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Positive Traits in the Bipolar Spectrum: The Space between Madness and Genius

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Key Words
Bipolar disorder · Creativity · Temperament · Personality · Genetics · Polygenic · Psychosis

Abstract
Bipolar disorder is a severe, lifelong mood disorder for which little is currently understood of the genetic mechanisms underlying risk. By examining related dimensional phenotypes, we may further our understanding of the disorder. Creativity has a historical connection with the bipolar spectrum and is particularly enhanced among unaffected first-degree relatives and those with bipolar spectrum traits. This suggests that some aspects of the bipolar spectrum may confer advantages, while more severe expressions of symptoms negatively influence creative accomplishment. Creativity is a complex, multidimensional construct with both cognitive and affective components, many of which appear to reflect a shared genetic vulnerability with bipolar disorder. It is suggested that a subset of bipolar risk variants confer advantages as positive traits according to an inverted-U-shaped curve with clinically unaffected allele carriers benefitting from the positive traits and serving to maintain the risk alleles in the population. The association of risk genes with creativity in healthy individuals (e.g., NRG1), as well as an overall sharing of common genetic variation between bipolar patients and creative individuals, provides support for this model. Current findings are summarized from a multidisciplinary perspective to demonstrate the feasibility of research in this area to reveal the mechanisms underlying illness.

Introduction

Bipolar disorder is a severe mood disorder that is characterized by alternating states of major depression and mania. Mania is accompanied by pathological elevations in energy and mood, racing thoughts and speech, a decreased need for sleep, grandiosity, and risk taking; whereas depression is associated with low energy and motivation, insomnia, and feelings of extreme sadness, failure, worthlessness, and hopelessness [1]. Psychosis is a common feature of bipolar mood episodes, with up to 50% of patients experiencing psychotic symptoms, more often during acute mania than depression [1, 2]. Bipolar disorder is common, affecting approximately 1% of the population in its most severe form and up to 6% when considered as a spectrum [3, 4].

Since bipolar disorder is a lifelong illness for which lasting remissions are uncommon, understanding the pathophysiology and genetic architecture is of paramount importance to diagnosis and treatment. Bipolar disorder

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is strongly familial with an estimated heritability of 60–93% [5–8]. Yet, despite the clear contribution of genetics to the etiology of bipolar disorder, little of the genetic architecture is currently understood. Large genome-wide association studies have suggested a significant role for common variation in explaining at least 25% of the genetic variance in bipolar disorder, 68% of which is shared with schizophrenia as a general risk for psychosis [9]. While such studies have identified several strong candidates for susceptibility genes [10], the mechanisms by which risk variants lead to disease are complex and remain largely unknown.

Some of the difficulty in identifying bipolar risk genes may stem from the use of diagnostic systems that group patients into discrete categories, which may have some utility for clinical care but do not adequately reflect the dimensional nature of psychiatric illness. Some investigators have suggested that bipolar disorder exists at the extreme of normal population variation in temperament, personality, and cognition [11–15]. Moreover, it has long been observed that certain positive traits or enhanced abilities, such as creativity, exist within the bipolar spectrum and in unaffected relatives. This may suggest a model in which large doses of risk variants cause illness, but mild or moderate doses hold advantages for unaffected allele carriers. Investigating these positive traits may not only enhance our understanding of bipolar disorder as a dimensional clinical phenotype but, as quantitative traits that are presumably closer to the actual transmitted phenotype, they can also be expected to improve our power to identify risk genes and ultimately provide novel therapeutic targets.

Bipolar Disorder and Creativity: "Madness versus Genius"

Western cultural notions of "mad geniuses" and "artistic temperaments" date back to Aristotle's observation that "no great genius has ever existed without a strain of madness" [16], and a wealth of investigations into this area, both formal and anecdotal, have supported this notion [17]. Overall, these studies suggest a tenfold increase in the rate of bipolar disorder among artists as compared with the general population [1, 18]. The association between creativity and bipolar disorder is well documented in eminently creative individuals, with artists like Vincent van Gogh, authors like F. Scott Fitzgerald and Ernest Hemingway, poets like Walt Whitman and Sylvia Plath, and composers like Rachmaninoff and Tchaikovsky all reportedly having struggled under the burden of illness [19]. Numerous studies have consistently reported an overrepresentation of affective disorders and psychosis among successful people in creative professions, as well as exceptional creative potential in relatives of individuals with bipolar disorder [19–27]. Large studies of noneminent, or "everyday," creativity in patients and their relatives have produced comparable findings. Recent Swedish population-based studies have demonstrated an overrepresentation in creative occupations of bipolar patients and their healthy first-degree relatives, strongly supporting the familial association of bipolar disorder with creativity [28, 29]. Similarly, the Epidemiologic Catchment Area Study found a disproportionate concentration of individuals with bipolar disorder in creative occupations [30].

