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Jeffrey Rakofsky, *Emory University*
Kerry Ressler, *Emory University*
Boadie W Dunlop, *Emory University*

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BDNF function as a potential mediator of bipolar disorder and post-traumatic stress disorder comorbidity

JJ Rakofsky[1], **KJ Ressler**[2], and **BW Dunlop**[1]

[1]Mood and Anxiety Disorders Program/Bipolar Disorders Clinic, Emory University Department of Psychiatry and Behavioral Sciences, Atlanta, GA, USA

[2]Department of Psychiatry and Behavioral Sciences, Center for Behavioral Neuroscience, Yerkes Research Center, Emory University, Atlanta, GA, USA

Abstract

Bipolar disorder (BD) and post-traumatic stress disorder (PTSD) frequently co-occur among psychiatric patients, leading to increased morbidity and mortality. Brain-derived neurotrophic factor (BDNF) function is associated with core characteristics of both BD and PTSD. We propose a neurobiological model that underscores the role of reduced BDNF function resulting from several contributing sources, including the met variant of the BDNF val66met (rs6265) single-nucleotide polymorphism, trauma-induced epigenetic regulation and current stress, as a contributor to the onset of both illnesses within the same person. Further studies are needed to evaluate the genetic association between the val66met allele and the BD-PTSD population, along with central/peripheral BDNF levels and epigenetic patterns of BDNF gene regulation within these patients.

Keywords

bipolar disorder; post-traumatic stress disorder; brain-derived neurotrophic factor

Introduction

Bipolar disorder (BD) and post-traumatic stress disorder (PTSD) are psychiatric illnesses associated with significant morbidity and mortality.[1–4] Both are common disorders, and often co-occur in the same individual. Estimates of rates of comorbid PTSD among adult BD clinical populations range from 5 to 41% (lifetime) and 4 to 75% (current), varying due to factors such as diagnostic methods and study population characteristics.[3,5–18] Child and adolescent patients with BD have comorbid PTSD rates of 2–20% (lifetime) and 3–38% (current).[19–22] These rates are higher than the rates of PTSD observed in the general population: 6.8%[23] and 3.7–6.3%[24] among adults and adolescents, respectively.

Although Berkson's Fallacy (ascertainment bias)[25] could explain higher comorbidity rates among clinical samples, community sampling conducted through the National Comorbidity Survey (NCS) and NCS-Revised also support a strong relationship between BD and PTSD. The NCS found that among individuals meeting the criteria for BD, 39% also met the PTSD

Correspondence: Dr JJ Rakofsky, Mood and Anxiety Disorders Program/Bipolar Disorders Clinic, Emory University Department of Psychiatry and Behavioral Sciences, 1256 Briarcliff Rd, 3rd Floor North, Atlanta, GA 30306, USA. Jrakofs@emory.edu.

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criteria.[26] Similarly, NCS-Revised identified PTSD in 24% of BD-spectrum participants.[27] The NCS also found that the risk of a lifetime manic episode among men and women with PTSD was increased by 10- and 4.5-fold, respectively. In contrast, the risk for a lifetime major depressive episode among men and women with PTSD was increased by seven- and fourfold, respectively. Thus, compared to the general population, the relative risk for lifetime manic episodes was as great or greater than the relative risk for depressive episodes among adults with PTSD.[28] This is a remarkable finding that has received too little attention, particularly given the substantial overlap in diagnostic criteria between PTSD and major depressive disorder (MDD).[29] An independent replication of this association was identified in the Early Developmental Stages of Psychopathology Study, which followed a cohort of German nationals over 10 years. The risk of comorbid PTSD among those with BD I was increased nearly 14-fold, while it was increased nearly sevenfold among those with major depressive disorder.[30] There is, to date, no published data assessing the prevalence rates of BD among clinical PTSD samples.

This high rate of co-occurrence of BD and PTSD has tremendous clinical importance because the conditions can be mutually reinforcing. PTSD comorbid with BD is associated with a worsening course of BD illness, manifested by greater illness severity and higher rates of substance abuse, hospitalization and suicide.[5,7,8] Greater treatment non-adherence in BD-PTSD patients may be one of several factors contributing to these poorer outcomes.[31] Although the impact of BD on PTSD course has not been studied as closely, risky-impulsive behaviors occurring during manic episodes can lead to more trauma exposure, exacerbating the course of PTSD. Moreover, treatment of PTSD in BD patients is complicated by the risk of manic induction with antidepressants often used for PTSD[32] and the lack of studies supporting the efficacy of prolonged exposure therapy for PTSD in BD patients.

Neuroimaging associations

Although a thorough review of the neuroimaging studies of BD and PTSD are beyond the scope of this review, relevant similarities in imaging findings across the two illnesses warrant highlighting. Fear extinction is the process of replacing a fearful response to a stimulus with a non-fearful response. Impairment in this function is a central feature of PTSD and is related to the PTSD patient's chronic avoidance of behaviors that activate trauma-related memories.[33] Studies in animals and healthy volunteers indicate that the ventromedial prefrontal cortex (vmPFC), hippocampus and amygdala all play an important role in the recall and maintenance of fear extinction memories.[34,35] Moreover, extinction memory in healthy subjects is correlated with thickness of the vmPFC, which incorporates the medial component of the orbitofrontal cortex (OFC), the rostral and ventral components of the anterior cingulate cortex (ACC) and the medial PFC.[36] Structural imaging studies in patients with PTSD demonstrate reduced overall PFC volume, with specific reductions in ACC and vmPFC.[37] BD patients have reduced grey matter most notably within the perigenual ACC,[38] but also within the dorsolateral-, dorsomedial-, and ventrolateral-PFC.[39] They also have reduced white matter volume in OFC,[40] and diminished integrity of white matter fibers connecting OFC with subcortical limbic regions.[41,42]

