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REVIEWS

Brain-derived neurotrophic factor and neuroplasticity in bipolar disorder

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Initial descriptions of bipolar disorder (BD) emphasized that patients returned to a baseline condition after acute episodes. Such definitions were operational in teasing bipolar disorder apart from schizophrenia, where patients were described to be permanently impaired after the initial episodes. However, this view of BD as a disorder where cognition and overall functioning was spared has been changing after the scrutiny of new research. Currently, the cognitive impairment and neuroanatomical changes related to cumulative mood episodes, particularly manic episodes, are well described. In terms of neuropathological findings, recent data suggest that changes in neuronal plasticity, particularly in cell resilience and connectivity, are the main findings in BD. Data from differential lines of research converge to BDNF as an important contributor to the pathophysiology of BD. Serum BDNF levels have been shown to be decreased in depressive and manic episodes, returning to normal levels in euthymia. Moreover, factors that negatively influence the course of BD, such as life stress and trauma, have been shown to be associated with a decrease in serum BDNF levels among bipolar patients. These findings suggest that BDNF plays a central role in the transduction of psychosocial stress and recurrent episodes into the neurobiology of bipolar disorder. The present review discusses the role of BDNF as a mediator of the neuroplastic changes that occur in portion with mood episodes and the potential use of serum BDNF as a biomarker in BD.

KEYWORDS: BDNF • bipolar disorder • brain-derived neurotrophic factor • neuroplasticity • neurotrophin • stress • trauma

Bipolar disorder (BD) is a chronic mood disorder, with a lifetime incidence of at least 1% [1]. Epidemiological studies indicate a role for both biological and environmental factors in the pathogenesis of BD. Among biological factors, impairment in synaptic plasticity and neuronal survival has been described, which are determined by several factors including the orchestrated action of neurotransmitters, hormones and neurotrophins. Synaptic plasticity can be defined as an experience-dependent change in synaptic strength [2]. Accordingly, such definition will be used in the present review.

BDNF has emerged as a key mediator for synaptic plasticity, neuronal connectivity and dendritic arborization [3,4]. BDNF is known to have a highly complex genomic structure containing multiple 5'-noncoding exons that are spliced to a common 3'-coding exon that encodes for the BDNF protein [5], and such a complex set of genomic promoters is thought to

mediate accurate control of BDNF production [6]. There is recent evidence showing that chromatin remodeling of the *BDNF* gene may be associated with the deleterious effects of stress and with antidepressant response. More specifically, Tsankova *et al.* found that chronic defeat stress, a mouse model of depression, induced a threefold downregulation of BDNF mRNA expression in the hippocampus, an effect that was mediated by repressive histone methylation and consequent decreased expression of BDNF transcripts III and IV [7]. Moreover, chronic treatment with imipramine increased histone acetylation at these same promoters, thereby normalizing the expression of BDNF transcripts III and IV and total protein. More recently, Yasuda *et al.* demonstrated that the mood stabilizers lithium and valproate increase BDNF transcript III (old rat nomenclature) in rat cortical neuronal cultured cells [8]. Together, these studies strongly suggest that the regulation of

BDNF transcription may be a key target for the effects of antidepressants and mood stabilizers. BDNF transcripts are translated into a precursor, pro-BDNF, which binds to sortilin in the Golgi to facilitate appropriate folding, trafficking and secretion [9,10]. It has been demonstrated that a single polymorphism in the *BDNF* gene, which substitutes a valine for a methionine at the codon 66 (val66met), can disrupt the BDNF–sortilin interaction, thereby reducing activity-dependent BDNF secretion [10]. Furthermore, knock-in BDNF^{met/met} mice have abnormal dendritic arborization in the dentate gyrus and display anxious-related behaviors that are not normalized by antidepressant treatment [11]. These findings are particularly important in light of recent evidence suggesting that the BDNF val66met polymorphism may be implicated in the pathophysiology of BD (as discussed in detail later).

BDNF binds with high affinity to the trkB receptor, while pro-BDNF preferentially binds to the p75 receptor. The activation of trkB initiates a number of intracellular cascades involved with cellular survival, growth and differentiation, such as the PI3K/Akt, MEK/ERK and PLC γ /PIP₂ signaling systems [12–14]. Along with slow effects that require protein synthesis, BDNF exerts rapid signaling events that regulate membrane potential, synaptic transmission and activity-dependent synaptic plasticity [15]. For instance, TrkB–MEK/ERK activation can induce phosphorylation of the synaptic vesicle protein synapsin, thereby increasing glutamate and GABA release [16]. Moreover, synaptic strength is increased in the presence of BDNF owing to increased ion influx through NMDA receptors [17]. Thus, the ability of BDNF to regulate synaptic plasticity and the recent hypothesis suggesting that mood disorders are associated with alterations in information processing within neural networks [18] have raised the possibility that the regulation of the BDNF signaling pathway may be relevant to disease mechanisms and the development of future medications for the treatment of mood disorders [3,19].