It must be noted that creativity is not a ubiquitous trait in bipolar disorder. In fact, a large study of psychiatric patients estimated that only 8% of those with a bipolar spectrum disorder could be considered highly creative [31]. Concerns have also been raised regarding potential biases across studies, as well as a lack of consistency in how both mood disorders and creativity are conceptualized [32]. For example, anecdotal studies of eminently creative individuals may suffer from incomplete biographical records and be skewed towards a sampling of individuals with more severe mood symptoms. Most studies also rely on creative occupation, which may serve as a poor proxy for creativity and introduce bias. Finally, it has been suggested that the overrepresentation of bipolar disorder observed in population-based studies of creativity may reflect a preference for the unconventional lifestyle provided by creative occupations, as many suffering with bipolar disorder have trouble maintaining stable employment. Indeed, the personality traits that seem to be most associated with choosing a creative occupation are openness and impulsivity [33], which are associated with bipolar disorder as discussed below [34–37]. However, a multitude of studies of both eminent and "everyday" creativity consistently suggest a relationship between creativity and risk for bipolar spectrum disorders that warrants further research.

Bipolar Disorder and Creativity: A Shared Vulnerability

While some studies have found increased creativity in those with bipolar disorder, comparable to that observed in creative individuals [38–40], others have indicated that

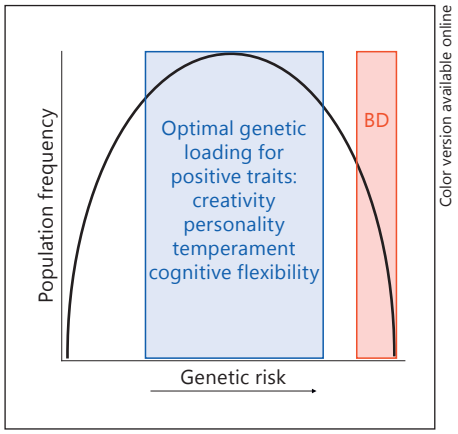

Fig. 1. Positive traits within the bipolar spectrum and a shared vulnerability. According to the inverted-U model, creativity and other positive traits would be expected to increase with genetic loading up to a threshold, beyond which they would start to diminish with the increasing impairment of illness [42, 48, 49]. Polygenic risk indicates genetic vulnerability due to common variation in aggregate, which is maintained in the population by clinically unaffected individuals, who benefit from the positive traits. BD, bipolar disorder.

professional success and creativity is significantly higher in their clinically unaffected first-degree relatives [28, 39, 41–43]. Similarly, creativity and eminence occur more often in individuals with affective temperaments, which may reflect the subclinical expression of bipolar disorder and the underlying genetic vulnerability [31, 42, 44–47]. These observations are consistent with the observed "inverted-U" relationship between creativity and psychopathology and a shared vulnerability, as shown in Figure 1 [42, 48, 49]. According to this model, creativity and other positive traits would increase with genetic risk for bipolar disorder up to a threshold, beyond which they would start to diminish with the increasing impairment of illness. Intriguingly, this model suggests that the phenotype being transmitted in the population is not bipolar disorder per se, but rather positive traits that modulate behavior in healthy individuals, with the disorder representing the extreme on a continuum of variation in these traits [11–15]. This model also suggests the influence of common variants distributed across the entire population, which is consistent both with the polygenic model of risk for bipolar disorder and with the observance of a stable worldwide prevalence rate [9]. Clinically unaffected individuals would thus serve as a genetic reservoir, maintaining bipolar risk alleles in the population and benefiting from the positive traits, with the disorder occurring only as an unfortunate side effect of extreme genetic loading. In short, as once observed by Paracelsus, "the dose makes the poison."

Positive Traits in the Space between Madness and Genius

Several temperament and personality traits are related to bipolar disorder, to creativity in individuals with bipolar disorder, and to creativity in healthy individuals, seemingly occupying the space between madness and genius. Both bipolar and creative individuals have higher cyclothymic, dysthymic, and irritable temperament scores compared with noncreative controls [36, 38, 50–52]. Hyperthymic temperament is further associated with creativity in healthy subjects, as are hypomanic personality traits, which predict risk for bipolar disorder [53–55]. Bipolar and creative individuals also have higher neuroticism, extraversion, and openness personality scores compared with noncreative controls [33, 36–38, 51, 52, 56–61]. Openness to experience is a central feature of creativity, with an estimated effect size of 0.71 [33, 62–66]. Openness is also heritable in bipolar families [67].

