequent relapses, and elevated rates of suicide, which has become one of the major mental health issues globally threatening human physical and mental well-being.[1] Statistically speaking, there are approximately 39.5 million patients with BD worldwide.[2] The lifetime prevalence (12-month prevalence) in the population is about 2.4% (0.6–1.5%), with BD-I type prevalence at approximately 0.6% (0.4%) and BD-II type at around 0.4% (0.3%).[3,4] The systematic analysis from the Global Burden of Disease Study 2019 revealed that the age-standardized prevalence rate indicates an average of 489.8 BD patients per 100,000 people and it is one of the top 30 causes of years lived with disability (YLDs) globally and the fifth leading cause of disability-adjusted life years (DALYs) in mental and substance use disorders.[2]

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Function and Disability in Bipolar Disorder

Currently, Various updated guides emphasize the importance of functional recovery, and many patients consider the restoration of normal psychosocial functioning as an essential indicator of remission. The human function is a general concept of which various organizations or scholars provide different definitions. The International Classification of Functioning, Disability, and Health (ICF) summarizes it in the following 3 points: Body structure and function, activity participation, and personal environmental factors,[5] of which are judged by assessing whether the person's eligibility to perform a specific task. It primarily refers to the ability to work, learn, live independently, participate in recreational activities, and maintain interpersonal relationships. Disability usually means an individual is experiencing one or more difficulties or challenges in functioning across various aspects of life.[6]

However, Studies on what contributes to functional alteration in patients with BD have reached mixed conclusions. Patients with BD often suffer damage in function, particularly evident in the following essential aspects: physical fitness, sleeping, cognition, interpersonal interactions, socio-economic status, family and marital relationships, work and academic performance, well-being, and life expectancy.[4] Up to 50% of patients have residual depressive symptoms in the interictal phase, and even euthymic patients and those with subsyndromes also have cognitive deficits. In these populations, the activity of the Dorsolateral Prefrontal Cortex (DLPFC), which plays an important role in advanced cognitive functions, and the Ventrolateral Prefrontal Cortex (VLPFC), which is closely related to activities such as language and emotion regulation, were found to be reduced during the Stroop task.[7] Residual symptoms compromise functional recovery and serve as a major contributor to relapse.[8] Besides, the diencephalic function of patients with long courses will likely be affected to varying degrees, leading to an increased risk of dementia.[9] Furthermore, there is a high rate of misdiagnosis at the first clinic visit for BD. The average duration of misdiagnosis correction is 6.46 years, even up to 10 years.[10] Age at onset is negatively correlated with a delay in treatment.[11] At least 1/5 of major depressive disorder (MDD) patients in China may not be appropriately diagnosed with BD,[12] the same indicator shown to be from 3.3% to 21.6% globally.[13] Admittedly, the earlier diagnosis and intervention are given, the fewer functional problems arise.

It is worth noting that cognition is heterogeneous in patients with BD, more prominent in BD-I. A subset of patients showed cognitive performance similar to that of unaffected individuals, and even exceeded the functioning of unaffected individuals in some domains.[14] Patients with a first episode of BD-I could be divided into three cognitive subgroups using latent class analysis of processing speed, verbal memory, nonverbal memory, executive function, attention, and working memory scores. Further use of neuroimaging scans to compare IQ, intracranial volume, whole brain volume, and regional volume before and after the onset of subgroups and HC revealed apparent differences between subgroups in whole gray matter and white matter volume.[15] Such cognitive difference might be associated with altered pathophysiological structures resulting from an abnormal neurodevelopmental process before the first episode.