A number of studies reported decreased BDNF levels in manic and depressive episodes [20,21], and this may have a direct effect on the pathophysiology of BD. In fact, it is now recognized that BD has a long-term outcome much less favorable than previously thought, with incomplete recovery between the episodes, cognitive impairment and functional decline [22]. Therefore, it is not appropriate to rely only on episodic alterations to fully explain the pathophysiology of BD. Impairments in neuronal plasticity and resilience could be the neuropathological hallmark of BD, corresponding to more enduring changes in the brains of patients. Morphometric studies have demonstrated that patients with BD have enlargement of the third and lateral ventricles, and reduced gray matter volumes of orbital and medial prefrontal cortices, ventral striatum and mesotemporal cortex, as well as an increase of the size of the amygdala [23]. Notably, some authors reported that such neuroanatomical changes tend to be more pronounced with repeated episodes [24]. Apart from neuroanatomical change, impairment in cognitive function has also been demonstrated in manic,

depressed as well as euthymic bipolar patients [25–27]. Such impairment seems to be related to indicators of the severity of the disease, such as the presence of psychotic symptoms, longer duration of illness and higher number of manic episodes [28].

In the present review, evidence of modulation of BDNF levels by psychosocial stress is presented. Such data are examined in the light of the neuroanatomical changes reported in BD. The potential use of BDNF as a marker of neuronal dysfunction is discussed and the possible relationship between changes in BDNF and the brain alterations reported in BD patients is highlighted.

BDNF & psychosocial stress

Epidemiological studies and clinical trials with large samples have revealed that stress and emotional trauma are associated with increased risk of psychopathology [29] and attempted suicide [30], particularly when experienced early in life [31]. Stressful life events are frequently associated with the development and progression of mood disorders [32]. Childhood maltreatment strongly predicts poor psychiatric and physical health outcomes in adulthood, and these individuals are more likely to become persistent users of medical care and emergency services [33]. Despite the consistent association of traumatic events and an adverse course of psychiatric illness, little is known about neurobiological mediators of this interaction. Recent evidence suggests that BDNF may be a potential candidate.

Unlike other growth factors which are secreted primarily via constitutive pathway, BDNF is preferentially sorted into a regulated pathway that secretes BDNF in response to neuronal activity [4]. This characteristic of BDNF supports and suggests a role for BDNF in experience-dependent processes during the formation and plasticity of circuits in the brain. Numerous pre-clinical studies have documented that stress decreases the expression of BDNF [4]. Early life events may have long-term effects in repeated activation of stress-responsive biological mediators and BDNF is believed to counteract the negative impact of stress hormones. In fact, it has been suggested that prenatal conditions may compromise cognitive function in adult life, in part, by altering BDNF expression in the hippocampus [34]. In an animal model of maternal separation, levels of BDNF are reduced in the brain. Furthermore, BDNF levels and genes have been implicated in mood disorders [35] and trauma [32]. A recent report from Savitz *et al.* showed that scores on the childhood sexual abuse scale were negatively associated with memory performance and that the low-activity BDNF-met allele interacted with sexual abuse scores to result in reduced memory test performance in adults recruited from BD families [36]. Kaufman *et al.* reported a three-way interaction between the met allele of BDNF and two short alleles of serotonin transporters, which was observed only in those with childhood maltreatment; the highest depression scores were associated with the presence of all three alleles [37]. In a BD sample, those with a history of traumatic experiences had lowered

serum BDNF (FIGURE 1) [38]. A recent report suggested that higher IQ scores were associated with a decreased risk of exposure to traumatic events and of post-traumatic stress disorder (PTSD) [39]. It is plausible that cognitive deficits mediated by changes in neurotrophins (BDNF) after a major traumatic situation contribute to a vicious cycle leading to an increase in morbidity and to a worse outcome, as observed in those exposed to childhood traumatic events.

In preclinical studies, BDNF expression has been shown to be regulated by stress responsive corticosteroids [40]. The interaction between BDNF and corticosteroids appears to play a key role in the environmentally mediated vulnerability to psychopathology [22]. Early exposure to traumatic life events and PTSD, as well as depression, has been associated with hypothalamic–pituitary–adrenal (HPA) axis dysfunction [41] and enduring stress response alterations [42]. In fact, a recent article from Schule and colleagues showed that patients with the BDNF met/met polymorphism had higher HPA axis activity during the dexamethasone/corticotropin-releasing hormone test [43]. Glucocorticoids and mediators of stress interact with neurotransmitter systems resulting in neuroplastic alterations seen in the hippocampus, amygdala and prefrontal cortex (PFC) [44]. For instance, chronic stress in animal models is related to abnormal neuronal remodeling in the PFC [45–47], particularly in glial cells [48] and the amygdala [49]. Structural and functional MRI studies in depression and Cushing's disease, as well as anxiety disorders provide evidence that the human brain may be similarly affected [50]. Consistent with these findings, two independent studies found that stress induced by immobilization diminished hippocampal BDNF mRNA in rodents [51,52].