Although the exact nature of the relationship is unclear, intelligence and cognitive style are associated with aspects of creativity [68]. Creative people tend toward divergent thinking, the cognitive ability of associational network activation and creative ideation, and an overinclusive cognitive style, which involves remote associations and may facilitate originality [69]. The hallmark symptoms of mania include increased word production and loose associations, and, not surprisingly, manic bipolar patients exhibit conceptual overinclusiveness, similar to creative writers [70]. Such loose associations may result from a failure to filter irrelevant stimuli from the environment, a process known as *cognitive disinhibition* [49], which has been associated with both psychosis proneness [64] and creativity [71]. While intelligence, particularly executive function, may be associated with performance measures of creativity, like divergent thinking [72–74], this effect appears only moderate ($d = 0.31$) [64]. In fact, above-average intelligence (IQ >120) appears to be necessary but not sufficient for high creativity [75], and once this threshold is met, personality factors like openness are more predictive of creative potential [76]. Still, higher executive function has been shown to mediate increased creativity during mania [77]. The combination of high IQ and cognitive disinhibition may also predict creative achievement [49]. Finally, a positive mood appears to

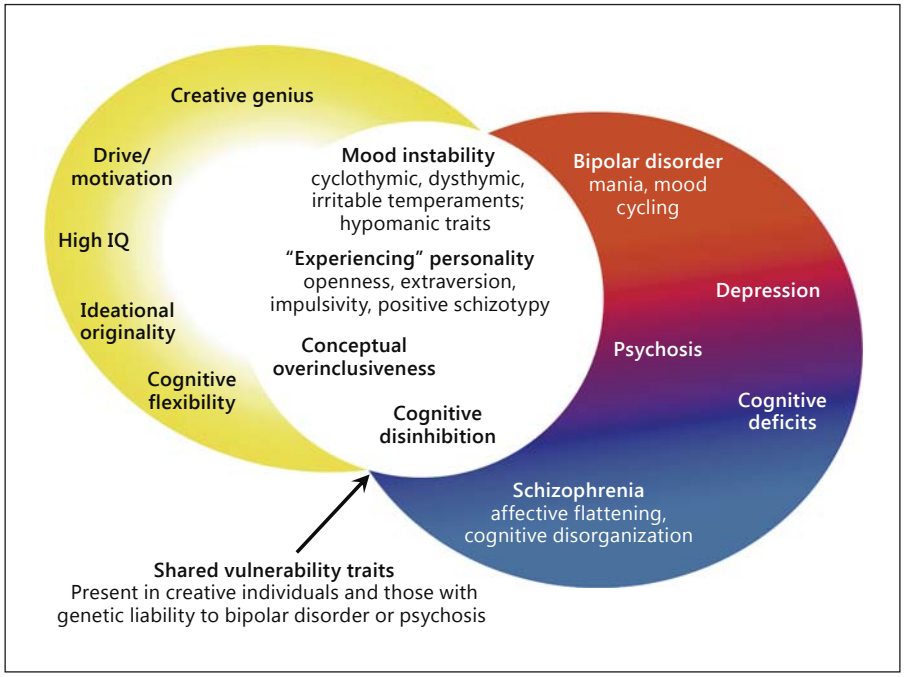

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Fig. 2. The space between madness and genius. Adaptation of Carson's model of the shared vulnerability between creative genius and psychopathology [49] summarizing the temperament, personality, and cognitive characteristics shared by creative individuals and those with genetic liability to bipolar disorder and/or psychosis. The clinical overlap between bipolar disorder and schizophrenia is also represented, as are the characteristics unique to each disorder.

provide a significant cognitive advantage in the performance of divergent thinking tasks, whereas a negative mood inhibits this process [78].