Genetic Factors and Familial Aggregation

BD is a polygenic inherited psychiatric disorder with up to 80% heritability. The age of onset, frequency of attacks, and type of symptom demonstrate a highly heritable and familial pattern.[16] Unfortunately, family members of patients have a 9-fold risk of developing BD and an approximately 2.5-fold risk of other affective disorders than HC.[17] The offspring of parents diagnosed with BD have a notably higher risk of major psychiatric disorders.[18,19] 72% of BD offspring matched DSM-IV criteria for Axis I diagnosed disease, 54% had mood disorders, 13% were diagnosed with BD, and 3% were diagnosed BD-I.[20] They have an increased risk of attention deficit hyperactivity disorder[21] and abnormal levels of immune-related factors such as BDNF, IGF-BP2, IL-7.[22]

In the field of molecular genetics, a genome-wide association study (GWAS) involving over 50,000 patients and healthy controls has identified 30 genetic loci associated with BD. These include genes like voltage-gated calcium channel (CACNA1C), neurotransmitter receptor (GRIN2A), synaptic component (ANK3), and several other candidate genes.[23] Subsequently, A GWAS study of 6472 Han Chinese patients discovered novel risk loci, including VRK1 and RHEBL2, suggesting genetic heterogeneity between different racial groups.[24]

In conclusion, Genetics play a considerable role in the development of BD and high incidence in offspring, demonstrating irrefutable evidence of familial aggregation. Childhood trauma and family functioning also contribute to

it.[25,26] However, it's still unclear how susceptibility genes lead to neural pathways or processes to generate clinical symptoms. And that is why clinical research tends to favor investigating patients, UFR, and HC to showcase the wonders of genetics in the occurrence and progress of BD.

Summary

As previously mentioned, genetic effects are seen in functioning differences among patients, UFR, and HC. While those UFR themselves have not experienced episodes of mania or depression, they may be affected to some extent in areas such as cognition and social functioning due to the potential presence of susceptibility genes. Therefore, it is imperative to consolidate research evidence spanning various domains of functional performance in individuals with BD and their UFR and discuss the mechanics behind it.

Cognition

Cognition and Related Neuroimaging Performance in BD Patients and UFR

It is widely recognized that patients have varying degrees of neurocognitive impairment. This conclusion is well illustrated both using the traditional Screen for Cognitive Impairment in Psychiatry (SCIP) tool and the newly developed Internet-Based Cognitive Assessment Tool (ICAT) recommended by the International Society for Bipolar Disorders (ISBD).[27] Cognition is closely associated with daily psychosocial functioning, employment and quality of life, more directly, a meta-analysis even indicated that cognitive functioning had a greater impact on patients' working capacity than subclinical depressive and manic symptoms.[28] Verbal memory and executive function have been found to be moderately positively correlated with career development.[29,30] As mentioned earlier, cognitive functions are heterogeneous among patients.[16] Some researchers collected data about cognition and structural magnetic resonance imaging (sMRI) of 80 patients with the first episode of BD-I and calculated brain-predicted age difference (brainPAD) via machine learning.[31] They found markedly lower global cognitive scores and prominent verbal memory deficits in the low-brainPAD group. That suggested that early cognitive dysfunction in BD-I was associated with a marked delay in age-related brain changes, and verbal memory was probably a core defect in BD-I. Meanwhile, cognitive differences were probably associated with various subtypes of BD. Patients with psychotic history and diagnosed with BD-I were more closely related to global cognitive impairment, including noticeably worse verbal memory, processing speed, executive function, social cognition, and working memory. Unfortunately, this difference has not been widely confirmed in oceans of studies, probably due to a mixture of varying symptom severity among the patients.[32] What's more, factors such as years of education, the number of hospitalizations, age, antipsychotic drugs, and childhood trauma have been also proven to affect cognition.[14] A resting-state magnetic resonance imaging study observing the striatum in patients and HC explored mechanisms for different levels of cognition. BD-I patients may have lenient brain effects, which allows for increased "compensatory" functional connectivity and higher choline concentrations required in the striatum to preserve cognitive function.[33]

Research on the neurocognition of BD patients and their UFR demonstrate that the verbal intelligence quotient (IQ) of UFR drops apparently.[34] And the verbal memory[35] and facial expression recognition of those with global cognitive disorders are impaired, however, other non-emotional cognition is not impaired.[36] Furthermore, UFR, compared to HC, exhibit an increased corrected intracranial volume,[37] a larger regional cortical surface area mainly concentrating on speech-related auditory areas in the temporal lobe,[38] bigger volume of the inferior frontal gyrus and decreased cerebellar volume;[39] Compared to patients, there is no significant enlargement of the intracranial volume of relatives, which suggests genetics effects may result in different intracranial volumes.[37] The association between familial predisposition to increased intracranial volume and IQ in BD's relatives is unclear.

