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Creativity and Bipolar Disorder: A Shared Genetic Vulnerability

Tiffany A. Greenwood

Department of Psychiatry, University of California, San Diego, La Jolla, California 92093, USA; email: tgreenwood@ucsd.edu

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Abstract

Bipolar disorder is a lifelong mood disorder characterized by extreme mood swings between mania and depression. Despite fitness costs associated with increased mortality and significant impairment, bipolar disorder has persisted in the population with a high heritability and a stable prevalence. Creativity and other positive traits have repeatedly been associated with the bipolar spectrum, particularly among unaffected first-degree relatives and those with milder expressions of bipolar traits. This suggests a model in which large doses of risk variants cause illness, but mild to moderate doses confer advantages, which serve to maintain bipolar disorder in the population. Bipolar disorder may thus be better conceptualized as a dimensional trait existing at the extreme of normal population variation in positive temperament, personality, and cognitive traits, aspects of which may reflect a shared vulnerability with creativity. Investigations of this shared vulnerability may provide insight into the genetic mechanisms underlying illness and suggest novel treatments.

Contents

1. INTRODUCTION

Despite many decades of research, defining the underlying genetic architecture of bipolar disorder has proven difficult, and little is currently understood of the molecular mechanisms underlying risk. The difficulty in identifying reliable risk variants has generally been attributed to genetic heterogeneity and the polygenic nature of the illness. However, the use of diagnosis as the phenotype for genetic studies fails to capture the tremendous clinical heterogeneity observed in bipolar disorder. It has been suggested that bipolar disorder is a dimensional phenotype existing at the extreme of normal population variation in temperament, personality, and cognition

(Akiskal 2002, Burmeister et al. 2008). Numerous studies have supported a familial connection between creativity and bipolar disorder (Jamison 1993). Bipolar spectrum traits provide prime candidates for mediating a shared vulnerability and may be evolutionarily adaptive (Akiskal & Akiskal 2007, Carson 2011, Greenwood 2017, Nettle & Clegg 2006). By investigating these traits, we may gain valuable insight into the genetic risk factors underlying the illness as well as a better understanding of its evolutionary context and relationship to creativity. Here we review the evidence that supports the connection between bipolar disorder and creativity as well as the implications for research and treatment.

1.1. Bipolar Disorder: Clinical Presentation and Treatment

Bipolar disorder is a severe mood disorder characterized by cycling between episodes of mania and major depression (Goodwin & Jamison 2007). Mania is accompanied by pathological elevations in energy and mood, a decreased need for sleep, racing thoughts, pressured speech, grandiosity, and extreme risk-taking behaviors. Depression is associated with low energy and motivation, insomnia, and feelings of extreme sadness, failure, worthlessness, and hopelessness. Up to 50% of patients also experience symptoms of psychosis in the form of hallucinations and delusions, which are most often associated with acute mania but can also accompany depression (Goodwin & Jamison 2007).

Bipolar disorder represents a spectrum of disorders with various forms classified according to the pattern and severity of the manic and depressive episodes. Bipolar I disorder is the most severe form and is defined by the presence of at least one lifetime manic episode lasting a minimum of 7 days or symptoms so severe as to require hospitalization. Although not required for diagnosis, the vast majority of people with bipolar I disorder also experience episodes of major depression. Bipolar II disorder is characterized by recurring episodes of major depression interspersed with periods of hypomania, a milder form of mania, lasting at least 4 days. Cyclothymic disorder, the mildest form of bipolar disorder, consists of cyclical mood swings between hypomanic and depressive symptoms over the course of at least 2 years with symptoms that do not quite meet the diagnostic thresholds for hypomanic and depressive episodes.

Bipolar disorder is common in the population and affects more than 5.7 million adults in the United States each year. In the National Comorbidity Survey Replication conducted from 2001 to 2003, among 9,282 adults aged 18 and older, the combined prevalence of bipolar I and II disorders was estimated to be 2.8%, with the majority of respondents (83%) reporting severe impairment (Kessler et al. 2005). Although mood symptoms often begin to manifest as early as childhood, the typical onset of illness occurs during the late teens to early adulthood and persists throughout one's life once diagnostic thresholds are met. Bipolar disorder is thus a lifelong illness, and spontaneous remissions are relatively uncommon. Given the symptom severity, bipolar disorder is often disabling and carries with it a lifetime risk of suicide as high as 20% (Barnett & Smoller 2009).

In many cases, the symptoms of bipolar disorder can be treated, and thus individuals with this illness may be able to lead full and productive lives. Treatment usually involves a mood stabilizer (e.g., lithium, lamotrigine, valproate) to maintain a remission of manic symptoms, often in combination with an atypical antipsychotic (e.g., quetiapine, olanzapine, risperidone). However, current treatments for bipolar disorder are far from maximally effective and often are associated with unpleasant side effects. An accurate diagnosis represents the first step in treatment but can prove difficult to achieve, given the complex presentation of bipolar disorder and the extensive clinical overlap with other psychiatric illnesses (Burmeister et al. 2008). Acute manic symptoms and the presence of psychosis often cause confusion and an initial misdiagnosis of schizophrenia, which shows a significant clinical and epidemiological overlap with bipolar disorder (Craddock & Owen 2005). Misdiagnosis of bipolar depression as major depressive disorder is especially

problematic because antidepressants can worsen the symptoms of bipolar disorder and even trigger a manic episode. A better understanding of the underlying pathophysiology is thus vital to proper diagnosis and treatment.

1.2. The Role of Genetics in Bipolar Disorder

Family, twin, and adoption studies have shown that bipolar disorder is highly familial with a substantial genetic contribution (Taylor et al. 2002). The heritability has been estimated to be as high as 80%, and first-degree relatives have a ninefold greater risk for illness compared with the general population (Barnett & Smoller 2009). Despite this high heritability, the many attempts over the last few decades to identify genetic variants contributing to risk for bipolar disorder have met with limited success. Genetic linkage and association studies have implicated numerous genomic regions segregating with illness in families and have identified candidate genes with significant evidence for an involvement in bipolar disorder. However, these early studies suffered from issues with replication, and the causal variants that presumably lie within these genes have remained elusive. What is clear from these studies is that bipolar disorder is not caused by a single gene of large effect but is instead a polygenic trait resulting from the combined action of multiple genes of small effect.

Recently, large genome-wide association (GWA) studies evaluating millions of variants across the genome in tens of thousands of individuals with bipolar disorder compared with healthy controls have begun to make progress. In the largest genetic study of bipolar disorder to date (29,764 bipolar cases and 160,118 controls), 30 distinct genomic regions exceeding a genome-wide significance P value threshold of 5×10^{-8} were identified, providing strong candidates for genes contributing to risk for illness (Stahl et al. 2019). Several of the implicated genes are consistent with leading hypotheses regarding pathophysiology; these include voltage-gated calcium channels (*CACNA1C*), neurotransmitter receptors (*GRIN2A*), synaptic components (*ANK3*), and other interesting candidates (e.g., *ITIH1*, *NCAN*, *SHANK2*). While the associated variants collectively explain 4% of the liability to illness, each contributing <0.05% of the risk, the combined polygenic signal of common variants across the genome accounts for 25% of the genetic variance in bipolar disorder, 70% of which is shared with schizophrenia and presumably reflects a genetic risk for psychosis. Thus, large-scale GWA studies clearly demonstrate a substantial role for common variation in risk for bipolar disorder, yet the pathways by which genetic variation contributes to the clinically observable signs and symptoms remain largely unknown.