Recent studies have made significant progress in defining the relationship between bipolar disorder and creativity. In one study of bipolar families, a network analysis of the observed phenotypic correlations revealed clusters of traits related to affective temperament, impulsivity, risk taking, and psychosis proneness (a "bipolar spectrum" component) and to executive function, processing speed, working memory, and long-term memory (a cognitive component) [79]. Interestingly, perceptual creativity was found to span these clusters. Another study examining individuals with bipolar disorder and their healthy co-twins found increased sharing of positive traits related to temperament, schizotypy, impulsivity, and sensation seeking that were further correlated with increased verbal learning and fluency in the co-twins [80]. These studies highlight the need to examine multiple dimensions of personality, mood, and cognition to fully understand concepts relating to positive traits within the context of creativity and illness.

Creativity thus appears to result from the complex interaction of multiple personality, cognitive, and affective traits [69, 81, 82], which may reflect a shared vulnerability with bipolar disorder [49, 83, 84]. A summary of the components that likely occupy the space between madness and genius is presented in Figure 2. However, the mechanisms by which these traits mediate creativity are unknown, and it is unclear as to whether they explain the association of creativity with bipolar disorder.

Bipolar Disorder, Schizophrenia, and Their Common Connection to Creativity

Schizophrenia is a severe psychotic disorder that is characterized by abnormalities in a patient's thoughts, perceptions, speech, affect, and behaviors, manifesting as auditory hallucinations, paranoid or bizarre delusions, and/or disorganized speech and thoughts. While schizophrenia is often thought to mainly affect cognition, it also usually contributes to chronic problems with behavior and emotion. Bipolar disorder and schizophrenia have historically been regarded as separate disorders with distinctive underlying etiologies, yet data across many disciplines have increasingly advocated for a functional psychosis continuum spanning these diagnoses [85–90].

The considerable clinical overlap between bipolar disorder and schizophrenia often causes confusion and misdiagnosis [91]. For example, acutely manic bipolar patients exhibit cognitive deficits, such as thought disorder and conceptual disorganization, which are typical of schizophrenia [92]. To some extent, parallels can be drawn between the negative symptoms of schizophrenia (e.g., asociality, avolition) and depression in bipolar dis-

order and between the positive symptoms of schizophrenia (e.g., delusions, hallucinations) and mania. Epidemiological and genetic data are also consistent with a substantial overlap in susceptibility for bipolar disorder and schizophrenia [6, 9, 10, 93–106]. It has been estimated that 63% of the shared genetic vulnerability between these disorders derives from additive genetic effects [6], with 68% of the shared genetic variance deriving from common variation [9]. It is possible that a portion of this shared common genetic variance may be a reflection of the historical connection of both bipolar disorder and psychosis to creativity.

As with bipolar disorder, large population-based studies have reported an overrepresentation in creative occupations of the healthy first-degree relatives of schizophrenia patients, supporting the familial association of schizophrenia with creativity [28, 29]. Some groups have also reported increased creativity in schizophrenia patients compared with normal controls [107, 108], as well as increased creativity in the adopted children of parents with schizophrenia [109, 110]. However, much research on creativity has focused on aspects of schizotypy, which is thought to reflect the subclinical expression of schizophrenia [111, 112], as well as the underlying genetic vulnerability [113]. Many studies have demonstrated strong associations between schizotypal personality traits and enhanced performance on tests of creativity and fluency, as well as elevated levels of schizotypy in individuals active in the creative arts [48, 55, 84, 114–124]. Interestingly, this association between creativity and schizotypal traits is also observed in bipolar patients, who score higher than controls on several measures of schizotypy [116, 125, 126]. Several of the personality traits discussed above with relationships to creativity, namely, neuroticism, openness, and cyclothymic temperament, are correlated with positive schizotypal traits [127–129]. Openness also demonstrated high sibling correlations in a study of multigenerational SZ families, as well as high heritability [130].

These data, like those for bipolar disorder, suggest that some aspects of the schizophrenia spectrum provide advantages in terms of creativity, many of which are summarized in Figure 2. Other personality factors, such as increased sociability, strong ambition, and a desire for recognition by others, characterize those who excel because of their creative talent and are features observed in bipolar patients and their relatives, which may partially explain the tighter link of bipolar disorder to creativity compared with schizophrenia [33, 83, 118, 131]. Additionally, the deficits in executive function in schizophrenia patients [132, 133], which are primarily associated with negative symptoms, may explain the relatively poor performance of schizophrenia patients for measures of creativity involving fluency and cognitive flexibility [134–136]. If creativity and psychosis result from a shared vulnerability, cognitive protective factors, such as high IQ and cognitive flexibility, may lead to enhanced creativity, whereas the cognitive deficits often present in full-blown illness may prevent the individual from fully realizing their creative potential [49, 115].