Admittedly, the amygdala and hippocampus are both involved in memory and learning. The right amygdala in BD-unstricken offspring exhibited significantly greater volume compared to BD-stricken offspring and HC. The amygdala may serve as a potential marker of susceptibility to BD.[40] Patients have a smaller hippocampal volume with greater variability in volume compared to UFR.[41] From the perspective of disease progression, late-stage patients has a reduction in hippocampal volume, and there was no significant difference in the early and middle stages compared to the HC.

Middle-and-late patients have poorer immediate recall than early-stage patients and HC.[42] The left para-hippocampal volume of BD relatives was larger than corresponding patients,[43] and unaffected offspring also enlarging apparently in left para-hippocampus/hippocampal gray matter volume compared to age-matching HC.[44]

The Hypothesis of Neurodevelopmental Defects

There is wide-ranging controversy about the potential mechanisms contributing to the cognitive heterogeneity in BD. Studies of cognitive deficits in schizophrenia (SCZ) align with the neurodevelopmental etiological model and suggest cognitive deficits in patients with SCZ may emerge as early as childhood development, earlier than the onset of symptoms.[45] Therefore, the researchers hypothesize whether the cognitive development of BD also applies to the above modal.

Some viewpoints argue that the more prominent neurodevelopmental problems in childhood, the higher the likelihood of developing BD with psychotic symptoms and the closer the alignment with the neurobiological characteristics of SCZ.[46] Indeed, the offspring with psychopathology arising in early adulthood have been found to have worse cognitive outcomes in adulthood than the ones with psychopathology in late adulthood and healthy offspring. A cohort study of male conscripts recruited healthy male conscripts (average age of 19.9 years) and discovered impaired visual-spatial reasoning before the onset of BD, SCZ, and other psychiatric disorders and that the dose-response relationship is very clear.[47] And most remarkably, the earlier the age of onset, the greater the impact on cognitive outcomes,[48] which seems to validate this hypothesis.

Surprisingly, if comparing BD patients alone in the above study, researchers found the lower scores in arithmetic reasoning before onset did not necessarily indicate an increased risk of BD. This finding appears to contradict the previous understanding. Furthermore, other large-sample observational studies have discovered no deficits in patients' cognition of early development. The result refutes the above theory. A cohort study with longitudinal follow-up recruited a total of 10,717 adolescent boys and young adult males in Sweden, where all subjects underwent cognitive tests at the age of 13 and were followed to observe the development of psychosis in adulthood. Although patient groups of SCZ and other non-affective psychosis all showed a certain degree of decline in cognitive function during early development, the results of BD demonstrated patients outperformed HC on all tasks at every time point before onset. Language decline at age 13 could be a valid diagnostic predictor.[49] It is worth noting that another large sample cohort in Sweden (n=1,017,691) observed a U-shaped association between BD and social maturity (low extraversion and high neuroticism have been identified as characteristics of BD, with social maturity reflecting extraversion and responsibility).[50] In response, Parellada proposed a linear risk trend for cognitive impairment in the SCZ but U-shaped risk trends in BD, more reasonably explaining the phenomenon of cognitive heterogeneity after compiling the articles about cognitive function and early developmental milestone data in SCZ and BD before onset. People at risk who are significantly higher or lower than the average cognitive function of their peers are more likely to develop BD eventually.[51]