Studies have also reported smaller hippocampal volumes in patients with early-life stress and child sexual abuse. Depressed women with a history of child abuse have an 18% smaller left hippocampal volume than nonabused women [53]. Remarkably, these apparent differences in hippocampal size may be reversible with antidepressant treatment, consistent with a function of neurotrophic factors in synaptic plasticity in the hippocampus [54]. Taken together, these data suggest that BDNF-related neuronal plasticity may be an important mediator of the effects of psychosocial stress on psychopathology.

Psychosocial stress, episode recurrence & brain rewiring

Adaptive plasticity is seen in response to acute and chronic stress, as indicated by synaptic and dendritic remodeling, neurogenesis and atrophy of neural structures, particularly in the PFC and hippocampus [44,55]. Some of the changes in

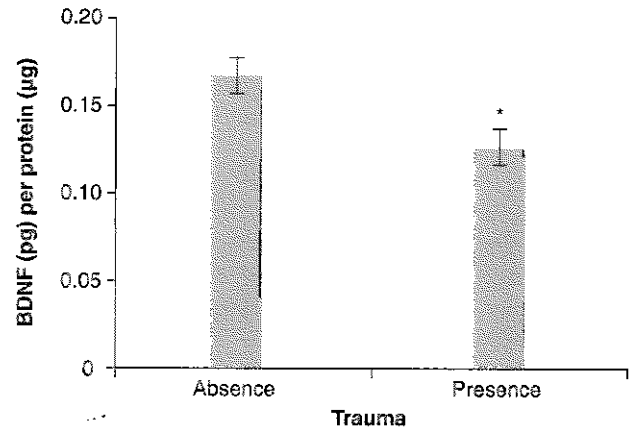


Figure 1. BDNF levels in the presence or absence of trauma in bipolar patients. * $p = 0.002$.

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brain morphology described to be associated with chronic stress have also been reported in patients with BD. It is noteworthy that some of the growth factors that are altered by stress have also been shown to be altered in BD. This is particularly true in the case of BDNF [56]. Decreased serum BDNF levels during both manic and depressive episodes have recently been demonstrated. Moreover, BDNF levels were negatively correlated with severity of mood symptoms (FIGURES 2 & 3) [20,21]. In addition, the BDNF val66met polymorphism is associated with impaired cognitive performance [57] and increased risk of rapid cycling [58,59] in BD patients. Euthymic patients (either val/val or met carriers) have similar serum BDNF levels in comparison with controls, suggesting that the normalization of BDNF levels may be associated with mood stability [60].

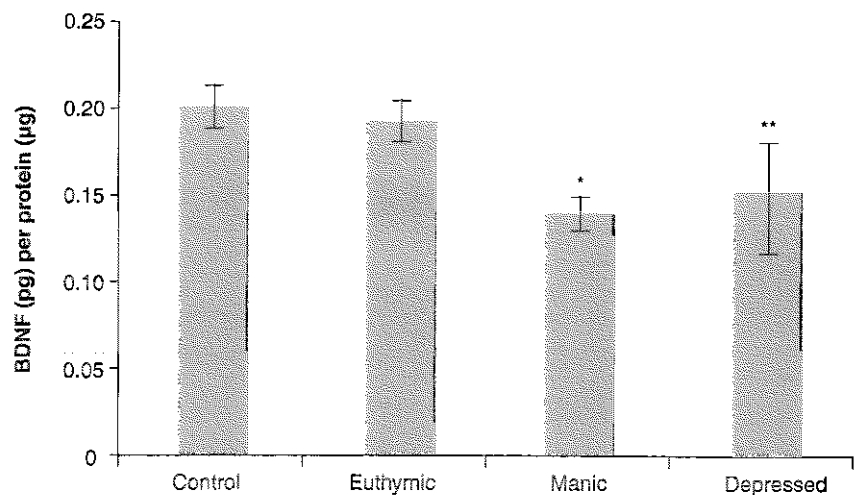


Figure 2. Serum BDNF levels in bipolar disorder patients and healthy controls.

* $p = 0.019$; ** $p = 0.027$.

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Interestingly, we found that serum neurotrophin-3 and GDNF are increased during acute mood episodes [61,62], which may indicate a compensatory response to BDNF decrease. We are tempted to speculate that such episode-related changes in neurotrophins may help to explain some of the brain structural changes that take place in BD patients. Such changes would include enlargement of amygdala and reduction in neuronal and glial size in the dorsolateral PFC (DLPFC) [63].

Chronic stress is known to induce amygdala hyperactivity, enhancing amygdala-dependent unlearned fear, fear conditioning and aggression [64]. Similarly, many of the symptoms experienced by patients with BD appear to be associated with abnormalities in emotional processing which involves amygdala circuitry. In this same vein, an enlargement of the amygdala has been described as one of the most prominent abnormalities in BD [65]. In addition to structural changes in this circuitry, functional neuroimaging studies indicate increased activity in the amygdala during mood episodes [66,67]. Data from amygdala-dependent tasks, such as facial recognition, demonstrated that manic and depressed subjects identify facial expressions less accurately than do euthymic bipolar or healthy comparison subjects [68]. A recent study using an amygdala-related cognitive task showed that bipolar patients lose the ability to confer salience to emotionally bound information [69]. In this study, patients with BD mislabeled 'neutral' information as 'emotional'. Accordingly, bipolar patients showed a blunting of the physiological pattern of increased memory performance for emotionally bound information, as

compared with what is seen in normal volunteers [70]. These findings suggest that amygdala-related circuits seem to be overactive but dysfunctional in patients with BD. As circuits related to the amygdala seem to account, at least in part, for conferring the emotional valence of experiences [65], it may be possible that the gate system to code experiences as stressful is overactive and defective in BD patients. Such malfunctioning would render bipolar patients more vulnerable to stress and its neurobiological consequences.