Many have also argued that bipolar disorder and schizophrenia are associated with different types of creativity, such as "artistic" versus "scientific," which may be mediated by varying aspects of temperament, personality, and cognitive style [19, 118, 137–140]. In support of this concept, some groups have demonstrated an association of positive schizotypal traits with artistic domains and negative schizotypal traits with math and science [116, 141]. Verbal divergent thinking is linked to creativity in writers and scientists and is correlated with a higher IQ than figural divergent thinking, which is more closely related to creativity in artists and musicians [75].

Bipolar Disorder and Evolution

Bipolar disorder exhibits substantial fitness costs in terms of increased mortality and significant impairment, yet it has persisted in the population with a high heritability and a stable prevalence [142]. This appears contrary to evolution theory, in which genetic variants associated with a loss of fitness are presumably pruned from the gene pool through the process of natural selection [143, 144]. Some have suggested that psychiatric illnesses result from polygenic mutation-selection balance, whereby genetic variants that reduce fitness are introduced through mutation and pruned from the gene pool at a rate proportional to their adverse effects on fitness [143–147]. While the mutation rate is low, the overall target size is large, involving many genes and regulatory regions. This model fits well with the apparent impact of rare structural and de novo variants on schizophrenia susceptibility [146–152], the reported effects of paternal age [153], and with the severe fertility disadvantages that have been observed in schizophrenia [154–156]. While structural variants do not appear to contribute significantly to risk for bipolar disorder, rare variants may play a role [157–160].

Other evolutionary models relating to balancing selection and fitness trade-offs have been widely debated. For example, it has been suggested that traits associated with

bipolar disorder and psychosis may provide fitness advantages in terms of sexual selection, mating success, or social skills, particularly in certain niches [144, 161–166]. Some have suggested that affective temperaments provide favorable evolutionary properties that serve to maintain bipolar risk alleles in the population [45, 46, 167]. Others have suggested that the observed association between schizotypal traits and creativity may partially explain the persistence of psychosis risk variants in the population [117, 141, 166, 168–171]. Consistent with these notions, studies have shown at least moderate evidence for reduced fecundity in individuals with bipolar disorder and increased fecundity in their unaffected siblings, who presumably carry a reduced burden of risk variants and may express these traits in a milder, more advantageous form [142, 155, 156]. Antagonistic pleiotropy provides an attractive evolutionary model in this context, wherein alleles associated with an increased fitness for one trait also decrease fitness for another [143, 144, 172]. As many alleles are likely involved, the fitness consequences of each allele would be closer to neutral. This would allow risk alleles to randomly drift to higher frequencies through neutral drift-mutation and become common in the population. As it is likely that no single trait in its extreme leads to bipolar disorder, a highly heterogeneous clinical phenotype, it is also likely that no single evolutionary model can fully explain the persistence of bipolar disorder in the population. This topic awaits a better understanding of the interacting phenotypes and the underlying genetic mechanisms involved in both illness and creativity.

Molecular Pathways and Genetic Links

There is strong evidence to suggest a role for the dopaminergic system in bipolar disorder and psychosis [173–175], as well as in creativity [42, 123, 176]. Mania and psychosis both partially reflect a hyperdopaminergic state [177, 178], whereas depression and cognitive deficits in bipolar disorder may relate to dopamine deficiencies [178, 179]. Acute amphetamine intoxication closely resembles mania, and chronic administration can provoke a manic episode in those with bipolar disorder and trigger psychosis in healthy individuals [180]. The dopamine transporter (DAT) plays a critical role in the regulation of dopamine availability and is the site of action of amphetamine, which increases synaptic dopamine by inhibiting reuptake [181]. Excess dopamine has also been reported to decrease inhibition of stimuli from the surrounding environment [182, 183], which is characteristic of both creativity [71] and psychosis [184–186]. Interestingly, the DAT gene (*SLC6A3*) has shown evidence of association and linkage with bipolar disorder [187–189], schizophrenia [190], neurocognitive deficits in schizophrenia [191], and, of particular relevance, sensorimotor gating deficits in schizophrenia [192, 193]. Furthermore, decreased thalamic D2 receptor densities are observed both in patients with psychosis [194–196] and in healthy subjects with high divergent thinking scores [197, 198]. The presynaptic D2 receptor is part of the inhibitory response to curb excessive dopamine release, similar to the function of DAT, and is the primary target of all antipsychotics [199]. Finally, the variants of the D2 receptor gene (*DRD2*) have been shown to be associated with both verbal creativity [197] and sensory motor gating deficits [200] in healthy individuals. These observations collectively suggest that higher dopamine availability may lower gating thresholds and increase creativity in the absence of psychosis.