Creativity

Creativity is the mental process of adopting new methods or approaches to solve problems and create entirely new value objects. As a complex and multidimensional brain function, creativity has cognitive and emotional components, which belongs to the most common process of human thinking and cognitive activity, with a certain degree of heritability. Since Aristotle proposed the viewpoint that "No Great Genius Has Ever Existed Without a Strain of Madness", creative geniuses have often been associated with BD. Initially, evidence for this association was presented mainly in biographies and case studies of extremely creative individuals and in group studies of artists and composers.[52] Subsequently, academic research on creativity and mental illness demonstrates a correlation between BD and creativity, professional achievement in specific fields such as humanities, arts, scientific research, and organizational leadership.

Writers and poets are more likely to suffer from mental illness than the HC, particularly mood disorders, and show a predisposition towards BD.[53] The long-term emotional changes of famous writers such as Yu Dafu, Goethe, and Hemingway are closely related to their literary creativity.[54,55] So a hypothesis was raised- "highly creative groups are at higher risk of developing BD" - and there is solid evidence to support it. BD is more prevalent in high-achieving

language arts students.[56,57] First- and second-degree relatives of university academics (defined as a highly creative population) were also discovered to have a higher risk of BD than the HC in a large-sample registry study.[58]

Surprisingly, Patients with BD and their UFR have increased creativity compared to the HC, which was confirmed in 29,644 individuals with major mental disorders. Both patients and their UFR wereS far more likely to be in creative occupations than the HC, and as the blood relationship with the patient diminishes, they are gradually less likely to engage in creative occupations.[59] Remarkably, the proportion of creative occupations did not increase in the MDD group. Another large (N = 4,454,763) case-control study of BD, SCZ, and MDD and siblings showed an association with artistic creativity only in families with BD, but not in SCZ and MDD.[60] What's more, BD high-risk offspring also have higher Barron-Welsh Art Scale (BWAS) scores than the HC.[61] BD and creative HC scored significantly higher on the BWAS-Total than MDD.[62] A small-sample pilot study of MDD also concluded that patients with the risk of mania scored higher on BWAS than those without bipolar risk.[63] Furthermore, patients in hypomania or stable asymptomatic phase scored higher than depressed states.[64]

In addition, some progress has been made in the genetics of BD and creativity. Some research investigated the relationship between music activity participation and mental health through polygenic scores and found that the higher the genetic risk of BD, the more participation.[65] The GWAS study of creativity also supports a shared genetic basis between psychiatric disorders and creativity.[66] Of course, despite the achievements of many BD patients, the majority of patients suffer from cognitive impairment and severe disability, leading to decreased psychosocial function and increased economic costs. This phenomenon is probably related to the spectrum of BD's inverted-U model.[52]

Work and Educational Performance

Educational achievement and occupational difficulties among patients and UFR have received attention in recent years. Meta-analysis has shown that people with BD have impaired work ability, higher unemployment rates, divorce and widowhood, low participation in social activities, and weak family relationships.[5] BD-I patients have worse psychosocial function than HC[67] and apparent deficits in social perception and emotional perception related to social cognitive impairment.[68]

Patients with SCZ and MDD and their UFR and BD patients show poor academic performance at different stages of education, with SCZ patients showing the earliest decline. It's consistent with the neurodevelopmental hypothesis in SCZ. And it's worth noting that UFR with BD were not worse off in academic achievement at all educational stages than the HC overall, supporting the conclusion of cognitive heterogeneity.[69] Consistently, data on the performance of 16-year-old students and their prevalence in adulthood in Sweden demonstrate that high-achieving students have a nearly fourfold increased risk of BD in adulthood and that the worst-achieving students also moderately increased their risk.[56]

50% of patients report problems with employment and work, including difficulty keeping a job, reduced productivity, greater absenteeism, and unsatisfactory earnings.[30,70] They have three times the unemployment rate than HC and lose twice as much productivity as those with MDD.[71] The relationship between subthreshold symptoms and cognition on work performance and disability deserves further investigation. Even euthymic patients have a long period of impaired function and unsatisfactory quality of life.[72] However, the influential pathways between residual symptoms, cognition, and work performance are not entirely clear. In addition, UFR show the same relatively poor socio-economic status as the patient.[73] But it remains to be explored whether the UFR's working competence itself has declined - after all, their economic status is greatly influenced by the caring burden.