These structural findings are supported by functional imaging studies. PTSD patients, compared to healthy control subjects, demonstrate greater activity in the amygdala, parahippocampal gyrus, insula, midcingulate cortex and percuneus during emotion processing tasks and hypoactivation of the vmPFC, dorsal ACC and anterior hippocampus.[43] Using positron emission tomography, women with sexual abuse-related PTSD demonstrated decreased activity in the OFC and medial PFC (including the ACC) compared to healthy control women during a fear extinction procedure.[44] Although extinction learning has not been studied with neuroimaging in BD patients, impairments in emotion regulation (incorporating the processes of monitoring, evaluating and modifying

emotional reactions to accomplish one's goals)[39] have identified abnormalities in neural activity in BD patients similar to those described above for fear extinction. Reduced vmPFC activity is present in manic[45] and remitted[46] BD patients during automatic emotional regulation tasks, along with greater activity in the amygdala and ventral striatum during states of depression, mania and euthymia.[39]

These findings suggest that impairments in emotion regulation in BD patients and fear extinction in PTSD patients may arise through dysfunctional interactions between vmPFC/OFC- and emotion-generating limbic regions. Both neuropsychological processes regulate the intensity of response to emotional stimuli through processes requiring new learning. Impairments in these functions in patients with BD and PTSD may contribute to the high rate of BD-PTSD comorbidity. As discussed below, brain-derived neurotrophic factor (BDNF) function within the PFC may be a critical mediator of PFC-dependent regulation of emotional reactivity.

Taken together, the epidemiological, clinical and neurobiological data suggest the existence of potential mediators that increase the risk of comorbidity between these two psychiatric conditions. These mediators may be clinical/developmental experiences, shared biological vulnerabilities or gene by environment (G×E) interactions that reflect a synergy between these mechanisms. For example, emerging work is identifying early childhood trauma as a risk factor for the later development of psychosis.[47,48] This clinical mediator, if validated, presumably produces some biological change in brain function, most likely through changes in gene expression. If early childhood trauma is a risk factor for developing psychosis, it would be reasonable to posit a similar relationship for BD and other mood disorders, which may thereby underlie the comorbidity of PTSD and BD for some patients.

Identifying genomic vulnerability and/or gene expression factors that may contribute to a shared vulnerability for both disorders will be important for the treatment of comorbid BD-PTSD patients. One particularly attractive protein for studying this relationship is BDNF. In this manuscript, we review studies demonstrating BDNF function and production as they relate to BD and PTSD pathophysiology. We then discuss a genetic variant that regulates BDNF production and its potential association with BD and PTSD. Finally, we synthesize this information to develop a model highlighting the putative role of impaired BDNF production in BD-PTSD comorbidity.

BDNF production and function

BDNF is a member of the neutrophin family, and plays a role in neuronal birth, maturation, differentiation, migration and survival. It is necessary for dendritic growth, synaptic plasticity and long-term potentiation.[49,50] The gene coding for BDNF consists of eight 5′-untranslated exons linked to individual promoter regions, and one protein coding 3′ exon[51] (see Figure 1). Although BDNF is present throughout the central nervous system (CNS), it is concentrated in brain regions involved in learning and memory, including hippocampus, amygdala, cerebral cortex and cerebellum.[52] Some CNS BDNF may derive from peripheral stores as the blood–brain barrier is permeable to BDNF in blood.[53] Although sequestered in platelet cells,[54] BDNF is synthesized and secreted into the periphery by vascular endothelial cells.[55] Serum levels of BDNF correlate positively with cortical CNS levels, providing a proxy measure of CNS BDNF changes in studies of human subjects.[56] Higher concentrations of BDNF in serum as compared to plasma are due to platelet release of BDNF as part of the clotting process.[57] Plasma BDNF follows a circadian rhythm with levels decreasing throughout the day,[58] and rises through the menstrual cycle, peaking just before ovulation.[59] Plasma BDNF is also negatively correlated with age and bodyweight.[57]

Thus, there are many variables that can confound studies of BDNF concentrations in human subjects, and which need to be controlled prospectively.

BDNF production and regulation

BDNF production in adulthood is affected by life stress exposure. Rats subjected to predator scent stress during both juvenile and adult periods have lower hippocampal CA1 region BDNF mRNA concentrations and more extreme anxiety responses to adult stress compared with those subjected to only adulthood stress or unexposed controls.[60] This greater anxiety response as an adult may be the result of early trauma-induced epigenetic regulation of *BDNF* genes. Infant rats subjected to maternal maltreatment reveal persisting DNA methylation of BDNF exons IV and IX into adulthood, along with reductions in PFC total BDNF mRNA.[61] Trauma-induced epigenetic regulation can also occur post-pubertally. Adult mice experiencing chronic defeat stress reveal a lasting increase in histone H3-K27 methylation at the P3 and P4 BDNF promoter sites, associated with decreased hippocampal BDNF exon III and IV mRNA.[62] Epigenetic chromatin and DNA changes following stress mediate enduring changes in BDNF production.