Several validated psychosis risk genes have been investigated as part of small candidate gene studies for association with creativity in healthy individuals and have shown marks of positive selection in humans (e.g., *NRG1, SLC6A4*) [201–203]. *NRG1* in particular provides an intriguing candidate for a shared vulnerability, with a functional promoter variant [204] that is associated with both an increased risk of psychosis [205, 206] and increased creativity in healthy subjects [201]. Interestingly, an unusually high percentage of genes involved in the phosphatidylinositol 3-kinase (PI3K) pathway appear to have been subject to selective sweeps [207], and a dysregulated activation of this pathway, mediated in part through the effects of *NRG1*, has been implicated in psychosis risk [208]. Both lithium and valproate, common treatments for bipolar disorder, are also thought to act, in part, through activation of PI3K [209–211]. While these findings remain to be confirmed in larger samples, they may provide clues as to the underlying mechanisms.

Perhaps the most convincing genetic evidence in support of a shared vulnerability between creativity and bipolar disorder/psychosis comes from a study conducted by Power et al. [212] of over 86,000 healthy subjects from an Icelandic cohort with a replication sample of more than 27,000 from Sweden and the Netherlands, all of who were genotyped. Approximately 1% of each sample was considered creative, as defined by membership in an artistic society or by creative profession. Using data from recent genome-wide association studies of bipolar disorder and schizophrenia, polygenic risk scores were calculated as the sum of associated alleles weighted by their effect sizes. Power's group found that higher genetic risk

for bipolar disorder and schizophrenia, measured as a polygenic risk score, was significantly associated with creativity, indicating shared genetic vulnerability. However, the primary limitation of this study, like many previous studies, is the use of creative occupation as the phenotype, rather than a direct measurement of creative ability. Large genomic studies evaluating the shared vulnerability model of bipolar disorder/psychosis and creativity utilizing more refined measurements of creative ability remain a topic of future investigations.

Brain Imaging Studies of Creativity

Creativity is difficult to directly measure in terms of brain activity. Some studies have instead evaluated fluid intelligence, the ability to think logically and solve problems in novel situations, which is independent of acquired knowledge (crystalized intelligence) and is a component of general intelligence (*g*) [213]. Fluid intelligence is moderately correlated with the novel, original idea generation processes encompassed by divergent thinking [54, 214, 215]. Results suggest that this reasoning ability is associated with activation of a network of frontal and parietal brain regions, specifically the dorsolateral prefrontal cortex (DLPFC), the superior parietal lobule, intraparietal cortices, and left temporoparietal regions [216–218].

Recent studies have attempted to directly evaluate brain activation during divergent thinking in artists. One study compared fMRI scans of rappers during freestyle (i.e., improvisation), which is analogous to divergent thinking, with those during the recitation of memorized lyrics [219]. A previous study by the same group had examined jazz musicians (pianists) using a similar paradigm of improvisation versus the performance of a standardized piece of written music [220]. Interestingly, both sets of artists showed decreased activity in the DLPFC during improvisation and increased activity in the medial prefrontal cortex. These studies suggested that a relaxation of executive functions and de-focused attention, allowing for uncensored processes and free associations to occur, may be the hallmark of creative cognition. Further evidence is provided by findings of inverse relationships between divergent thinking ability and both cortical thickness and white matter integrity in frontal lobe regions [221, 222]. Another study comparing musicians with matched controls using near-infrared spectroscopy observed enhanced divergent thinking in the musicians supported by increased bilateral frontal cortical activity [223]. In addition to enhanced creativity, this study also observed increased verbal ability and schizotypal personality in the musicians compared with the nonmusicians. In general, structural imaging studies have revealed positive correlations between both creative achievement and divergent thinking and the right DLPFC, right posterior cingulate, right parietal lobe, bilateral caudate, and right midbrain regions and inverse correlations with the left lateral orbitofrontal gyrus, lingual gyrus, inferior parietal gyrus, and fusiform gyrus [222, 224–226]. This complex pattern that spans lobes and hemispheres likely reflects the inherent complexity of human creativity [227]. Whether the pattern of activation in bipolar individuals engaged in creative cognition resembles that of healthy creative individuals remains to be shown.