Social Functioning

People with BD appear to have more pronounced deficits in social functioning, including poorer interpersonal relationships, diminished interests and recreation, and less general satisfaction. It seems that BD patients are more isolated and communicate less with their neighbors than HC.[6] Furthermore, intimate partners of patients are slightly more introverted, with narrower social circles and compromised psychosocial functioning compared to HC.[74]

A Danish Demographic Registry study assessed familial load (FL) in a large sample of first-degree relatives of BD patients and found that impaired social functioning may not be attributable to familial aggregation. Neither the patients

nor their UFR experienced higher levels of functional deficits in the context of a higher burden of psychopathology. Further exploration into the causes of impaired social functioning may be worthwhile.[73,75,76]

BD and their UFR are often affected by varying degrees of social stress due to social interaction and financial factors. It exacerbates the emotional symptoms and further results in a heavy burden.[77] The rate of disability service utilization among patients with MDD and BD is 2.03 times higher than that of HC, with the same rate among BD patients approximately 2.37 times higher than that of MDD patients. Cognitive deficits are an important cause of social function decline and occupational disorders.[78] Therefore, improving the cognitive and social function of patients with BD is also a carefully considered aspect by clinicians.

Family Functioning

For the patient and UFR, the damaged family function reflects more in the burden of caregiving and emotional stress. Health insurance claims data show that patients have a heavy financial burden due to illness. In 2015, the total cost of medical care for BD-I in the United States was estimated at $202.1 billion ($81,559 per capita), and the total excess cost (the difference in medical costs between those diagnosed with BD-I and those without) was estimated at $119.8 billion, equivalent to $48,333 per capita.[79] Another study showed that the All-cause total health care for patients diagnosed with BD-I alone and no other mental disorders was $26,396, compared to $51,085 for people diagnosed with SCZ and BD-I.[80] Annual Medicare payments for BD-I are much higher than for many other mental illnesses. The out-of-pocket cost per capita was estimated at $568 in 2003, twice as high as other mental illnesses.[81] The latest longitudinal cohort study suggested that BD patients' average annual direct medical costs have risen by €6910. However, the costs could be dropped by more than 50% based on two-year follow-up observations for the subgroup with skilled nursing treatment.[82] Notably, in addition to the cost of treatment, impaired academic performance, unemployment, loss of productivity, and reduced interpersonal interactions due to symptoms and cognitive impairment also impose incalculable financial costs on patients.[83]

Moreover, the burden faced by BD families cannot be ignored. More than 90% of families have reported it.[84] On the one hand, it is reflected in families with children and adolescents. The marital survival for parents of pediatric patients is associated with family stress, and the speculation is that it may cause conflicts about children's management. Families with young people with BD are worse at problem-solving and communication.[85] Such families show more quarrels, parent relationship tension, negative emotional expression, lower intimacy, cohesion, intellectual-cultural orientation, and active entertainment behaviors.[86,87] The functional impairment of the family mentioned above is affected by the age of the offspring and is mainly mediated by the psychosocial functioning of the parents.[88] But it has to be said it's acknowledged that better family function and parenting skills for children with BD can help improve treatment and function.[89] On the other hand, BD also significantly impacts the spouse of an adult with BD, including caregiving burdens, marriage, self-sacrifice, and personal development.[90,91]