1.3. Bipolar Spectrum Traits

Various mood-related traits and disorders with a range of severity are often observed in the families of bipolar patients, yet current categorical diagnostic systems (DSM and others) are limited in their ability to capture this phenotypic variation (Kelsoe 2003). It has been suggested that bipolar disorder may be better conceptualized as part of a spectrum of affective phenotypes ranging from very mild, subclinical affective traits to severe affective psychoses (Akiskal 2002). This bipolar spectrum model is consistent with that of a polygenic trait for which interactions between many genes of small effect produce a continuous variation in a phenotype. The use of quantitative phenotypes to model aspects of this variation may provide a powerful tool for identifying genes contributing to risk for bipolar disorder. For example, it has been suggested that extreme variation in temperament, which establishes a person's baseline level of mood, energy, and reactivity, is associated with an increased risk for illness (Kelsoe 2003). This model is summarized in **Figure 1**. It has also been suggested that bipolar disorder represents a dimensional phenotype on a continuum with normal population variation in temperament, personality, and cognition (Akiskal 2002, Burmeister et al.

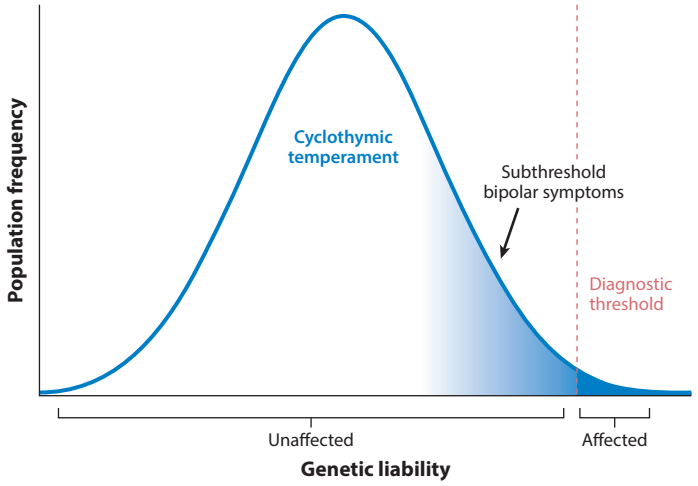

Figure 1

Temperament as a quantitative trait model for bipolar disorder. Although normal variations in temperament exist within the population, it has been suggested that a dysregulation of temperament is the fundamental abnormality that predisposes to the development of bipolar spectrum disorders, with more extreme variations in temperament conferring greater risk (Kelsoe 2003). In this model, cyclothymic temperament, for example, is influenced by numerous genes of small effect, resulting in a continuous distribution of mood regulation and reactivity. More extreme manifestations of cyclothymic temperament might in turn predispose individuals to episodes of mania and depression. By focusing on the underlying affective dysregulation, temperament might be a phenotype that is more sensitive and closer to the underlying biological abnormalities.

2008). Bipolar spectrum traits presumably mediate between the upstream biological mechanisms and downstream clinical diagnosis and more closely reflect the underlying genetic architecture.

1.4. Summary

Bipolar disorder is a common, highly heritable illness, and little is understood of its underlying genetic architecture. The complexity of the phenotype, combined with the substantial genetic heterogeneity, has frustrated many attempts to identify genes that contribute to risk. However, the observance of a low genetic signal in GWA studies and of a significant role for common variation in risk for bipolar disorder has several important implications. First, it implies that a large portion of the genetic risk for bipolar disorder is maintained in the population by clinically unaffected individuals. Second, it suggests that the bipolar phenotype, as currently conceived, is poorly understood, indicating a need to define measures that better reflect the underlying pathophysiology.

2. THE CONNECTION BETWEEN MENTAL ILLNESS AND CREATIVITY

2.1. "No Great Genius Has Ever Existed Without a Strain of Madness" (Aristotle)

Bipolar disorder has long been associated with heightened creativity, with notions of mad geniuses and artistic temperaments persisting in Western culture since the time of Ancient Greece. Indeed, history is rife with examples of creative geniuses who bore the burden of illness, including artists like Vincent van Gogh, authors like F. Scott Fitzgerald and Ernest Hemingway, poets like Walt

Table 1 Summary of key findings from selected studies evaluating the relationship between creativity and psychopathology

Study	Sample description	Key findings
Andreasen (1987)	30 creative writers and 30 matched controls	Eighty percent of the writers had a mood disorder; the rate of bipolar disorder (43%) was fourfold that of controls; the milder form of bipolar disorder was more prevalent than the severest form (30% bipolar II versus 13% bipolar I).
Jamison (1989)	47 British eighteenth-century writers	Thirty-eight percent had been treated for mood disorder; 6.5% had been treated for mania; 26% reported periods of elated mood.
Ludwig (1992)	1,005 eminent individuals across all fields of accomplishment	Rates of mania (8.2%), depression (41.2%), psychosis (6.8%), and suicide attempts (7.6%) were two to three times higher among artists compared with people in other professions (a six- to sevenfold higher rate of involuntary hospitalization); poets had the highest rates of mania (13%), depression (77%), psychosis (17%), and completed suicide (20%) among the artistic groups.
Wills (2003)	40 eminent American modern jazz musicians	Among the sample, 28.5% had a major mood disorder, 7.5% had a psychotic illness, 10% received inpatient treatment for depression, and 2.5% committed suicide.

Whitman and Sylvia Plath, and composers like Rachmaninoff and Tchaikovsky, to name a few (Jamison 1993). Across many decades of research, biographical studies of eminently creative individuals and group studies of artists and writers have consistently revealed an overrepresentation of bipolar spectrum disorders (Andreasen 1987; Jamison 1989, 1993; Ludwig 1992; Wills 2003). Key findings from selected studies are summarized in **Table 1**.

Studies of noneminent creativity (or "everyday" creativity) have produced comparable findings and suggest a 10-fold increase in the rate of bipolar disorder among artists compared with the general population (Goodwin & Jamison 2007). Swedish population-based studies have revealed a significant overrepresentation of bipolar patients and their healthy first-degree relatives in creative occupations (Kyaga et al. 2011, 2013). No such enrichment was observed for individuals with schizophrenia or major depression, although first-degree relatives of those with schizophrenia were more likely to have creative occupations. The Epidemiologic Catchment Area Study similarly found a significantly disproportionate concentration of individuals with bipolar disorder in creative occupations (Tremblay et al. 2010). Finally, several studies evaluating creative performance have reported that individuals with bipolar disorder show a preference for complex stimuli that is comparable to the preference shown by creative individuals (Santosa et al. 2007, Simeonova et al. 2005, Srivastava et al. 2010).