Current stress can also reduce hippocampal BDNF production as observed in rodent studies using immobilization, footshock, social defeat and other stress-inducing paradigms.[63] In healthy human subjects, current psychological stress is negatively correlated with serum BDNF.[64]

Production of BDNF is influenced by the singlenucleotide polymorphism (SNP), val66met allele (rs6265), an amino-acid substitution of methionine in place of valine at position 66 in the coding region of the *BDNF* gene[65] (see Figure 1). In cultured hippocampal neurons, this polymorphism has been associated with differing activity-dependent secretion of BDNF protein and failure of BDNF protein to localize to secretory granules or synapses.[66,67] Two studies, one including patients with a lifetime history of major depression and another with rhesus macaques, reported decreased peripheral BDNF levels among met carriers with early childhood trauma.[68,69] Additional mechanisms regulating BDNF synthesis exist. Various neurotransmitters, such as glutamate and GABA, have reciprocal effects on hippocampal BDNF expression.[70] Light and physical activity can increase CNS levels of BDNF in the visual cortex and hippocampus, respectively,[71,72] and estradiol increases BDNF plasma levels.[59]

Activity of the hypothalamic-pituitary-adrenal (HPA) axis also impacts BDNF function. Hypothalamic secretion of corticotropin-releasing hormone induces release of adrenocorticotropin from the anterior pituitary, which enters the systemic circulation and induces cortisol secretion from the adrenal gland. Cortisol feeds back negatively at the level of the hippocampus and pituitary, leading to a reduction in HPA axis activity and maintenance of homeostatic cortisol levels.[73] Cortisol and corticosterone (the rat equivalent of cortisol) decrease BDNF hippocampal mRNA production and impair BDNF function in cultured neurons.[74–76]

BDNF function

BDNF activity contributes to many forms of emotional and cognitive learning, including fear acquisition and social defeat,[77–79] and spatial and contextual learning. [80,81] Animal and human studies demonstrate that BDNF is pivotal in learning fear inhibition, which is impaired among those with PTSD.[33]

Mice with the BDNF met/met genotype[82,83] and those with hippocampal-specific deletion of the *BDNF* gene[84] show reduced extinction of fear learning compared with wild-type

mice. BDNF met/met mice also have smaller vmPFC volume, decreased cFos expression and decreased dendritic arborization in the vmPFC.[83]

In healthy humans, met-allele carriers demonstrate abnormal hippocampal activation on functional magnetic resonance imaging during the N-back working memory task, lower hippocampal *N*-acetyl aspartate levels (a neuronal viability marker) and reduced prefrontal and hippocampal gray matter volume.[66,85] Met-allele carriers, compared to val/val homozygotes, are slower to extinguish fear responding and this difference is associated with decreased vmPFC and increased amygdala activity on functional magnetic resonance imaging.[82] Met-allele-carrying status is also associated with differential performance on neuropsychological tests of declarative and episodic memory recall.[66,86] Taken together, the val66met SNP is associated with hippocampal BDNF production, prefrontal and hippocampal structural and functional changes, and differential peripheral BDNF levels.

Impaired fear extinction in rats is improved by infusion of BDNF into the infralimbic medial PFC.[87] In mice, a systemic BDNF receptor agonist enhances extinction in healthy animals. Furthermore, extinction deficits are reversed in mice with a history of stress through administration of an agonist for the BDNF receptor, tyrosine kinase B.[88] Histone deacetylase inhibitors, such as valproate, increase histone acetylation resulting in increased BDNF mRNA expression and enhanced fear extinction in mice.[89] These findings suggest that the reduced function of cortical BDNF leads to impaired fear extinction and abnormal amygdala–vmPFC neural circuitry. Given its role in fear acquisition as mentioned above, it appears that modulation of BDNF function can both increase risk and increase recovery through this same pathway.

BDNF has many other functions throughout the brain and periphery, potentially related to mood and anxiety regulation. In the CNS, BDNF modulates the activity of serotonin, dopamine and glutamate, neurotransmitters involved in mood-related circuits.[90–92] BDNF mediates adult-onset neurogenesis, which may be crucial for antidepressant efficacy.[63] Increased levels of BDNF in the mesolimbic dopamine circuit, the brain's reward pathway, mediate its role in social defeat stress and other depression-like behaviors in rodents.[78,79] BDNF regulates autonomic activity through synapses in the nucleus tractus solitarius, which is thought to play a role in states of psychological arousal.[93] BDNF protein may also participate in the CNS stress-response cascade, as it is co-expressed with cortisol-releasing hormone in the parvocellular neurons of the hypothalamus and increased following stress-inducing paradigms, in correlation with corticosterone levels.[94,95] It also is involved in the immune system response, as it is released by Tcells, B cells and macrophages in response to antigen activation.[96] Studies of human atherosclerotic plaque suggest its involvement in vascular injury repair.[97] These states of chronic inflammation and immune-functioning may contribute to the pathophysiology of mood disorders, [98] and suggest an indirect role in mood regulation for peripheral BDNF.

BDNF and BD

BDNF is suspected to play a role in BD pathophysiology. Post-mortem studies of BD patients reveal decreased hippocampal BDNF, proBDNF and p75 receptor protein expression.[99,100] Serumconcentrations of BDNF are decreased during manic and depressive episodes, which correlate inversely with symptom severity and increase with episode recovery.[101–103] Serum BDNF levels also decline during later stages of BD illness,[104] and are lower in BD patients with a trauma history, independent of symptom severity or PTSD diagnosis.[105] Medications used in the treatment of bipolar disorder, such as lithium and valproate, increase hippocampal BDNF levels in rat models and increase the level of exon IV-containing BDNF mRNA and BDNF promoter IV activity in cultured rat neurons.[106–108] The fluctuations in BDNF levels during mood episodes may reflect an important role for

BDNF in the regulation of mood states; alternatively, BDNF levels may be a marker of illness.