Inverted-U Hypothesis

The broad spectrum of BD includes typical manic and depressive symptoms as well as cyclothymic and hypomanic. Based on the classification of affective states, they can be divided into hyperactive, depressive, irritable, and cyclothymic moods.[92] Studies have shown that UFR is more likely to be diagnosed with cyclothymic temperament (CT) than the general population. After examining emotional temperament and cognitive function in symptomatic offspring (SO) and without asymptomatic offspring (AO), it's found that the SO group has higher emotional temperament scores than the AO group and that those in the SO and AO groups who are CT have a higher cognitive function such as processing speed, verbal learning, and attention, than in the other emotional states. BD's cognitive functions and emotional temperament may share a common neurogenetic basis.[93] BD represents an overall continuous and dimensional phenotypic change in temperament, personality, and cognition of the population, and the studies about cognitive, creative and emotional temperament support the U-shaped distribution pattern. Greenwood argued that the U-shaped pathology hypothesis is a result of the cumulative effect of small effector genes.[52] Positive traits such as creativity and cognition may be enhanced with increased genetic risk. However, once the genetic risk for bipolar disorder reaches a critical threshold, these positive traits are attenuated as the genetic load continues to increase. This relationship shows a distribution similar to an inverted "U" curve, which can be seen in more detail in Figure 1.

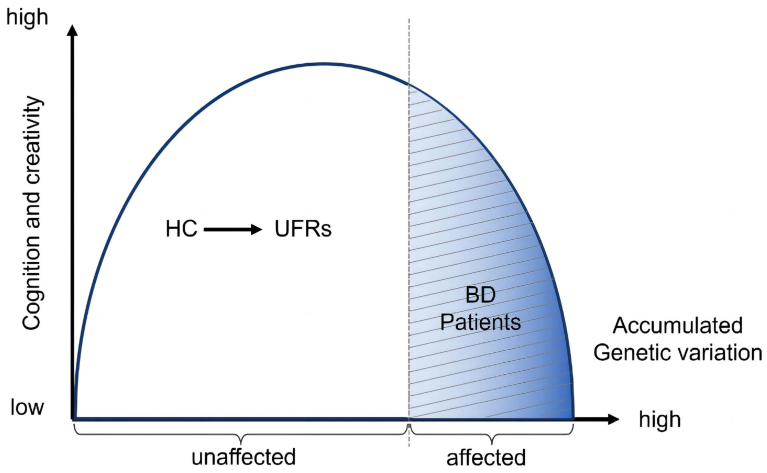

Figure 1 Inverted-U model of positive features such as cognition and creativity in BD patients.

Conclusions

Over the past decade, increasing attention has been focused on the functional performance of patients with BD as well as UFR. This is due to the high prevalence, misdiagnosis, delayed diagnosis, and progressive neurologic impairment experienced by patients, which has a critical impact on their work, school, and social interactions. One of the main goals of clinical treatment and scientific research is to achieve remission of clinical symptoms while focusing on restoring cognitive and psychosocial functioning. Of particular importance are those functions that are closely related to the patient's professional accomplishments, such as cognition, creativity, and IQ. Although some studies support the hypothesis of an inverted U-shaped relationship between positive traits such as cognition and creativity and genetic risk in patients with bipolar disorder, more large-scale cohort studies and meta-analyses are needed to validate this idea. Indeed, the heterogeneity of positive traits such as cognitive functioning and creativity in BD patients and UFR is triggered by a common set of genetic risk genes that lead to structural and functional changes in specific brain regions. In addition, the burden on the whole family increases due to high unemployment and poorer interpersonal relationships in patients, while UFR show a decline in economic status and well-being. However, to date, no large-scale longitudinal studies have been conducted to monitor the performance of BD patients and their UFR across the three dimensions of quality of life, symptoms, functioning, and cognition. The urgent task at hand is to determine the relationship between psychosocial functioning, cognition, and clinical variables, and to find clinical predictors and interventions that influence the prognosis of functioning in order to improve the level of functioning of patients, to help those severely afflicted by dysfunction to return to work, and to alleviate the burden on them, as well as on their families.

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Disclosure

The authors report no conflicts of interest in this work.

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