2.2. "The Dose Makes the Poison" (Paracelsus)

While some studies have provided evidence for increased creativity among those with bipolar disorder, others have shown that creativity and professional success are significantly enhanced among the clinically unaffected first-degree relatives (Coryell et al. 1989, Juda 1949, Kyaga et al. 2011, Richards et al. 1988, Simeonova et al. 2005). Creativity and eminence are also more often associated with affective temperaments, which are thought to reflect the genetic vulnerability that underlies the bipolar spectrum. For example, Akiskal & Akiskal's (1994) study of accomplished blues musicians revealed higher scores on measures of hypomanic and cyclothymic temperaments rather than more severe symptoms meeting diagnostic criteria for bipolar disorder. Similarly, Richards et al. (1988) found those with cyclothymia (a milder form of bipolar disorder) and unaffected

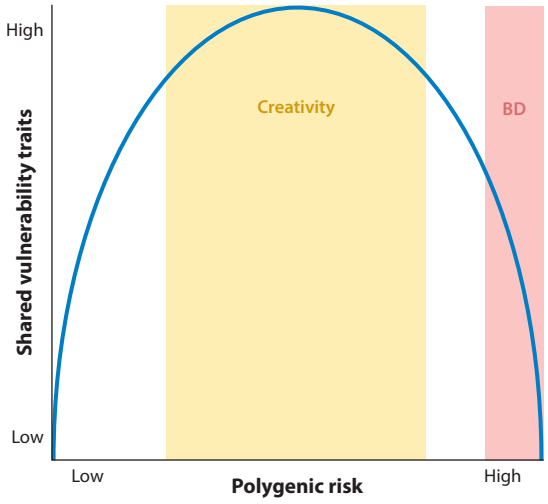

Figure 2

Depiction of the inverted-U model with moderate genetic loading for bipolar disorder (BD) conferring increased creativity. Building on Richards and colleagues' (1988) inverted-U hypothesis between psychopathology and creativity, the expression of shared vulnerability traits would increase with genetic loading for bipolar disorder up to a threshold, beyond which it would start to diminish with the increasing impairment of illness at higher levels of genetic loading. Polygenic risk indicates the combined genetic effect of common variants that confer risk for bipolar disorder (i.e., genetic loading). The risk variants are presumably maintained in the population by clinically unaffected individuals, who benefit from the shared vulnerability traits. Increased creativity is conferred by peak levels of shared vulnerability traits, which are associated with moderate genetic loading for bipolar disorder.

first-degree relatives to have greater creative achievement than either those with the most severe form of the disorder (bipolar I) or healthy controls. These observations led to the inverted-U hypothesis of creativity and psychopathology, which posits that risk for bipolar disorder or milder, subclinical presentations of bipolar symptoms enhance creativity but that more severe expressions interfere with creativity achievement (Richards et al. 1988). Under this model, which is summarized in **Figure 2**, creativity would increase with genetic risk for bipolar disorder up to a threshold, beyond which it would begin to diminish along with the increasing impairment associated with higher genetic loading. Increased creativity would presumably result from the combined expression of bipolar spectrum traits, each of which is influenced by many genes of small effect.

2.3. Summary

Anecdotal studies of eminently creative individuals combine with large population-based studies to provide strong support for a familial connection between creativity and bipolar disorder. However, these studies also suggest that while some aspects of the bipolar spectrum may confer advantages for creativity, the more severe expressions of symptoms associated with illness may negatively influence creative accomplishment.

3. THE SPACE BETWEEN MADNESS AND GENIUS

Creativity, which is typically defined as behaviors or thoughts that are both novel and useful, represents a complex, multidimensional construct with both cognitive and affective components

(Eysenck 1995, Feist 1998, Russ 1993, Srivastava et al. 2010). Building on the inverted-U model of Richards et al., some have suggested that bipolar disorder and creativity result from a shared vulnerability (Carson 2011, Murray & Johnson 2010, Richards et al. 1988, Schuldberg 2001). Several temperament and personality traits associated with bipolar disorder, creativity in bipolar disorder, and creativity in healthy individuals seem to occupy the space between madness and genius (Greenwood 2017). Several cognitive traits also represent candidates for shared vulnerability traits, while others may function as protective factors against mental illness (Carson 2011).

3.1. Affective Temperament and Hypomanic Traits

As discussed in Section 2.2, affective temperaments reflecting milder aspects of bipolar symptomatology are often observed in eminently creative individuals (Akiskal & Akiskal 1994, 2007; Richards et al. 1988). Temperaments measured by the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) are significantly heritable and have been shown to predict risk for bipolar disorder and to discriminate between bipolar patients, unaffected first-degree relatives, and healthy controls (Akiskal et al. 2005, Evans et al. 2005, Greenwood et al. 2013b). Additionally, the cyclothymic, dysthymic, and irritable temperaments show strong correlates with creativity (Nowakowska et al. 2005, Srivastava et al. 2010, Srivastava & Ketter 2010, Strong et al. 2007).

Bipolar spectrum traits related to increased sociability, strong ambition and drive to succeed, and a desire for recognition by others characterize those who excel because of their creative talent and are commonly observed in bipolar patients and their relatives (Feist 1998, Johnson et al. 2009, Murray & Johnson 2010, Sass 2001). Hypomanic traits, as measured by the Hypomanic Personality Scale, reflect aspects of the high energy, unstable high mood, inflated sense of self, and extreme sociability that are associated with hypomania and predict risk for bipolar spectrum disorders (Eckblad & Chapman 1986, Meyer & Hautzinger 2003). Higher scores for hypomanic traits are also associated with increased creativity in healthy subjects (Furnham et al. 2008, Schuldberg 2001). Impulsivity, a key feature of bipolar disorder and hypomania, is correlated with hypomanic traits and creative performance (Schuldberg 2001). In a meta-analysis combining 29 studies and 4,397 participants and evaluating personality traits associated with choosing an artistic occupation, impulsivity emerged as the most important factor (effect size = 0.75) (Feist 1998).

3.2. Personality Traits: Openness and Schizotypy

Openness is one of the domains used to describe personality under the Five Factor model and reflects dimensions of imagination (fantasy), aesthetic sensitivity, attentiveness to inner feelings, preference for variety, and intellectual curiosity (Costa & McCrae 1992). People who score high on measures of openness are motivated to seek new experiences and have a fluid style of consciousness that allows them to make novel associations between remotely connected ideas. Interestingly, both bipolar and creative individuals score higher on measures of openness compared with noncreative controls (Barnett et al. 2011, Feist 1998, Nowakowska et al. 2005, Srivastava et al. 2010). Openness is also a heritable trait, both in bipolar families and in the general population (Hare et al. 2012, Jang et al. 1996). Data across numerous studies suggest that openness to experience is a central feature of creativity (effect size = 0.71) (Dollinger et al. 2004, Feist 1998, Ma 2009, McCrae 1987, Parson et al. 1984). Openness correlates with divergent thinking and has been linked to both artistic and scientific creativity (Feist 1998, McCrae 1987). Openness has also been shown to mediate the link between hypomanic traits and engagement in daily creative activities (Furnham et al. 2008).