A genome-wide association study identified an association among African-American BD patients with an SNP within *NTRK2*, a gene that codes for the BDNF receptor, tyrosine kinase B, although this finding failed to maintain significance after correction for multiple testing.[109] Among German and African- American samples of patients with major depressive disorder, SNPs within the *NTKR2* gene were associated with a lifetime history of suicide attempt.[110] These NTRK2 findings suggest that variability within the BDNF signaling machinery at the receptor level may also be related to BD development and illness phenomenology, underscoring the role of the BDNF system in mood illnesses. However, additional replication studies in BD samples are needed to confirm these findings.

BDNF and PTSD

Fewer studies have looked at the role of BDNF in patients with PTSD. One study comparing plasma BDNF levels among 18 drug-naïve PTSD patients without psychiatric comorbidity and 18 healthy controls demonstrated significantly lower levels among those with PTSD.[111] In contrast, a study measuring serum levels of BDNF among 34 PTSD or acute stress disorder patients (comorbid BD, 5.9%) and 34 healthy controls, found significantly higher BDNF levels among the patients. Furthermore, patients with trauma exposure in the last year maintained this difference, while those with more remote trauma did not.[112] The difference in treatment history, psychiatric comorbidities, primary diagnosis, blood component (serum vs plasma), and recency of trauma exposure among the patient groups in these two studies may explain these divergent results. The only study to explore cerebrospinal fluid BDNF levels among patients with PTSD found no difference compared with healthy controls; however, the sample size was small, and comprised mostly of female civilians with moderate PTSD severity.[113] In addition, CNS BDNF may derive from multiple sources, such as the periphery, hypothalamus, hippocampus and ventral tegmental area. Thus, cerebrospinal fluid levels may obscure important BDNF changes occurring in specific brain regions among these patients. Although the direction of change in peripheral BDNF levels appears less consistent in PTSD than in BD studies, BDNF concentrations in PTSD patients differ significantly from those in healthy subjects, suggesting that BDNF may play a role in PTSD. A 12-week, open-label study using escitalopram (5–20 mg) in the treatment of males with chronic PTSD demonstrated that those with the lowest BDNF levels had the greatest improvement in PTSD severity.[114]

The clinical impact of BDNF genetic variants on BD and PTSD

Bipolar disorder

The relationship of val66met to illnesses like BD and PTSD could be informative as this SNP is associated with reduced hippocampal BDNF production, and BDNF levels may play a role in the emotional learning and regulation deficits central to these illnesses. Inconsistent findings have emerged from case– control and family-based genetic association studies examining the relationship between BD and BDNF gene variants[65,115–134] (see Table 1). One family-based genetic association study of euthymic South African BD I and II patients revealed a trend level ($P = 0.006$, threshold $P = 0.002$) association between carrying the met variant of BDNF val66met polymorphism and higher hyperthymic temperament scores.[135] Hyperthymia, which describes subthreshold lifelong hypomanic symptoms, is often seen among BD patients and their unaffected relatives.[136,137] Some studies found that the val allele was associated with rapid cycling,[126,129] early age onset[124,125,130] and suicide attempt,[123] whereas others found that the met allele was associated with early age at onset[120] and suicide attempt.[119] BD met-allele carriers were more likely than non-met-allele

carriers to develop their worst depressive episode following stressful life events occurring in the previous 6 months, suggesting a gene–environment interaction between the met allele and life stressors.[115] Among BD patients with an 'excellent response' to lithium prophylaxis, a higher percentage had the val/met genotype, suggesting that this SNP may predict treatment response,[138] although this finding was not replicated in a study of naturalistically treated patients.[139] Differences in methodology, comorbidity, sample race and ethnicity, and statistical limitations likely contribute to the variability in results presented above. Although most studies utilized structured diagnostic interviews, they did not stratify results by comorbid psychiatric diagnoses and none assessed a potential moderating effect of early childhood trauma. Thus, it remains uncertain whether risk for comorbid BD and PTSD is mediated in part by the val66met polymorphism.

In contrast to the inconsistency observed in syndromal-level associations between BD diagnosis and the BDNF val66met SNP, neuropsychological studies have repeatedly identified impairments for met-allele carriers with BD. Medicated, euthymic or mildly depressed BD I met-allele carriers performed worse on the Wisconsin Card Sorting Test than those with the val/val genotype, indicating that the met allele is associated with greater impairments in setshifting tasks, a prefrontal lobe cognitive function. [140,141] BD I and II patients with early sexual trauma and carrying at least one met allele performed worse on verbal and visual memory tasks compared to non-met allele-carrying patients.[142] Val66met heterozygotes with BD have smaller anterior cingulate, dorsolateral PFC and anterior hippocampal volume than val/val homozygotes.[143,144] In addition, BD I patients carrying the met allele experienced greater reduction of temporal lobe grey matter volume over 4 years as compared to non-met-carrying patients.[145] Proton magnetic resonance spectroscopy of met-allele-carrying euthymic and non-euthymic, medicated BD I and II patients found lower levels of phosphocreatine/creatine levels in the left dorsolateral PFC compared to those with the val/val genotype, suggesting that the met allele is associated with abnormal cellular energy metabolism in this brain region.[146]