The PFC is a key brain region involved in the regulation of emotional behavior, executive function and fear extinction. This area is sensitive to the remodeling effects of stress and morphological changes in this particular brain region may mediate, at least in part, some affective changes observed after prolonged exposure to stress [71]. There are several indicators of structural and functional frontal lobe abnormalities in BD, such as in the anterior cingulate and subgenual PFC [40]. These findings are consistent with the cognitive deficits found in BD, especially those in executive function [27]. In addition, post-mortem studies have reported decreased glial cells in the subgenual [63,72] and in the DLPFC [63,73], and decreased number of pyramidal neurons in the DLPFC in individuals with BD [74]. Consistent with these neuropathological findings, proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) studies showed decreased N-acetyl-aspartate (NAA; a marker of neuronal viability) in the orbital frontal cortex [75] and in the DLPFC [76] of BD patients. The PFC is related to an overall set of executive functions that people initiate when facing stress. These self-regulatory processes that are volitionally and intentionally enacted specifically in response to stress are called coping [77].

The majority of methodologically well-designed studies failed to demonstrate differences in hippocampal volumes between BD patients and healthy controls [78]. Conversely, an age-group comparison (BD adolescents vs healthy control adolescents) demonstrated that hippocampal volume was significantly decreased in BD adolescents, whereas such a difference was not observed between adult BD and adult healthy controls. Frazier *et al.* compared children and adolescents with BD against matched healthy controls and found that patients had smaller hippocampal volumes [79]. In a recent study, Lupien *et al.* assessed hippocampal volume in 177 healthy men and women aged from 18 to 85 years of age and showed that smaller hippocampal volume attributed to the aging process in previous studies could in fact represent hippocampal volume determined early in life [80]. They also report that within similar age groups, the percentage of difference in hippocampal volume between the individuals with the smallest quartile volume and the group average is greater than the percentage of difference reported to exist between psychiatric populations and normal controls in recent meta-analyses. They raise the possibility that predetermined interindividual differences in hippocampal volume in humans may influence the vulnerability for age-related cognitive impairments or psychopathology throughout the lifetime.

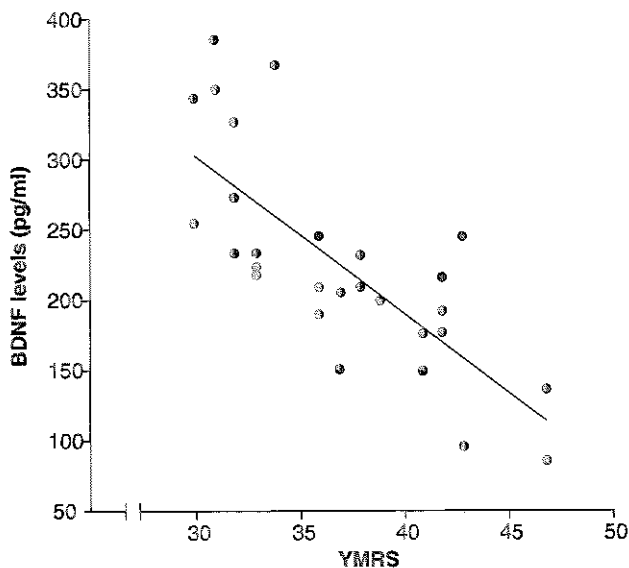


Figure 3. Correlation between YMRS values and plasma BDNF levels in unmedicated manic patients ($p = 0.001$; $r = 0.78$).

YMRS: Young Mania Rating Scale.

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Corroborating with the idea of psychosocial stress and/or episode recurrence on brain rewiring are data suggesting that there was an association between premorbid IQ score and risk of BD, but lower IQ was associated with increased risk of schizophrenia, severe depression and other nonaffective psychoses [81]. In addition an important population-based historical cohort study with 555,326 adolescents born in Israel, which used record linkage for psychiatric hospitalization during an 8–17-year follow-up period, found that lower than expected IQ at age 17 years was associated with increased risk for schizophrenia, but was not associated with BD, major depression or anxiety disorder even after controlling for potential confounders [82]. These findings suggest that cognitive impairment in BD could be related with nurture rather than nature (FIGURE 4).