Much research on creativity has focused on aspects of schizotypy, which is thought to reflect the subclinical expression of psychosis (Raine 2006), as well as the underlying genetic vulnerability (Vollema et al. 2002). As some have demonstrated, schizotypy and psychosis proneness not only are associated with creative ability but also tend to run in families (Brod 1997, Prentky 1980). In fact, many studies have demonstrated strong associations between schizotypal personality traits (primarily positive schizotypal traits related to unusual beliefs and perceptual experiences) and enhanced performance on tests of creativity and fluency as well as elevated levels of positive schizotypy in individuals active in the creative arts (Barrantes-Vidal 2004; Batey & Furnham 2008, 2009; Burch et al. 2006; Green & Williams 1999; Nelson & Rawlings 2010; Nettle 2006; O'Reilly et al. 2001; Sass 2001; Schuldberg 2001; Schuldberg et al. 1988; Tsakanikos & Claridge 2005; Woody & Claridge 1977). Interestingly, this association between creativity and schizotypal traits is also observed among individuals with bipolar disorder, who score higher than controls on several measures of schizotypy (Mahon et al. 2013, Nettle 2006, Rybakowski & Klonowska 2011). In one study, poets and artists reported elevated levels of positive schizotypal traits (particularly those related to unusual perceptual experiences) that were as high as those observed in schizophrenia patients, while mathematicians reported lower levels of positive schizotypy than were observed in the general population (Nettle 2006). Another study similarly reported that professional artists and musicians scored higher than biologists and mathematicians on measures of positive schizotypy, hypomania, and a tendency to make loose associations (Rawlings & Locarnini 2008). Finally, positive schizotypal traits are correlated with other personality traits with relationships to creativity—namely, openness, cyclothymic temperament, hypomanic traits, and impulsivity (Asai et al. 2011, Morvan et al. 2011, Ross et al. 2002, Schuldberg 2001).

3.3. Intelligence and Cognitive Style

While intelligence and cognitive style are associated with aspects of creativity, the exact nature of this relationship remains unclear (Kaufman & Plucker 2011). What is known is that creative people tend toward divergent thinking and an overinclusive cognitive style (Eysenck 1995). Divergent thinking, which refers to the cognitive ability of associational network activation and creative ideation, represents an advantageous trait that drives invention and achievement across many domains (e.g., writing, science, business). Assessments of divergent thinking evaluate originality of thought, fluency of ideas, and creative problem-solving ability. In a study of 128 high school–aged students, Furnham et al. (2008) found a significant correlation between hypomanic traits and higher scores for the unusual uses test. Perhaps unsurprisingly, verbal divergent thinking is linked to creativity in writers and is correlated with a higher IQ than figural divergent thinking, which is more closely related to creativity in artists and musicians (Guilford 1967). Finally, a positive mood appears to provide a significant cognitive advantage in the performance of divergent thinking tasks, whereas a negative mood inhibits this process (Vosburg 1998).

Overinclusiveness involves remote associations and may facilitate originality. Typical symptoms of mania include increased word production and loose associations. Not surprisingly, manic bipolar patients have been shown to exhibit conceptual overinclusiveness similar to that observed in creative writers (Andreasen & Powers 1975). However, the quality of overinclusiveness differed: Writers showed more richness in their associations, while manic bipolar patients revealed more bizarre associations. Similarly, Henry et al. (1971) evaluated individuals with bipolar disorder during both manic and euthymic periods and observed that fluency, as measured by a word association task, tripled during mania but produced idiosyncratic associations.

The loose associations observed in mania may result from a failure to filter irrelevant stimuli from the environment. This process is known as sensory gating [or cognitive disinhibition (Carson

2011)] and is associated with both psychosis proneness (Grillon et al. 1990) and creativity (Carson et al. 2003). It has been suggested that lowered gating thresholds may foster creativity in the absence of psychosis.

Finally, intelligence, particularly executive function, has been shown to be associated with performance measures of creativity, like divergent thinking (Benedek et al. 2012, Gilhooly et al. 2007, Silvia 2008). However, a meta-analysis of 111 studies revealed a modest effect size of 0.31 (Ma 2009). It has been suggested that above-average intelligence is necessary but not sufficient for high creativity (Guilford 1967). Once an IQ threshold of 120 is reached, personality factors like openness to experience become more predictive of an individual's creative potential (Jauk et al. 2013). Higher executive functioning has, however, been shown to mediate increased creativity during mania (Soeiro-de-Souza et al. 2011). If creativity and bipolar disorder result from a shared vulnerability, cognitive protective factors, such as high IQ and cognitive flexibility, may lead to enhanced creativity, whereas cognitive deficits may limit creative potential. The combination of high IQ and cognitive disinhibition may also predict creative achievement (Carson 2011).

3.4. The Shared Vulnerability Model

Shared vulnerability traits occupy the space between madness and genius and are present in creative individuals, unaffected relatives, and presumably others with a genetic liability to bipolar disorder. These may include aspects of mood instability, experience-seeking personality traits, and cognitive traits related to conceptual overinclusiveness and disinhibition. A summary of the components that likely occupy the space between madness and genius is presented in **Figure 3**.

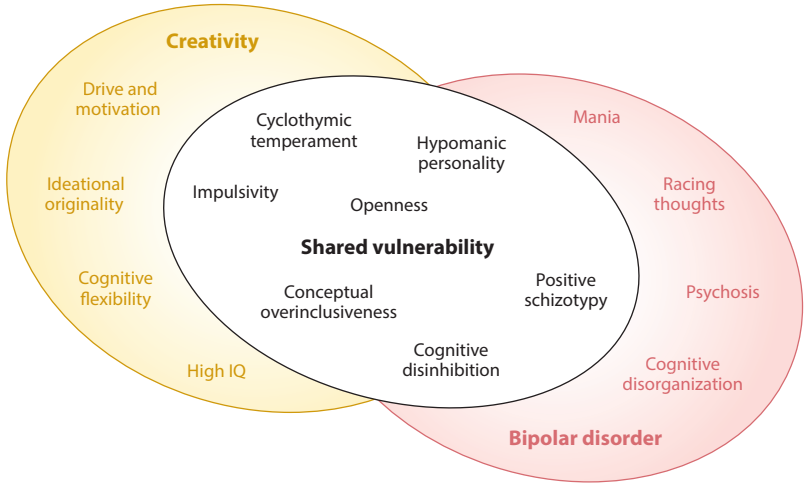

Figure 3

Shared vulnerability traits in the space between madness and genius. This model builds on Carson's (2011) hypothesis of a shared vulnerability between psychopathology and creativity to summarize the temperament, personality, and cognitive characteristics that may be shared by creative individuals and those with a genetic liability to bipolar disorder. All shared vulnerability traits listed are characteristic of both bipolar patients and creative individuals and correlate with enhanced creativity in bipolar disorder. Cyclothymic temperament reflects mood instability. Hypomanic personality reflects milder bipolar traits (high mood, increased energy, etc.). Openness reflects imaginative, curious, and open-minded qualities. Positive schizotypy refers to unusual beliefs (magical thinking) and unusual perceptual experiences. Conceptual overinclusiveness relates to divergent (i.e., outside-the-box) thinking and involves loose associations that facilitate originality.

In a recent 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) (Fears et al. 2014). 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 temperament traits, schizotypy, impulsivity, and sensation seeking. These personality features were correlated with increased verbal learning and fluency in the co-twins (Higier et al. 2014). These data provide further evidence to suggest that creativity may result from the combined effects of bipolar spectrum traits and enhanced cognition.

3.5. Summary

Creativity appears to result from the complex interaction of temperament, personality, and cognitive traits, which may reflect a shared vulnerability with bipolar disorder. However, the exact mechanisms by which these vulnerability traits mediate creativity are unknown, and it is unclear whether they fully explain the association of creativity with bipolar disorder.