Another region of genetic variation in the *BDNF* gene is the microsatellite 'G–T repeat'. This polymorphism is located in an area referred to as the BDNF-linked complex polymorphic region (LCPR), 1.0 kb upstream of the translation initiation site. It consists of three types of dinucleotide repeats, insertion/deletion and nucleotide substitutions resulting in 23 unique allelic variants.[147] The A1 allele has been associated with lower transcriptional activity of BDNF in cultured neurons.[147] Three family-based genetic association studies[65,125,126] and two case–control studies[133,147] demonstrate an association between variations in the LCPR and developing BD, although two case–control studies failed to show an association.[121,123] Six studies showed strong linkage disequilibrium between the val66met allele and LCPR allelic variants. Four demonstrated strong linkage to the val66 allele,[65,126,133,147] one showed strong linkage to the val or met allele varying by LCPR allelic variant[121] and one study did not specify which val66met allele was more commonly associated.[128] One study failed to show linkage disequilibrium between these two gene regions[123] (see Table 2).

The results of these genetic studies indicate that the relationship between the BDNF val66met SNP and BD is a subtle one. At a diagnostic level, there is little indication that the met allele is associated with increased risk for BD diagnosis. Several studies suggest that allelic variants in the LCPR are associated with increased BD risk and that many of these variants are in strong linkage disequilibrium with the val66 allele; thus, it may be that the inconsistent val66met findings arise owing to an over-representation of the val66 allele among some sample containing LCPR variants that increase BD risk.[147] Beyond the syndromal level, several studies suggest the met variant is associated with specific cognitive, neuroanatomical, neurochemical and temperamental abnormalities commonly found in BD

patients. These deficits may represent a mechanism through which BD patients carrying the met allele become more vulnerable to developing PTSD after trauma.

PTSD

The role of the BDNF val66met polymorphism in PTSD has only recently come under investigation. Two case–control genetic association studies failed to show a relationship between the val66met SNP and PTSD diagnosis, although both studies were limited by small sample sizes.[148,149] Other studies have explored possible connections between this SNP and general markers of anxiety. Met/met homozygous mice in stressful situations display increased anxietyrelated behaviors, which are not reduced with fluoxetine, in contrast to val carriers.[150] Case–control genetic association studies have found an association between the met allele and increased harm avoidance scores, an anxiety-related personality trait encompassing anticipatory worry, fear of uncertainty, shyness and fatigability.[151,152] Levels of neuroticism, which may be a risk factor for PTSD development,[153] are significantly lower among met-carrying as compared to non-met-carrying subjects;[154] however, one study revealed increased neuroticism, anxiety and depression among met-allele carriers with early life stress.[155] A meta-analysis found a small, nonsignificant association between met-allele-carrying status and the presence of anxiety disorders, including PTSD.[154] There have been no studies exploring the relationship between the BDNF-LCPR allelic variants and PTSD.

Too few studies have explored an association between genetic variants of the *BDNF* gene and PTSD diagnosis to make firm conclusions about a potential relationship. However, the alterations observed in PTSD patients' peripheral BDNF levels, combined with the increased anxiety responses among met carriers, suggest that the met variant of the BDNF val66met may contribute to PTSD illness onset or maintenance.

Model of BDNF function in comorbid PTSD and BD

We propose that reduced BDNF production, arising from several potential causes, may be one of the neurobiological contributors to the onset or maintenance of both illnesses within the same person.

Although the genetic association studies reviewed here do not suggest the met variant of the BDNF val66met SNP is associated with BD or PTSD, these studies did not control for the effects of early trauma. Early trauma is commonly reported by psychiatric patients,[15] and this early stress can lead to epigenetic changes with large effects in expression of gene products important to psychiatric illnesses.[156] A G×E interaction may exist for BD, whereby people with a family history of BD and who also carry the met variant become more likely to develop BD after early life trauma. The met allele is associated with the development of major depressive disorder among women with two or more childhood stressors, suggesting a similar G×E interaction may occur in other mood disorders as well.[157] None of the reviewed studies specifically evaluated BD-PTSD samples, leaving an association between BD-PTSD and the met variant undetermined. The risk for comorbid BD-PTSD may be mediated by impairments in new learning arising from the met-allele carrier status, as suggested by the cognitive, fear extinction, neuroanatomical and neurochemical associations reviewed here. Comorbidity risk may be further increased by other genetic and environmental factors that alter functional BDNF levels, such as epigenetic changes, treatment effects and ongoing stress.

Figure 2 depicts a model proposing a putative link between BDNF and developing comorbid BD-PTSD. BD patients often have experienced significant amounts of early childhood trauma,[9] which might act both as a trigger for unmasking BD mood episodes and as a

priming experience for later-onset PTSD arising in response to a trauma experienced in adulthood. Building on the animal studies discussed above, a BD patient with early life stress experiencing a trauma in adulthood could have lower BDNF function as a result of: (1) carrying the met-allele variant; (2) early life stress-induced epigenetic modifications of the *BDNF* gene; and (3) stress from the adulthood trauma itself. This reduction in BDNF activity may then impair the brain's ability to engage the amygdala-prefrontal-hippocampal circuits required for fear extinction[34] and to modulate other aberrant neural circuits driving BD mood episodes. Such impairments would then set the stage for a patient to develop both PTSD and a greater recurrence of BD mood episodes.