Optimizing Study Design

Although there have been many attempts to evaluate the nature of the relationship of creativity to bipolar disorder and psychosis, very few have administered a comprehensive battery in a reasonably large sample. Most studies have been small, underpowered, or employed a very limited number of phenotypes. Large population-based studies have focused solely on diagnosis and creative occupation or involvement, which may not adequately reflect creative ability. Many other studies have focused on healthy subjects and evaluated, for example, schizotypal personality traits and creativity. While these studies collectively provide an abundance of data to support the connection between bipolar disorder and creativity, the lack of consistency prevents cross-study comparisons.

To truly understand the complex relationship between bipolar disorder and creativity, all traits of potential relevance must be evaluated in the same sample using a design intended to capture the full spectrum of shared phenotypic and genetic variation. Only then can we definitively determine which traits are relevant in this context. A study design including individuals with bipolar disorder, unaffected relatives, and both creative (i.e., artists, musicians, writers, etc.) and noncreative controls would be ideally suited for a direct evaluation of the shared vulnerability model shown in Figure 1. Using a polygenic risk score method analogous to that of Power et al. [212], one would expect the positive trait values to approximate an inverted-U-shaped curve with noncreative controls and bipolar individuals anchoring the curve at each end, representing the lowest and highest genetic risk, respectively. Creative controls and unaffected relatives would presumably fall in the center of the curve with higher pos-

itive trait values conferred by mild-to-moderate risk for illness. The inclusion of twins discordant for bipolar disorder would be useful for disentangling genetic and environmental effects [80].

The use of a comprehensive, standardized battery would facilitate cross-study comparisons and allow for the sample sizes needed to resolve these issues. For inclusion in such a battery, a task should show evidence of reliability and stability; provide a range of phenotypic variation in both clinical and nonclinical samples; relate to the bipolar spectrum; and, most importantly, have the potential to function as a positive trait. Options for such a battery that meet many of these criteria are listed in online supplementary Table 1 (www.karger.com/doi/10.1159/000452416). For some traits, such as temperament and personality, we would expect relatively intermediate values to provide an advantage, whereas extreme values on either end would be expected to confer a disadvantage. Other traits, such as creativity or cognitive flexibility, would be expected to function more simply, with higher (more extreme) values conferring the advantage.

The administration of an array of creative tasks is also necessary to capture the range of creative ability and gain insight into the mechanism by which the various personality, cognitive, and affective traits associated with the bipolar spectrum impact creativity. While creativity is generally conceptualized as a spontaneous process that may be difficult to fully capture within a laboratory setting, several standardized and validated measurements exist, including figure preference and divergent thinking tasks. Divergent thinking involves originality of thought, fluency of ideas, and creative problem solving ability and thus represents an advantageous trait that drives invention and achievement across many domains (e.g., writing, science, business, etc.). Divergent thinking tasks can be conceptualized as the opposite of fluid intelligence tasks, which measure logical reasoning, and high performance across both types of tasks would particularly promote success across a number of disciplines. In addition to mood and personality, assessments of creativity should thus be combined with comprehensive cognitive assessments to allow for an evaluation of overall intelligence and the full range of individual capabilities.

Implications and Future Directions

Little is currently understood of the molecular mechanisms underlying bipolar disorder, and current treatments are far from maximally effective. Part of the value of research in this area is to better understand the genetic pathways contributing to risk. The low signal produced by genome-wide studies, with individual allelic effect sizes on the order of 0.5–1%, suggests that a large portion of the variance operates in clinically unaffected individuals [9, 10]. This also suggests that the phenotype is poorly understood, implicating the need to define better measures to detect the common alleles contributing to 25% of the risk for bipolar disorder and operating in the general population. Through the assessment of positive traits, we broaden the concept of bipolar disorder into a fully dimensional spectrum and presumably capture specific portions of the variance, which will facilitate the detection of the underlying genes and pathways contributing to risk. Understanding the relationship between positive traits and bipolar disorder may thus provide insight into the mechanisms of illness, which may someday lead to novel therapeutic targets.