4. CREATIVITY, BIPOLAR DISORDER, AND EVOLUTION

4.1. Bipolar Disorder: An Evolutionary Paradox

The persistence of severe mental illness has long puzzled evolutionary psychologists and psychiatric geneticists. Bipolar disorder and schizophrenia in particular are common, highly heritable disorders that are associated with substantial fitness costs related to social and cognitive impairment and increased mortality. Additionally, these disorders often manifest before or during the peak reproductive years and follow a lifelong course. This seems contrary to the expectations of natural selection, which maintains long-term stability of the species by removing genetic variants associated with a loss of fitness, primarily those with effects on fertility and survival. Genetic variants associated with risk for illness should therefore be subject to strong negative selection. Given the apparent relationship to creativity, a possible selective advantage for mood and psychotic disorders has long been speculated. Here we explore the prominent evolutionary models and the supporting evidence.

4.2. Polygenic Mutation–Selection Balance

It has been suggested that psychiatric illnesses result from mutation–selection balance. In this model, genetic variants that reduce fitness are continually introduced through mutation and pruned from the gene pool at a rate that is proportional to their adverse effects on fitness (Keller & Miller 2006). While the rate of de novo mutations is low ($\sim 2.5 \times 10^{-8}$ per nucleotide per generation), the overall target size in the human genome is large and involves many genes and regulatory regions. This model fits reasonably well for schizophrenia, which has been associated with a significant burden of rare, disruptive genetic variants (Purcell et al. 2014). Rare structural and de novo variants have also been observed in schizophrenia patients (Rees et al. 2012, Walsh et al. 2008). In further support of this model, severe fertility disadvantages have been observed in patients with schizophrenia, and reduced fertility rates have been observed among their unaffected siblings (Power et al. 2013).

This evolutionary model would seem to imply that risk is solely the result of rare variation, yet GWA studies clearly demonstrate that common variation plays a significant role in risk for psychiatric illness, with each individual variant contributing a small effect (Stahl et al. 2019). Given

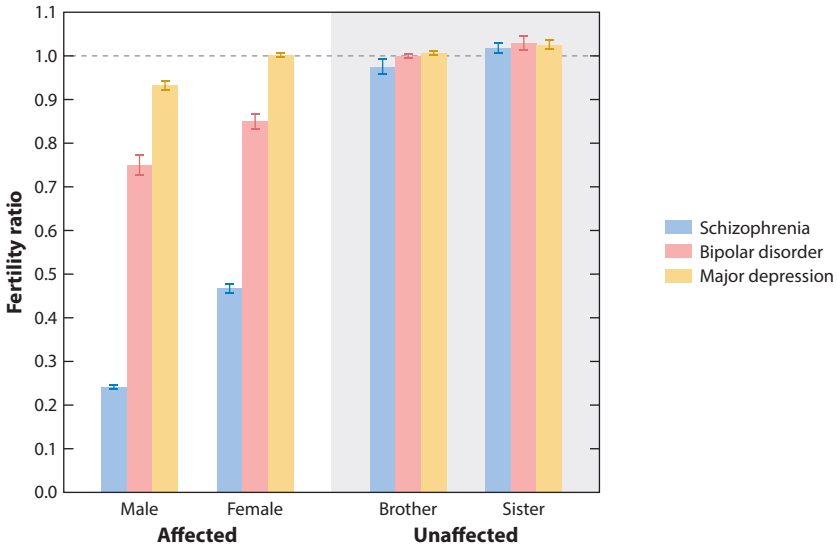

Figure 4

Evidence for strong selection against schizophrenia but not bipolar disorder. Data from the 1950–1970 Swedish Birth Cohort confirm prior reports that schizophrenia is under strong negative selective pressure, with reduced fertility rates observed for both male and female schizophrenia patients, consistent with an evolutionary model of mutation–selection balance (Power et al. 2013). However, bipolar disorder does not appear to be under strong negative selective pressure, and increased fertility rates are observed for unaffected siblings, consistent with an evolutionary model involving a balancing selection model. Fertility rates for individuals with major depression are shown for reference and do not differ from rates for the general population. For each observation, error bars are included to reflect the 95% confidence interval. The gray dashed line at 1.0 represents the baseline fertility of the general population. A ratio above 1.0 indicates increased fertility compared with the general population; a ratio below 1.0 indicates decreased fertility.

the highly polygenic nature of psychiatric illness, it is likely that individual mutations are subject to varying degrees of selective pressure. Some mutations, like large structural variations affecting multiple genes, may be more harmful than others and subject to strong purifying selection, in which case they would remain very rare before their eventual removal. Other risk variants may only exert a small effect on fitness and thus be subject to weak selective pressure, which might allow them to drift to the common frequencies that are detectable via GWA (Keller 2018).

The mutation–selection model does not, however, adequately explain the persistence of bipolar disorder. The hypersexuality that is often observed in association with mania should be adequate in and of itself to provide individuals with bipolar disorder an advantage in propagating their genes. Indeed, recent population-based studies have provided little evidence to support significantly reduced fecundity in individuals with bipolar disorder (Power et al. 2013). As summarized in **Figure 4**, these data suggest that, unlike schizophrenia, mood disorders are not under strong selective pressure and may instead be characterized by a large contribution of common genetic variants and gene–environment interactions that may facilitate adaptability (Uher 2009). More than one evolutionary mechanism may thus be involved.

4.3. Balancing Selection: An Alternative Hypothesis

Many have speculated that the persistence of bipolar disorder in the population may be explained by balancing selection. Under this model, variants contributing to risk for illness also confer

adaptive advantages for associated traits in affective and cognitive domains that increase fitness in the first-degree relatives of patients and other allele carriers in the general population (Akiskal & Akiskal 2005, Gardner 1982, Nettle & Clegg 2006). The observation of increased fertility rates among the unaffected siblings of individuals with bipolar disorder is consistent with this hypothesis (Power et al. 2013) because they presumably carry a reduced burden of risk variants and may express the associated traits in a milder, more advantageous form. This model suggests the influence of common variants distributed across the entire population, which is consistent both with the polygenic risk model of bipolar disorder and with the observance of a stable worldwide prevalence rate.

4.3.1. Balancing selection models. Balancing selection serves to maintain advantageous genetic and phenotypic diversity in human populations through a variety of mechanisms (de Filippo et al. 2016, Key et al. 2014). Under antagonistic pleiotropy, an allele is associated with both an increase in fitness for one trait and a decrease in fitness for another (Keller & Miller 2006). Accordingly, the negative fitness consequences of at least some bipolar risk alleles would be partially offset by the positive effects on the fitness of other traits, such as creativity. The net effect on fitness would thus be closer to neutral, allowing risk alleles to drift to higher frequencies and become common in the population. A cliff-edged fitness model has also been proposed, wherein the increased expression of a trait is associated with increased fitness up to a threshold, above which a sharp drop in fitness is observed (Nesse 2004). According to this model, a small number of alleles may be beneficial, with contributions to favorable affective or cognitive traits. However, extreme variation in these traits as a result of increased genetic loading would be maladaptive and lead to illness.