Interactions between early childhood trauma and met-allele carrier status have been identified and are associated with poorer memory among bipolar patients, [142] and with more depression, anxiety and neuroticism among healthy volunteers.[155] High neuroticism may contribute to future mood episode relapses in the face of stress,[158] and the combination of high neuroticism and impaired episodic memory may contribute to recalcitrant, memory-based, PTSD symptoms such as intrusive recollections and trauma-related amnesia.[159,160] Low hippocampal BDNF secretion may be the consequence of similar met-allele–early childhood trauma interactions. Lower BDNF levels could lead to reduced synaptic plasticity in the hippocampus and mPFC, resulting in poorer episodic and extinction memory,[66,87] and could lead to impaired modulation of the serotonin system, potentially contributing to higher levels of neuroticism.[161]

If the animal models implicating the role of BDNF and the met allele in mediating fear extinction translate to humans, this would further support reduced BDNF function as a link between PTSD and BD. The brain regions active in fear inhibition (ACC, anterior hippocampus and mPFC)[34,35] are either hypoactive or reduced volumetrically in patients with PTSD[44,162,163] and are reduced volumetrically in BD patients with the met allele.[143,144] Fear inhibition in BD patients has not been extensively studied; however, pediatric and adult BD patients have a reversal learning deficit on probabilistic response reversal tasks.[164,165] Both reversal learning and fear extinction require learning to associate new emotional valences with reward-contingent or previously threatening objects. Impairment in both of these functions may derive from low BDNF states that hinder synaptic formation and new learning.

Alterations in HPA axis activity associated with mood disorders may be another source of reduced BDNF for BD-PTSD patients. BD patients demonstrate hyper-cortisol states during the dexamethasone suppression test and the dexamethasone/corticotropin- releasing hormone test, which persist during mood-episode remission.[166,167] These data suggest that BD patients have an ongoing risk for reduced BDNF function, even when euthymic.

In contrast to patients with BD, PTSD patients demonstrate hypo-cortisol states as assessed by the dexamethasone suppression test and dexamethasone/corticotropin-releasing hormone test.[168] For some PTSD patients, this may be the result of early life trauma-induced, epigenetic modification of the glucocorticoid receptor, making it hyper-responsive to cortisol feedback.[168] Although cortisol levels impact BDNF production, the relationship between HPA axis suppressor status and BDNF function is unclear. Whether such non-suppressors are more or less sensitive than suppressors or super-suppressors to developing PTSD in the wake of a traumatic event, and whether these effects are mediated by BDNF function, is worthy of further study. HPA axis activity in comorbid BD-PTSD patients has not been characterized. Hence, it is unclear how the effect of early life trauma and PTSD, both common among BD patients, affects the long-term functioning of their HPA axis.

The proposed model may also apply to other anxiety disorders that occur comorbidly with BD, including panic disorder, specific phobias or social anxiety disorder.[11] Similar to PTSD, patients with these other anxiety disorders often experience early life trauma[169] and may be unable to extinguish fear memories.[170] The role of BDNF in these illnesses has yet to be determined. Although it is outside the scope of this review focused on BD, this model may equally apply to PTSD comorbidity with major depressive disorder, as there is substantial data demonstrating BDNF deficits[63] and the impact of early childhood trauma[171] among these patients.

Antidepressants increase BDNF levels in patients with major depression,[63] suggesting that according to our model, antidepressants should be efficacious for those with PTSD. However, influential reviews have concluded that antidepressants lack convincing evidence of efficacy for PTSD,[172] although other reviews challenge that conclusion.[173] The weakness of antidepressant efficacy for PTSD is not in conflict with our model, because the evaluated trials studied only antidepressant monotherapy, specifically excluding concomitant exposure therapy treatment for trial participants. For the BDNF elevating effects of antidepressants to improve core PTSD symptoms, we propose the patient must be engaging in a form of exposure to permit the new synaptic formations required to extinguish fear responding.[174] This hypothesis could be tested in clinical trials in which PTSD patients receive standard exposure-based psychotherapy along with concomitant, randomized, blinded treatment with either an antidepressant or placebo.

Limitations to this model are that the associations between the met variant of the val66met SNP and the findings reported above may have been the result of linkage disequilibrium between val66met and another gene loci, such as the BDNF-LCPR. In addition, low BDNF levels may be a state marker of illness and not necessarily a pathophysiological agent in either BD or PTSD. If this were the case, then perhaps the increased PTSD comorbidity rate among BD patients might be due to more trauma experienced as a result of risky-impulsive manic behaviors rather than underlying BDNF dysfunction occurring during manic episodes. Studies could be designed to control for the effects of intrinsic BDNF activity and mood state at the time of trauma. Further studies are needed to evaluate the genetic association between the val66met allele and the BD-PTSD population, central/peripheral BDNF levels and epigenetic patterns of BDNF gene regulation within these patients.