BDNF as a marker of neuronal dysfunction

The expression of BDNF is high in the cerebral cortex and hippocampus, brain areas that are known to regulate complex brain functions such as memory and emotion. It has been demonstrated that BDNF plays a key role in long-term potentiation (LTP), one of the most accepted models of learning and memory. For instance, the administration of exogenous BDNF to genetically modified mice deficient in BDNF or its receptor TrkB rescue the impairment in LTP processes [83]. In addition, transgenic mice lacking BDNF or TrkB demonstrate poorer performance than their wild-type littermates in the Morris water maze, a hippocampal-dependent spatial learning task [84]. These and other studies suggest that abnormalities in the BDNF-signaling system might be implicated in the cognitive decline observed in certain neuropsychiatric disorders, such as BD [14], major depression [40] and schizophrenia [85].

It has been demonstrated by some [86–88] but not all [89,90] genetic studies that the BDNF val66met polymorphism may confer susceptibility to BD. This may be particularly true for certain subtypes of BD, since two independent studies with large sample sizes showed that the val66met polymorphism is associated with increased risk for rapid cycling [58,59]. In addition, a number of studies found that this gene polymorphism is associated with differential response to lithium prophylaxis [91], poorer memory performance [92] and decreased prefrontal cortical volume [93] in individuals with bipolar disorder. Likewise, a ¹H-MRS study recently demonstrated that BD subjects that are met-carriers for the BDNF val66met polymorphism have lower, while val/val subjects have higher creatine plus phosphocreatine levels in the left DLPFC [94]. This finding is consistent with a number of studies conducted in healthy humans showing that the BDNF val66met polymorphism is associated with altered hippocampal memory and function [85,95], and decreased hippocampal [96,97] and prefrontal cortical volumes [97,98]. Taken together, these studies support the notion that the BDNF val66met polymorphism affects brain anatomy and function in humans [99], and further suggest that this polymorphism may be implicated in the pathophysiology of BD. However, it is not

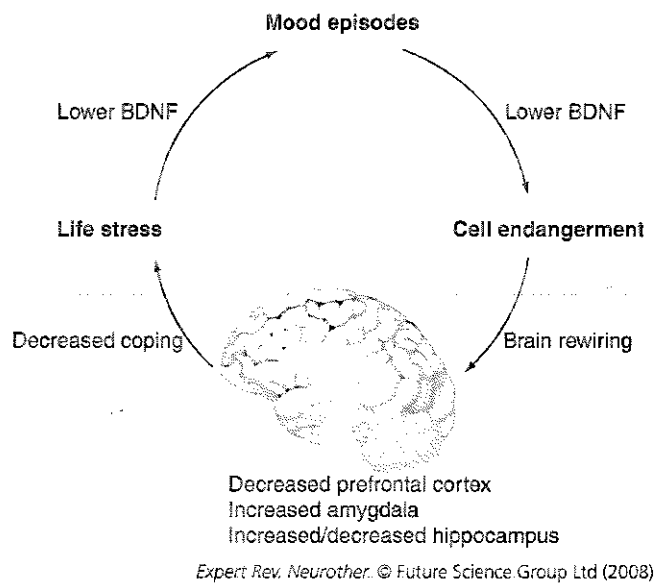


Figure 4. Proposed relationship between life stress, lower BDNF, recurrent mood episodes and brain rewiring in bipolar disorder.

clear how such polymorphism would be mechanistically related to structural brain changes. While the search for the exact mechanisms underlying impaired BDNF-signaling transmission are underway, it has been proposed that it might include fewer dendritic branching, lower synaptic efficacy, decreased neurogenesis and increased cell death [99–101]. Consistent with this hypothesis, knock-in BDNF^{met/met} mice exhibit a number of brain abnormalities, such as decreased hippocampal volume and decreased dendritic complexity in the dentate gyrus [11]. Notably, these structural changes were accompanied by impairment in contextual-dependent fear conditioning, a hippocampal-dependent memory test.

There is a growing body of data indicating that BDNF is associated with the mechanism of action of antidepressants and mood stabilizers [102,103]. More specifically, it has been clearly established that chronic antidepressant treatment increases BDNF expression in the cerebral cortex and hippocampus, as reviewed by Schimdt and Duman [40]. In addition, the phosphorylation of TrkB receptors is necessary for antidepressant-induced response in the forced swim test [104]. Conversely, Shirayama *et al.* demonstrated that the blockage of BDNF signaling with either a tyrosine receptor kinase or a MEK/ERK inhibitor attenuates the antidepressant effects of BDNF [105]. In this same line, chronic administration of lithium and valproate increases BDNF content in the rat hippocampus and PFC (FIGURE 5) [106,107]. It is worth mentioning that the behavioral effects of BDNF may be opposite, depending on the brain region. Notably, infusion of BDNF into the ventral tegmental area induces behavioral despair in the forced swimming test, a depressive-like phenotype [108]. Furthermore, the depressive

behavior induced by social defeat stress is prevented by blockage of BDNF in the ventral tegmental area [109]. These results are opposite to what is found in the hippocampus and indicate that the effects of BDNF on depressive-like behavior are region specific. Therefore, a deeper understanding about the molecular determinants involved in BDNF-signaling cascades may provide a means for the development of novel agents for the treatment of BD.