Although this discussion has focused on positive traits, it is important to note that the patients themselves exist at the extreme and may be pushed beyond the limit of positive value, either at euthymia or in a state-dependent manner. Behavioral traits conforming to a shared vulnerability model may provide excellent targets for evidence-based therapies. For example, individuals with bipolar disorder often exhibit poor judgment in terms of impulsivity or reward-based decision-making [34, 35, 228]. Modulation of risk-reward valuation can easily be viewed according to this model, as a slight overvaluation of risk, in appropriate balance with reward valuation, can lead to great accomplishments, yet a large overvaluation of risk as compared with reward, which is correlated with mania, may have disastrous consequences [229, 230]. Even individuals with subsyndromal hypomanic symptoms show a greater hedonic impact of reward and a preference for immediate over delayed, but superior, rewards [231, 232]. There is thus likely a threshold along the bipolar spectrum at which a loss of inhibition and false positive error rates increase for tasks of impulsivity and risk-reward valuation, which would implicate a possible point of intervention and suggest a target for behavioral therapy to improve emotion-based decision-making or enhance self-control. In general, treatments aimed at reducing subsyndromal symptoms and relapses may indirectly improve the cognitive deficits associated with the disorder. Adjunctive therapies that improve focus and concentration, such as yoga therapy, also hold promise for improving cognitive function across several domains in both bipolar disorder and schizophrenia [233]. Additionally, cognitive behavioral therapy and self-monitoring techniques can be used to

help patients modulate cognitive disorganization and perform better on executive function tasks [234]. Finally, although controversial, there is evidence to suggest that cognitive training exercises can not only increase working memory but also improve fluid intelligence, which includes such abilities as pattern recognition, abstract reasoning, and problem-solving [235, 236]. Although more research in this area is needed, this is potentially promising for bipolar patients with complex cognitive deficits, and all tasks improving cognitive functioning in bipolar disorder may ultimately improve performance in those with creative abilities [77]. Thus, the investigation of behavioral traits that follow this model may not only further our understanding of the underlying neural networks involved in bipolar disorder but also facilitate treatment.

Conclusions

It has long been conventional wisdom that positive traits or enhanced abilities occur in the unaffected relatives of individuals with bipolar disorder, as well as many patients themselves, a view supported by numerous studies. If it can be shown that bipolar disorder is merely an extension of normal population variation in beneficial traits, it may erase some of the stigma still associated with this severe mental illness. Studies evaluating positive aspects and character strengths associated with bipolar disorder are aligned with the growing interest in research on the impact of positive psychological traits on health [237, 238]. Positive psychological traits of spirituality, empathy, creativity, realism, and resilience are frequently observed in bipolar individuals [239]. By gaining a better appreciation for the positive aspects of mental illness and exploring methods to enhance these traits, we may improve clinical outcomes [240].

Current practice in psychiatry is geared more towards controlling the symptoms of bipolar disorder, rather than understanding a patient's true needs and potential capabilities. Creative expression is a source of well-being, and many of those struggling with bipolar disorder consider increased creativity a truly positive aspect of their illness [241, 242]. In fact, bipolar patients often discontinue their medications due to subjective experiences of diminished creativity, among other unpleasant side effects [243, 244]. Some patients, once stabilized on lithium, will even decrease their own dosage toward achieving a "controlled cyclothymia," risking relapse of severe symptoms, all in the name of creative expression [19]. Others find the hypomanic phase so enjoyable and so integral to their creative work that they prefer to go untreated rather than risk limiting or losing it [244]. However, bipolar disorder usually worsens with time. While the side effects of medications may be unpleasant for some, the consequences of the disorder left untreated can be fatal, as evidenced by the ninefold increase in suicide rate and the countless artists and writers with bipolar disorder who have committed suicide [19]. Studying the link between creativity and bipolar disorder will thus promote a deeper understanding of patients' needs and experiences and facilitate better treatment, thereby enhancing patient compliance.

While the "Madness versus Genius" debate dates back to the time of Aristotle, research in this area is still in its infancy. Still, reports across several disciplines now provide scientific evidence to bolster what was once a collection of anecdotal evidence and lend legitimacy to these claims. Future studies will need to evaluate potential positive traits in the appropriate samples to identify those that will be most useful for exploring the genetic architecture of the shared vulnerability and the evolutionary context of bipolar disorder. An understanding of the role of bipolar risk genes in the general population as they relate to positive traits may provide insight into the mechanism of illness and thus facilitate the development of novel therapeutic treatments. Additionally, while the mild to moderate expression of these positive traits may hold advantages, more extreme expressions likely contribute to the severe symptoms associated with illness. A better understanding of the nature of this relationship will enable a suite of cognitive behavioral therapy techniques to improve decision-making, self-control, and cognitive functioning in patients, effectively "bending the curve" towards the positive aspects of these traits where functioning is increased and is truly beneficial. Further research in this area would thus represent an important step toward advancing our understanding of bipolar disorder, from both etiological and population perspectives, and toward promoting better patient care.

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