If the val66met SNP, patterns of BDNF transcription silencing or lower BDNF levels are more often associated with the PTSD-comorbid subgroup of BD patients, then treatments aimed at combining exposure therapy with medications that could enhance fear extinction would be worthy of further study. These medications could include: (1) replacement BDNF or a BDNF receptor agonist with effects as described above;[88,175] (2) D-cycloserine, a partial NMDA receptor agonist that facilitates extinction in patients with phobias,[176] social anxiety disorder,[177,178] panic disorder[179] and obsessive-compulsive disorder, [180,181] and was found to rescue the extinction deficit in mice with the human BDNF met allele;[83] or (3) histone deacetylase inhibitors, like valproate, which increase histone acetylation resulting in increased BDNF mRNA expression and enhanced fear extinction in mice.[89]

These approaches could potentially improve the patient's impaired extinction learning capacity while avoiding the potentially destabilizing effect of antidepressants on BD illness.[32] In addition, if impaired fear extinction and the emotional dysregulation characteristic of BD were subserved by the same neural networks, then medication treatments aimed at enhancing fear extinction could also provide mood stabilization, as already demonstrated in BD prophylactic studies using valproate.[182,183]

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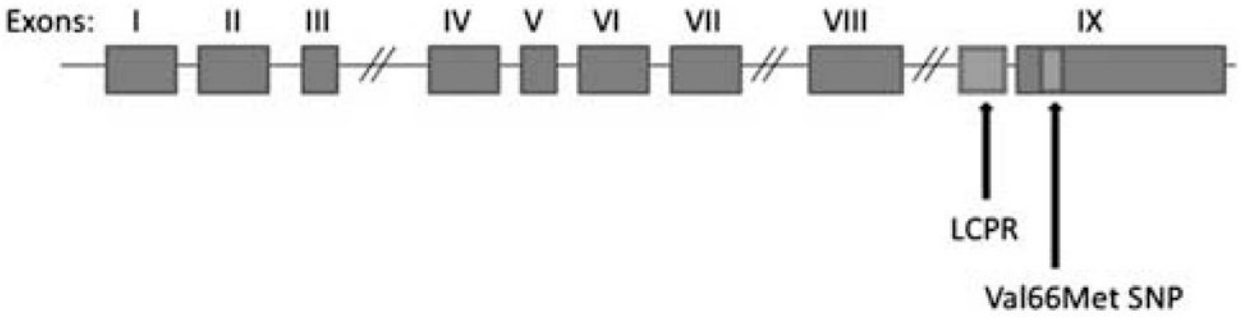

Figure 1.
The *brain-derived neurotrophic factor* (*BDNF*) gene. The gene is comprised of eight 5′-untranslated exon regions linked to individual promoter regions and one protein coding 3′ exon.[51] The linked complex polymorphic region (LCPR) is located 1.0 kb upstream of the translation initiation site. It consists of three types of dinucleotide repeats, insertion/deletion and nucleotide substitutions resulting in 23 unique allelic variants.[147] The val66met single-nucleotide polymorphism (SNP) is located within the coding region.[65] Hatch marks represent intron regions that are spliced out of the final protein product.

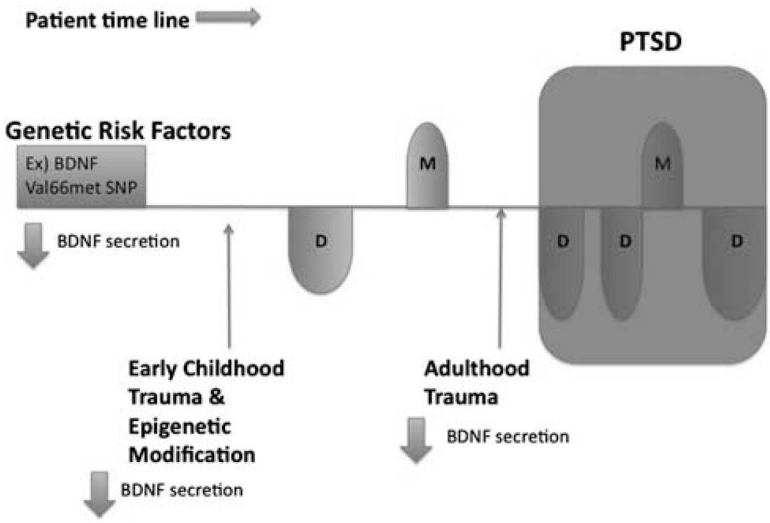

Figure 2.

A putative model linking trauma and brainderived neurotrophic factor (BDNF) function to the development of bipolar disorder and post-traumatic stress disorder. Patients may carry genetic risk factors, including BDNF val66met single-nucleotide polymorphism (SNP) variants, BDNF-linked complex polymorphic region (LCPR) allelic variants and other unidentified markers increasing their risk for altered BDNF protein production[66,67] and bipolar illness.[115,134,147] Exposure to early childhood trauma may induce epigenetic modification in the form of histone and DNA acetylation and methylation, leading to further reductions of BDNF protein production.[61] This may trigger the onset of bipolar illness in the form of depressive and manic episodes.[101–103] Adulthood trauma may occur, once again interrupting BDNF production.[62–64] Reduced BDNF function may interfere with fear extinction leading to the development of post-traumatic stress disorder (PTSD)[82–84] and increased emotion dysregulation. This could lead to a worsening course of bipolar illness, in the form of increased mood episodes over time, followed by further reductions in BDNF levels. Abbreviations: D, depressive episodes; M, manic episodes.