The potential use of BDNF as a biomarker of neuronal dysfunction deserves further discussion. In the peripheral blood, BDNF can be stored and released by platelets, lymphocytes and endothelial cells [110–112]. Preclinical studies found that BDNF can cross the BBB, moving from the periphery to the brain and *vice versa* (FIGURE 6) [113], and that there is a strong correlation between blood and brain BDNF levels [114]. Dawood *et al.* have recently proposed an alternative technique of assessing brain BDNF production in individuals with major depression by collecting blood from the brachial artery and internal jugular vein simultaneously [115]. In this latter study, subjects with high risk of suicide had a lower veno-arterial BDNF concentration gradient than those with low suicide risk, suggesting that suicide risk may be associated with reduced BDNF overflow from the brain. However, this technique is at best indirect and additional studies are needed to better determine whether peripheral BDNF findings can indeed represent what is happening in the human CNS. In this regard, a recent ^1H -MRS study investigated the correlation between serum BDNF and NAA levels in the anterior cingulate cortex and hippocampus of 36 healthy volunteers [116]. The authors found that peripheral BDNF positively correlated with NAA levels in the anterior cingulate cortex but not in the hippocampus, indicating that serum BDNF may reflect, at least in part, prefrontal neuronal integrity in the living human brain [116]. Therefore,

although the use of peripheral BDNF levels as a biomarker is promising, there is a need to prospectively investigate BDNF levels during acute mood episodes and in periods of remission to better determine the usefulness of this method in individuals with BD.

Expert commentary

Current diagnostic criteria for major mood disorders are essentially based on clinical symptomatology, and the need for biological markers as complements in diagnostic and prognostic purposes has been extensively recognized. In this search, recent evidence suggests that BDNF might be a potential marker. The fact that serum BDNF levels are decreased during manic and depressive episodes, whereas euthymic BD subjects have similar serum BDNF levels than healthy controls [20], and that serum BDNF levels are negatively correlated with manic and depressive symptoms [20,21] strongly suggest that the normalization of BDNF levels may be associated with clinical stabilization. However, these assumptions are based on case-control studies and longitudinal studies are clearly necessary to test this hypothesis in individuals with BD. Nevertheless, a number of prospective studies conducted in major depressive (unipolar) disorder demonstrated with consistency that serum levels of BDNF increase after successful antidepressant treatment, as reviewed by Duman and Monteggia [35]. Another limitation of this hypothesis is that it is based fundamentally on studies conducted with animal models or human peripheral blood, and the presumption that such findings might be occurring in the human brain needs to be confirmed. In this regard, a post-mortem study showing that individuals under antidepressant medications at the time of death had higher hippocampal BDNF expression than individuals not on antidepressants further supports the

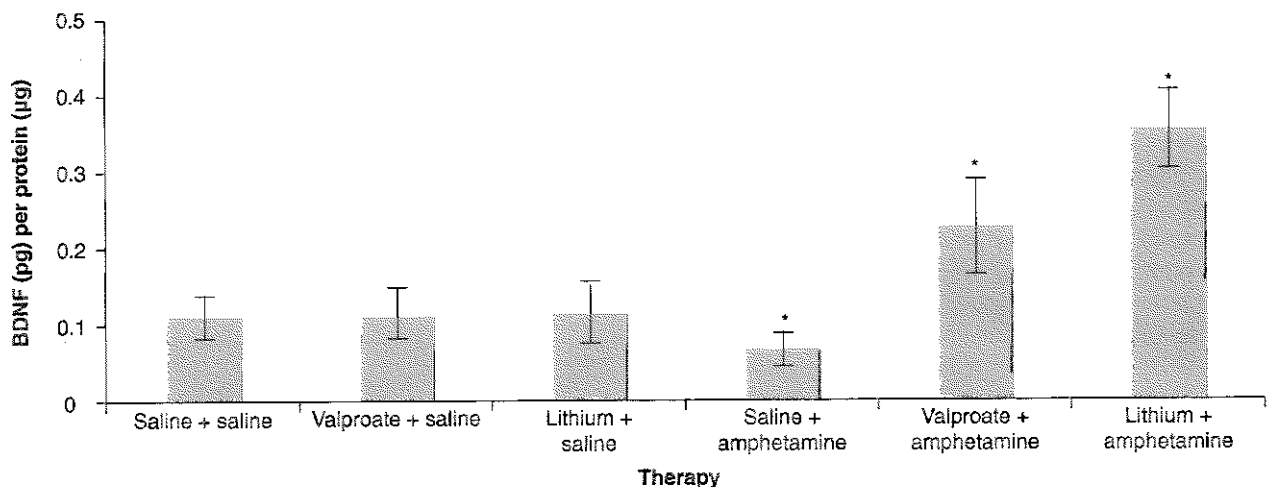


Figure 5. BDNF levels in rat hippocampus after 7 days of treatment with mood stabilizers and 7 days of mood stabilizers and amphetamine. * $p < 0.05$.