4.3.2. The role of shared vulnerability traits. Under a balancing selection model, the phenotype being transmitted in the population would not be bipolar disorder per se but rather the associated traits that modulate behavior in healthy individuals. As many have suggested, illness would represent the extreme on a continuum of variation in the affective and cognitive traits and occur only as a side effect of increased genetic loading (Akiskal 2002, Burmeister et al. 2008). Some have suggested that affective temperaments represent the most prevalent phenotypic expression of the genes underlying bipolar disorder and that their favorable evolutionary properties serve to maintain bipolar risk alleles in the population (Akiskal & Akiskal 2005, 2007). For example, the social and energetic hyperthymic temperament may provide advantages for leadership and exploration, whereas a dysthymic temperament may promote sensitivity to the suffering of others and strengthen marital bonds. The emotional intensity represented by the cyclothymic temperament is associated with both increased romantic pursuits and creativity and may provide advantages for mating and reproductive success. Positive temperamental traits related to social ease, confidence, and optimism have also been suggested as fitness-promoting traits related to bipolar disorder, as have enhanced verbal skills (Higier et al. 2014). Others have suggested that the observed association between schizotypal traits and creativity may partially explain the persistence of psychosis risk variants in the population, with possible fitness benefits deriving from sexual selection, mating success, and insight problem solving (Karimi et al. 2007, Miller 2001, Nettle & Clegg 2006, O'Reilly et al. 2001, Shaner et al. 2004). The balancing selection model is consistent with the observed inverted-U relationship between creativity and bipolar disorder, a relationship that may be mediated by shared vulnerability traits (Carson 2011, Richards et al. 1988). Thus, what once arose as beneficial mutations to increase the cognitive, creative, and social nature of developing humans may have eventually incurred the cost of mental illness at the extreme.

4.4. Summary

Evolutionary models related to fitness trade-offs offer an attractive explanation as to why bipolar disorder has persisted in the population despite clear fitness costs. Such models predict that risk alleles are maintained in the population by clinically unaffected individuals with moderate genetic loading for bipolar disorder, who express the associated traits in a milder, more advantageous form. It is certainly easy to envision how aspects of mania in a milder presentation could provide an advantage in today's society, particularly with regard to mood, energy, self-confidence, thought production, drive, and risk-taking. Social skills, leadership ability, exploratory and risk-taking behavior, insight problem solving, and creativity are often enhanced among unaffected relatives (Feist 1998, Johnson et al. 2009, Murray & Johnson 2010, Sass 2001). These observations, combined with the finding of increased fertility rates among unaffected siblings of bipolar patients (Power et al. 2013), suggest that genes contributing to risk for bipolar disorder may have originated to promote human advancement and expansion and may continue to provide advantages. However, balancing selection models have been subject to much debate, and their feasibility remains to be shown. Bipolar disorder is an extremely complex clinical phenotype. As no single vulnerability trait in its extreme leads to illness, it is also likely that no single evolutionary model can fully explain the seemingly paradoxical persistence of bipolar disorder in the population. This topic awaits a better understanding of the genetic architecture of both illness and creativity and their relationship to shared vulnerability traits.

5. CLUES TO THE GENETIC UNDERPINNINGS OF A SHARED VULNERABILITY

5.1. Candidate Genes, Pathways, and Selection

Some of the most striking pieces of evidence to support a genetic connection between bipolar disorder and creativity derive from an interdisciplinary view. For example, several candidate gene association studies of creativity have revealed associations with genes implicated in bipolar disorder and psychosis (Bachner-Melman et al. 2005, Keri 2009, Reuter et al. 2006). Interestingly, many of the genes associated with creativity in healthy individuals, like *NRG1* and *SLC6A4*, have also shown marks of positive selection along the human lineage (Bachner-Melman et al. 2005, Crespi et al. 2007, Keri 2009). *SLC6A4*, the serotonin transporter, modulates synaptic serotonin and is the site of action of most antidepressants, which inhibit serotonin reuptake. *NRG1* provides a particularly intriguing candidate for a shared vulnerability gene: A functional promoter variant in this gene (Law et al. 2006) is associated with both an increased risk of psychosis (Hall et al. 2006, Keri et al. 2009) and increased creativity in healthy controls (Keri 2009). Furthermore, an unusually high percentage of genes involved in the phosphatidylinositol 3-kinase (PI3K) pathway, which has an important role in brain growth, appear to have been subject to selective sweeps (Voight et al. 2006). A dysregulated activation of this pathway, mediated in part through the effects of *NRG1*, is associated with increased risk for psychosis (Kalkman 2006). Additionally, common treatments for bipolar disorder, such as lithium and valproate, are thought to act, at least in part, through activation of PI3K (Chalecka-Franaszek & Chuang 1999, De Sarno et al. 2002, Kozlovsky et al. 2006). These data seem to provide support for balancing selection models and may provide clues as to the biological mechanisms underlying the shared vulnerability between creativity and psychopathology.

5.2. The Role of Common Polygenic Variation

Some of the most convincing genetic evidence to support a shared vulnerability between creativity and bipolar disorder comes from a recent study conducted by Power et al. (2015) of over 86,000

healthy controls from an Icelandic cohort with a replication sample of more than 27,000 from Sweden and the Netherlands. Approximately 1% of each sample was considered creative, which was broadly defined in this study as either involvement in a creative occupation or membership in an artistic society. Using data from recent GWA studies of bipolar disorder and schizophrenia, polygenic risk scores were calculated as the sum of alleles associated with illness weighted by their effect sizes. These genomic risk summaries were applied to the samples of healthy controls, and the results demonstrated the significant association of higher genetic risk for both bipolar disorder and schizophrenia, as transmitted by common genetic variation, with creativity.

The primary limitation of this study, as in most prior studies, is the use of creative occupation as a proxy for creativity rather than a direct measurement of creative ability. Thus, it was not actually creativity that was examined here with regard to genetic risk for psychopathology but rather involvement in creative pursuits, which presumably requires creative abilities. Large genomic studies evaluating the shared vulnerability model through more refined measurements of both illness and creative ability are recommended for future investigations.

5.3. The Dopaminergic System

There is strong evidence to suggest that disturbances in dopaminergic systems underlie both bipolar disorder and psychosis (Diehl & Gershon 1992, McKenna 1987) and may also play a role in increased creativity (Burch et al. 2006, Folley & Park 2005, Richards et al. 1988). With prolonged use, the effects of dopaminergic stimulant drugs, such as amphetamine and cocaine, closely resemble psychosis, whereas the effects of acute administration more closely resemble mania (Jacobs & Silverstone 1986). Chronic administration of amphetamine can also provoke a manic episode in those with bipolar disorder and can trigger psychosis in healthy individuals (Angrist 1994). Excess dopamine in the prefrontal cortex has also been reported to decrease inhibition of stimuli from the surrounding environment (Ellenbroek et al. 1996), which is characteristic of both creativity (Carson et al. 2003) and psychosis (Grillon et al. 1990). The dopamine transporter 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 (Giros et al. 1992). The dopamine transporter gene (*SLC6A3*) has been implicated in bipolar disorder (Greenwood et al. 2001, 2006) as well as both cognitive and gating deficits in psychosis (Greenwood et al. 2011, 2012, 2013c). The presynaptic D2 receptor functions similarly to the dopamine transporter as part of the inhibitory response to curb excessive dopamine release, and it is the primary target of all effective antipsychotics (Madras 2013). Decreased thalamic D2 receptor densities are observed both in drug-naïve patients with psychosis (Buchsbaum et al. 2006, Talvik et al. 2003, Yasuno et al. 2004) and in healthy subjects with high divergent thinking scores (de Manzano et al. 2010). Variants of the D2 receptor gene (*DRD2*) have been shown to be associated with both verbal creativity (Reuter et al. 2006) and gating deficits (Volter et al. 2012) in healthy controls. These observations collectively suggest a model in which higher dopamine availability lowers gating thresholds and increases creativity in the absence of psychosis.