Table 1

Results of studies exploring an association between BD and the val66met allele

Source	No. of BD patients	Bipolar measure	Design	Ethnicity/nationality	Genotype of BD participants: %			Val transmission/non-transmission
					vv	vm	mm	
Positive association with the val allele								
Vincze *et al.*[123]	447	DIGS	Case–control	Caucasian	60.1	38.1	1.81	NA
Kremeyer *et al.*[121]	224	DIGS	Family-based	Antioquian	Genotypes not provided			370/70
Muller *et al.*[126]	350	SCID	Family-based	95% White-European origin 3.4% Asian 0.8% Native American 0.8% African American	Genotypes not provided			114/70
Lohoff *et al.*[127]	621	DSM-IV	Case–control	European descent	67.8	28.7	3.5	NA
Strauss *et al.*[125]	258 families; BD no. ?	ISCA-D	Family-based	Hungary	Genotypes not provided			83/52
Cichon *et al.*[128]	281	DSM-IV	Case–control	German origin	Genotypes not provided			NA
Geller *et al.*[124]	53	KSADS	Family-based	88.7% Caucasian	Genotypes not provided			21/9
Neves-Pereira *et al.*[65]	282	Not reported	Family-based	95% European origin 2.5% Asian 1.4% Native American 1.1% African American	Genotypes not reported; val allele = 76.9%; met allele = 23.1%,			NA
Sklar *et al.*[122]	282	RDC, DSM-IV	Family-based	Euro-caucasian	Genotypes not provided			53/34
No association with either allele								
Kim *et al.*[119]	169	SCID	Case–control	Korean	31.4	47.3	21.3	NA
Liu *et al.*[117]	785	DIGS	Family-based	European American	Genotypes not provided			654/644
Tang *et al.*[130]	197	DSM-IV	Case–control	Han Chinese	37.1	46.7	16.2	NA
Green *et al.*[129]	962	SCAN, DIGS, SADS-L	Case–control	White, United Kingdom origin	66.9	30.1	3.0	NA
Kunugi *et al.*[116]	519	DSM-IV	Case–control	Japanese	36.2	46.1	17.7	NA
Oswald *et al.*[131]	108	MINI	Case-control	Belgian origin	55.6	42.6	1.9	NA
Skibinska *et al.*[120]	352	SCID	Case–control	Caucasian	70.2	26.7	3.1	NA
Strauss *et al.*[133]	23	SCID, ISCA	Case–control	81% Caucasian	AA: (all patients)			NA
				16% African American, 3% Mixed	80	20	0	
					Caucasian:			
					58.2	35.4	6.3	

Source	No. of BD patients	Bipolar measure	Design	Ethnicity/nationality	Genotype of BD participants: %			Val transmission/non-transmission
					vv	vm	mm	
Hong *et al.*[118]	108	DSM-IV	Case–control	Chinese	29.6	50	20.4	NA
Nakata *et al.*[132]	130	DSM-IV	Case–control	Japanese	32.3	52.3	15.4	NA
Positive association with the met allele								
Hosang *et al.*[115]	488	SCAN	Case–control	Not reported	61.0	38.0	1.0	NA
						Controls:		
					68.0	28.0	4.0	
Xu *et al.*[134]	498	DSM-IV	Case–control	Han Chinese	30.5	43.6	25.5	NA

Abbreviations: BD, bipolar disorder; DIGS, Diagnostic Interview for Genetic Studies; DSM-IV, Diagnostic and Statistical Manual-Fourth Edition; ISCA, Interview Schedule for Children and Adolescents; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MINI, Mini-International Neuropsychiatric Interview; NA, not applicable; SADS-L, Schedule for Affective Disorders and Schizophrenia-Lifetime version; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCID, Stuctured Clinical Interview for DSM-IV.

Table 2

Results of studies exploring an association between BD and the BDNF-LCPR

Source	No. of BD patients	Bipolar measure	Design	Ethnicity/nationality	LCPR-associated alleles (A1–4)	Haplotype associations of LCPR alleles with val66met
Vincze *et al.*[123]	447	DIGS	Case–control	Caucasian	No associations	No associations
Kremeyer *et al.*[121]	224	DIGS	Family-based	Antioquian	No associations	Overtransmission of val allele 227 (LCPR), $P = 0.006$
Muller *et al.*[126]	350	SCID	Family-based	95% White-European origin 3.4% Asian 0.8% Native American 0.8% African American	A3 frequency of transmitted allele: frequency of untransmitted allele— 0.75:0.25. All other alleles —0.25:0.75, $P = 0.004$	A3-val, $P = 0.003$
Okada *et al.*[147]	153	DSM-IV	Case–control	Japanese	A1 patients 11.8%, controls 4.6%, OR = 2.8, 95% CI (1.5–5.3), $P = 0.001$	A1, 2 and 3 linked to val, while A4 linked to met, $P = 0.0069$
Strauss *et al.*[125]	258 families; BD no. ?	ISCA-D	Family-based	Hungary	A1, $P = 0.040$ A3, $P = 0.036$	Not studied
Cichon *et al.*[128]	281	DSM-IV	Case–control	German origin	Not examined	rs988748-(GT)n (LCPR)-rs6265 (val66met), $P = 0.0057$
Strauss *et al.*[133]	23	SCID, ISCA	Case–control	81% Caucasian 16% African American 3% Mixed	A4, OR = 3.94, 95% CI (1.72–9.04),	Val-(A4 or A5), $P = 0.0003$
Neves-Pereira *et al.*[65]	282	Not reported	Family-based	95% European origin 2.5% Asian 1.4% Native American 1.1% African American	A3, $P = 0.042$	A3-val, $P = 0.00039$. A1-met associated with decreased transmission to BD probands, $P = 0.013376$

Abbreviations: BD, bipolar disorder; CI, confidence interval; DIGS, Diagnostic Interview for Genetic Studies; DSM-IV, Diagnostic and Statistical Manual-Fourth Edition; ISCA, Interview Schedule for Children and Adolescents; LCPR, linked complex polymorphic region; OR, odds ratio; BDNE, Brain-derived neurotrophic factor.