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role of BDNF in the treatment of mood disorders [117]. We are not aware of any technique that allows the direct measurement of BDNF in the human brain *in vivo*. The development of specific ligands for TrkB receptors could be extremely valuable in future PET studies in humans.

Several transversal and longitudinal brain imaging studies demonstrated that lithium treatment increases cerebral cortical gray matter content and hippocampal volume in patients with BD [118–123]. Although it is not possible to directly measure BDNF content in the human brain *in vivo* to date, the authors presumed that these findings may be related to neurotrophic effects of lithium, especially by increasing cerebral BDNF [122,123]. This hypothesis is largely supported by studies in rodents showing that lithium, valproate and antidepressants increase BDNF levels in the hippocampus and PFC, brain regions known to be involved with mood regulation [106,107,124]. Thus, we believe that substances that are able to increase cerebral BDNF expression have the potential to affect human affective responses and exert mood stabilizing effects, and that this rationale should be included in the investigation of new treatment approaches. In this regard, recent new promising drugs in the field of BD, such as PKC inhibitors [125] and glutamate modulators [126], may regulate the expression of BDNF through downstream effects on transcriptional factors and gene expression.

Finally, genetics is another promising field of research with a potential to unravel individual differences in treatment response related to distinct genetic predisposition. For instance, while a recent study demonstrated that the BDNF val66met polymorphism is not associated with antidepressant-induced mania [127], another study found that individuals val/met for this polymorphism may be better responders to lithium prophylaxis [91]. Obviously, longitudinal studies are necessary to better determine the role of the val66met polymorphism in treatment response. In addition, studies addressing the involvement of other single nucleotide polymorphisms of the *BDNF* gene, as well as the interaction between BDNF and other functional genes are warranted.

Five-year view

BD is among the oldest and most stable clinical syndromes in medicine. However, the complete clinical description was carried out by Kraepelin, 100 years ago [128]. Since then, the differentiation between schizophrenia and BD owes much to Kraepelin's early descriptions, which emphasized that cognitive decline was a central feature of schizophrenia. However, current research has challenged the classical notion that schizophrenia follows a deteriorating course after the initial episodes whereas cognition tended to be spared in the course of BD. Currently, the cognitive impairment that takes place among BD patients has been well described and it differs from the impairment seen among patients with schizophrenia in various aspects, including the pattern of appearance. The cognitive

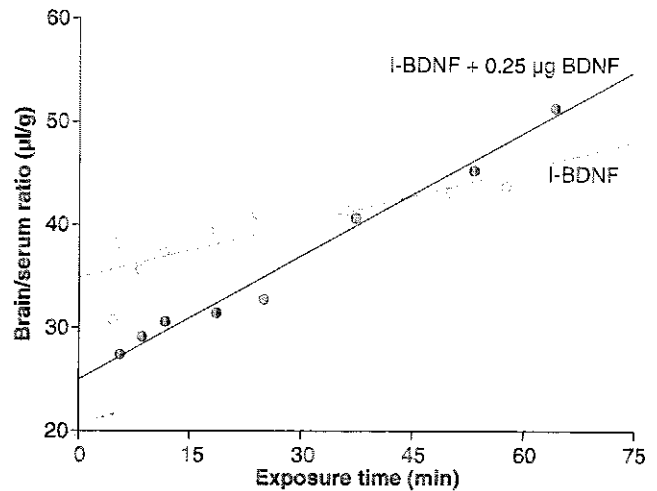


Figure 6. Influx of ^{125}I -BDNF after intravenous injection, with or without unlabeled BDNF in the injection solution.

There was a statistically significant difference between the two regression lines. I-BDNE: ^{125}I -BDNE only ($r^2 = 0.70$); I-BDNF + 0.25 mg BDNE ($r^2 = 0.98$).

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impairments seen in schizophrenia follow a pattern described as 'one hit', meaning that the period of approximately 2 years that antecedes the first episode and during the first episode would be the time where cognition would decline and remain stable thereafter [129]. In a differential manner, recent findings suggest that the cognitive impairment in BD occurs in part with the occurrence of new episodes [MARTINEZ-ARAN *ET AL.*, PERS. COMM.]. This has led to the notion that cognitive impairment occurs as a consequence of cumulative episodes [130]. It is noteworthy that lowering in serum BDNF has been reported in the context of BD episodes. Thus, a plausible explanation is that the cognitive impairment related to BD episodes takes place as a consequence of neurotrophic changes set in motion by mood episodes or subsyndromal mood symptoms.

The rationale summarized earlier has the potential to produce a shift of paradigm in the treatment of BD. While controlling acute symptoms of BD may have been the initial goal of clinicians in the past few decades, the notion that episodes may be self-engendered has brought to the field a more cautious approach [131]. Accordingly, without a proper quenching of episodes, the propensity to develop further episodes would be inflated [132]. Recent findings suggesting that each new episode may carry the potential to engender further cognitive damage, may lead the field to a stronger prophylactic attitude. If one considers that preventing episodes may be a means to avoid deleterious changes in the brain and the progression of the disorder, the approach to the treatment of BD would then resemble the attitude of clinicians in the field of epilepsy, where patients tend to be medicated in terms of achieving maximal protection and solid prophylaxis. A sharper focus on avoiding new episodes does not exclude the permanent trade-off

between improving symptoms and avoiding unwanted side effects. However, it puts a stronger emphasis in efficacy rather than tolerability. It is reasonable to foresee such a trend developing in the field of BD, particularly in the case of patients who have already experienced manic and/or psychotic episodes.