6. LIMITATIONS AND FUTURE DIRECTIONS

The connection between madness and genius dates back to the time of ancient Greece, yet research in this area is still in its infancy and is inherently difficult. Concerns have been raised regarding potential biases and the lack of consistency in how both mood disorders and creativity are conceptualized across studies (Johnson et al. 2012b). For example, it has been suggested that biographical studies of eminently creative individuals—studies that laid the groundwork for this area of research—have been skewed toward individuals with more severe symptoms, resulting in

a sampling bias that may have artificially inflated the rate of bipolar disorder among creative individuals. Such studies may also suffer from incomplete biographical records, which would influence the resultant diagnoses attributed to such individuals. This may, in part, explain the high degree of variability in the rates of bipolar spectrum disorders across studies. Along these lines, it has been suggested that studies reporting increased rates of schizophrenia among creative individuals may have been mischaracterizations of bipolar disorder because of the presence of psychosis and limited data regarding mood symptoms (Goodwin & Jamison 2007).

While large population-based studies may overcome these issues, they are fraught with biases of their own. Unlike studies of eminently creative individuals in whom creative ability is unquestionable, population-based studies use creative occupation, which does not provide an accurate representation of creativity and likely results in the sampling of individuals with a broad range of creative abilities. These studies also typically rely on databases of medical records, with psychiatric diagnoses obtained by various means, introducing considerable noise. Finally, it has been suggested that the overrepresentation of bipolar disorder and psychosis among those involved in creative occupations reflects a preference for an unconventional lifestyle due to difficulties maintaining stable employment. Indeed, the personality traits most associated with choosing a creative occupation are openness and impulsivity (Feist 1998), which are also strongly associated with bipolar disorder and have been suggested to reflect a portion of the shared vulnerability (Barnett et al. 2011, Carson 2011, Nowakowska et al. 2005, Peluso et al. 2007, Swann et al. 2001). Despite these flaws, the consistent observation of a relationship between creativity and bipolar disorder across a multitude of studies suggests that this area warrants further research.

While an abundance of data across numerous studies collectively supports a strong connection between bipolar disorder and creativity, the inconsistent methodologies prevent cross-study comparisons. Some studies have employed small samples of creative and affected subjects to evaluate a limited selection of shared vulnerability traits. Large, well-powered studies have relied on creative occupation as a proxy for creativity to examine the relationship with psychopathology. Many other studies have focused on unaffected individuals and evaluated the relationship of creativity to hypomanic and schizotypal personality traits. To fully understand the complex relationship between bipolar disorder and creativity, all personality and affective traits that may represent a shared vulnerability must be evaluated in a sufficiently large sample of bipolar patients, unaffected relatives, and both creative and noncreative controls. There is no convention for measuring creativity, and it is likely that no single metric can capture it fully. However, by administering an array of cognitive and creative tasks, we may more fully capture the range of creative abilities and gain insight into the mechanisms by which bipolar spectrum traits may facilitate creative processes.

7. CLINICAL IMPLICATIONS

Despite the evidence supporting a shared vulnerability, creativity is far from a ubiquitous trait in bipolar disorder. Indeed, a large study of psychiatric patients estimated that only 8% of those diagnosed with a bipolar spectrum disorder may be highly creative (Akiskal & Akiskal 1988). Still, for those who are both creative and bipolar, there are important considerations for clinical care. Current practice in psychiatry is geared more toward controlling the symptoms of bipolar disorder than toward understanding a patient's true needs and potential capabilities. However, many aspects of creative occupations tend to exacerbate the symptoms for bipolar disorder, including the extremes of achievement and frustration, increased stress, alcohol and substance abuse, and chaotic schedules (Murray & Johnson 2010). Involvement in a creative occupation thus poses a challenge and may necessitate an individualized treatment plan.

7.1. Positive Aspects of Illness: Patient Perceptions

Among the common diseases, both medical and psychiatric, bipolar disorder is somewhat unique in that it is associated with positive aspects. A recent case study of 10 individuals with bipolar disorder demonstrated that the positive aspects cluster into several themes, the first of which concerned a direct positive effect on daily life during elevated mood states (Lobban et al. 2012). One such positive effect, which was termed "amplification," involved an increased perceptual sensitivity, creativity, focus, and clarity of thought. Another related to "ease and ability," by which tasks that were usually difficult or time-consuming would suddenly feel incredibly easy. Participants reported that they could achieve at a high level during these times and would often embark on complex tasks (e.g., attempting to write a novel despite lacking relevant experience or talent). There was also a sense of "human connectedness," in which participants reported experiencing a drive to share their positive emotions with others, as well as increased self-confidence, leading to a perception of more open interactions that would not have occurred otherwise. The second theme, termed "lucky to be bipolar," concerned the fact that most participants viewed their illness as a gift for which they felt extremely grateful. The third theme concerned the relationship of bipolar disorder to self; the illness was generally perceived as an inherent part of identity and not separately as a disorder that needed to be managed. In another recent study, 62.2% of the 111 patients with bipolar disorder surveyed reported advantages associated with their illness, most commonly citing increased empathy (18%), self-awareness (13%), and creativity (14%) (Parker et al. 2012). Notably, patients with bipolar II disorder formed the majority of the sample (82.9%) and were three times more likely than patients with bipolar I disorder to endorse advantages associated with their illness. In addition to increased empathy, many patients with bipolar disorder have reported increased spirituality and a sense of cosmic relatedness (Galvez et al. 2011), which may predict resilience by facilitating regeneration following intense manic or depressive episodes. This increased spirituality is also reflected in the higher scores for self-transcendence observed among individuals with bipolar disorder compared with unaffected relatives, healthy controls, and individuals with depression (Greenwood et al. 2013a, Nowakowska et al. 2005). Research in this area will facilitate a better understanding of bipolar disorder and its unique association with positive traits.

7.2. Implications for Treatment

Because many individuals with bipolar disorder consider increased creativity a truly positive aspect of their illness—one that is directly related to the extreme fluctuations in mood (Parker et al. 2012)—the goal of mood stabilization may not be motivating. In fact, many bipolar patients discontinue their medications because of the perception of diminished creativity (Polatin & Fieve 1971). Even when stabilized on lithium, some will risk the relapse of severe symptoms by decreasing their own dosage in an attempt to achieve a "controlled cyclothymia" that they believe will enhance their creativity (Jamison 1993). 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 (Polatin & Fieve 1971).