As far as changes in neurotrophins are concerned, current research conducted in our laboratory and others is searching for the clinical applications of serum BDNF levels as a marker of illness activity, in the same way that serum tests with low specificity are used as indicators of illness activity as in the case of rheumatic disorders. Moreover, we and other groups are currently exploring the potential of BDNF as an indicator of response to medication. In this sense, it seems reasonable that early and more pronounced increases in serum BDNF levels would perhaps predict an earlier or more complete resolution of acute episodes.

Another potential application of neurotrophins and other biomarkers would be to differentiate schizophrenia from BD. In this regard, we have recently described very promising results showing a differential profile of serum neurotrophins among schizophrenia and BD patients [133]. In this latter study, we found that serum BDNF levels were increased in SZ subjects as compared with BD patients and healthy controls. In addition, the use of peripheral markers may be potentially useful for the clinical staging of BD [134]. As mentioned earlier, the cognitive and functional impairment that takes place in BD patients suggest that apart from transversal phenomenological differences, BD patients may vary in their degree of severity and response to medication according to the stage of the disorder. Berk *et al.* have put forward the notion that patients with BD could be grouped into stages of severity, ranging from populations that are at risk for developing the disorder up to patients who despite being treated remain symptomatic without returning to a baseline state [134]. In this sense, we would expect much more

severe and permanently symptomatic patients to retain some of the changes reported in acutely ill BD patients, such as lowering in BDNF levels.

Conclusions

Converging evidence points to an important role of BDNF in the neuronal plasticity changes that take place in BD. BD patients have been reported to display amygdala enlargement and reduced size of PFC [135]. There are some reports of reduced hippocampal size in BD, however, such data have not been so well established [78]. Similar anatomical changes have been reported in animal models of chronic stress [64]. Thus, mood episodes and chronic stress may share some similarities in their effects in the brain. Both mood episodes and chronic stress have been associated with reduced levels of BDNF. In this sense, both chronic stress and mood episodes could set in motion the same type of detrimental changes in the brain. Recent evidence suggests that an interaction between stress, BDNF activity and cognitive functioning may indeed take place in BD [36,43]. Accordingly, the fact that both trauma and chronic stress are associated with less neurotrophic activity via BDNF is coupled with episode-induced lowering in BDNF levels found among BD patients. Clinically, such a summation of effects would translate into the more severe forms of BD which have been described among BD patients with a history of trauma [56].

The assessment of serum BDNF levels may offer an important tool to assess the biological findings associated with mood episodes. BDNF assessments could also provide a means of early identification of treatment response. Theoretically, the fact that both depressive and manic episodes are associated with lower BDNF levels may offer an explanatory link of cumulative mood episodes and worse cognitive performance [28], and ventricle enlargement among BD patients [24]. Thus,

Key issues

- Changes in cell resilience and connectivity are the main neuropathological findings in bipolar disorder (BD). Such findings point to a central role of neuroplastic changes in the pathophysiology of BD.
- The progression of BD from a prodromic phase into a clinically overt presentation and up to refractory cases may be related to neuroplastic changes that occur in the context of recurrent mood episodes.
- Mood episodes and intermittent life stress would engender a brain sculpting pattern that leads patients to be more vulnerable to environmental stress (via amygdala overactivity) and less competent to set in motion the coping strategies orchestrated by the prefrontal cortex.
- Neuroplastic changes occurring in the context of BD would lead patients to be more prone to develop further episodes and to develop interval dysthymia, cognitive impairment and psychiatric comorbidities.
- Serum BDNF levels are reduced in acute mood episodes and normalized in euthymia. Thus, the assessment of serum BDNF levels may offer a means to identify the activity of BD.
- Serum BDNF levels increase with the use of mood stabilizers and therefore may be useful in the early identification of responders to a given intervention.
- Drugs that are able to increase BDNF levels and protect against the detrimental changes related to mood episodes and chronic stress deserve attention as potential targets in the development of new interventions for the treatment of BD.
- The investigation of the role of neurotrophins in the cognitive decline and neuroanatomical changes that take place in BD may help to foster the understanding of the pathophysiology of BD and help create new avenues for effective treatment and prophylaxis.



evidence suggests that stress and mood episodes can produce deleterious effects in the brain, which may take place via reduced neurotrophic activity. In terms of a rationale for drug development, interventions designed to increase BDNF expression in the brain may deserve further attention as a means to treat BD. It should be highlighted that this neuronal plasticity model in BD fits with the notion that preventing the neurotoxic effects of chronic stress and quenching mood episodes may be the best way to prevent a deteriorating course of BD.

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