However, bipolar disorder usually worsens with time, and 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 (Jamison 1993). Additionally, there is no evidence that bipolar symptoms themselves result in increased creativity. In fact, most research suggests that creative bipolar individuals are most productive when their symptoms are properly managed (Andreasen & Glick 1988). For some patients, there may be a fine line between being overmedicated, with a resultant loss of creativity and nonadherence to treatment, and undermedicated, in which the severity of symptoms prevents creative achievement. Studying the

link between creativity and bipolar disorder is thus crucial to promoting a deeper understanding of patients' needs and experiences and facilitating more personalized treatment, thereby enhancing medication compliance.

7.3. Reducing Stigma

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 and wellness (Seligman et al. 2005). Spirituality, empathy, creativity, realism, and resilience are all positive traits frequently observed in individuals with bipolar disorder (Galvez et al. 2011). Research in this area will provide a better appreciation of the potentially positive traits associated with bipolar disorder, potentially reducing stigma and suggesting methods to enhance these attributes (Duckworth et al. 2005). Additionally, many have suggested that bipolar disorder exists at the extreme of normal population variation in personality and cognitive traits, many of which are beneficial (see, e.g., Akiskal 2002, Burmeister et al. 2008). By investigating this link, we may gain a better understanding of the evolutionary context of bipolar disorder and increase public acceptance of this severe mental illness.

7.4. Bending the Curve

While the mild to moderate expression of shared vulnerability traits may hold advantages for increased creativity, more extreme expressions likely contribute to the severe symptoms associated with illness. For example, bipolar patients often exhibit poor judgment in terms of impulsivity and reward-based decision making (Johnson et al. 2012a, Peluso et al. 2007). However, when present in moderation, impulsivity may promote unrestrained expressiveness and foster originality in creative individuals. One can easily conceptualize the modulation of risk–reward evaluation as a fitness trait with a slight overvaluation of risk being adaptive and necessary to achieving greatness. Yet, a large overvaluation of risk that is unbalanced with appropriate reward valuation is maladaptive and is associated with mania (Mason et al. 2014). Subsyndromal hypomanic symptoms, which reflect a vulnerability to bipolar disorder, are similarly associated with impulsive decision making and a strong preference for immediate reward (Mason et al. 2012). A better understanding of the nature of these relationships may suggest the utility of mindfulness training and other cognitive behavioral interventions to improve decision making, self-control, and cognitive functioning in bipolar patients, effectively bending the curve toward the positive aspects of these traits.

7.5. Mechanistic Insight

By examining bipolar disorder as a dimensional clinical phenotype that reflects, in part, a shared vulnerability with creativity, we may also gain valuable insight into the mechanism of illness, which is currently lacking. Shared vulnerability traits in affective and cognitive domains are presumably closer to the actual phenotype that is being transmitted, and possibly maintained, in the population and provide increased specificity compared with analyses of diagnosis. Additionally, as quantitative measures of genetic liability, vulnerability traits are up to 100 times more efficient and provide up to a 10-fold increase in power to identify genetic risk variants compared with the standard, dichotomized analysis of bipolar patients versus healthy controls (Blangero et al. 2003). Investigations in this area are thus expected to enhance our understanding of the underlying causes of illness and provide novel targets for the development of new and more effective treatments for bipolar disorder.

8. CONCLUSIONS

It has long been observed that certain positive traits or enhanced abilities, such as creativity, exist within the bipolar spectrum, particularly in unaffected relatives. Many decades of research have indeed produced consistent evidence to support a familial connection between bipolar disorder and creativity. While less is known about the creative process to support this relationship, there is evidence that a moderately elevated mood may increase fluency and divergent thinking, but extreme elevations in mood interfere with creative accomplishment. Indeed, milder presentations of symptoms in the form of bipolar spectrum traits, such as cyclothymic temperament and hypomanic personality, appear to confer increased creativity and/or productivity in a less dramatic and more consistent manner. These and other shared vulnerability traits that reflect both a predisposition to creativity and genetic risk for illness may represent candidates for adaptive traits under balancing selection that serve to maintain bipolar disorder in the population despite the inherent disadvantages of the illness. The examination of shared vulnerability traits from a genetic perspective may shed light on the biological mechanisms underlying risk for illness and provide new targets for pharmacological and psychosocial interventions. Further research in this area is thus key to advancing our understanding of bipolar disorder, from both etiological and population perspectives, and toward promoting better patient care.

SUMMARY POINTS

1. Numerous biographical studies of the eminently creative combined with large population-based studies of everyday creativity provide strong support for a familial connection between creativity and bipolar disorder. While these studies have found a 10-fold increase in the rate of bipolar disorder among creative individuals, they have also shown that creativity and professional success are particularly enhanced among unaffected first-degree relatives and individuals with bipolar spectrum traits. This suggests that milder expressions of bipolar spectrum traits may confer advantages for creativity, whereas the more severe expressions of symptoms associated with illness negatively influence creative accomplishment.
2. Under a shared vulnerability model, creativity would increase with genetic risk for bipolar disorder up to a threshold, beyond which it would diminish with the increasing impairment of illness. As such, the phenotype being transmitted in the population would not be bipolar disorder per se but, rather, a collection of bipolar spectrum traits that modulate aspects of mood, behavior, and cognitive style. Clinically unaffected individuals with moderate genetic loading for bipolar disorder would express these spectrum traits in a milder, more advantageous form and thus serve as a genetic reservoir to maintain bipolar risk alleles in the population.
3. Several temperament, personality, and cognitive traits are associated with creativity, bipolar disorder, and creativity in bipolar disorder. Such traits represent prime candidates for the shared vulnerability and include hypomanic personality traits, cyclothymic temperament, impulsivity, openness to experience, positive schizotypy, conceptual overinclusiveness, and cognitive disinhibition.
4. Bipolar disorder is somewhat unique among common medical illnesses in that many patients view their illness as an inherent part of their identity that imbues them with positive attributes of self-confidence, self-awareness, empathy, spirituality, and creativity.

Yet, bipolar disorder comes at a high cost in terms of disability and suicide, and treatment noncompliance poses a significant concern, particularly among those who believe that their creative abilities are directly related to their mood fluctuations. Individualized treatment strategies that consider each patient's full range of experiences and that seek to preserve the positive aspects may improve clinical outcomes in bipolar disorder.

FUTURE ISSUES

1. The low signal produced by large genome-wide studies of bipolar disorder and the significant role of common variation suggest that a large portion of the genetic risk is maintained in the population by clinically unaffected individuals. By conceptualizing bipolar disorder not as a state of illness but rather as a dimensional trait existing at the extreme of normal population variation in temperament, personality, and cognition, might we gain critical insight into the underlying pathophysiology?
2. While evolutionary models related to balancing selection and fitness trade-offs offer an attractive explanation for the persistence of bipolar disorder in the population, the feasibility of such models remains a topic for future investigations. Large genomic studies using more refined measurements of both illness and creativity will be needed to definitively test the shared vulnerability model and shed light on the evolutionary context of bipolar disorder.
3. A primary limitation of most studies investigating the link between bipolar disorder and creativity is the reliance on creative occupation as a proxy for creative ability. Yet, how can one reliably measure creativity? The administration of a broad array of creative and cognitive tasks, combined with measures of creative achievement, is needed to more fully capture the range of creative abilities and evaluate what cognitive strengths may promote creativity.
4. What implications might the study of a shared vulnerability with creativity have for the treatment of bipolar disorder? Can this knowledge help identify novel treatment strategies to improve decision making, self-control, and cognitive functioning in bipolar patients?

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