ILL Document Delivery

REG-14800223

SDUSOD

NLM -- W1 EX520M (Gen); E-Journal w/ILL access

The University of South Dakota
USD University Libraries-ILL
414 E Clark St
Vermillion, SD 57069

ATTN:
PHONE: 605-677-5349
FAX: 605-677-5488
E-MAIL: ill@usd.edu

SUBMITTED: 2009-10-13 16:08:31
PRINTED: 2009-10-14 10:35:13
REQUEST NO.: REG-14800223
SENT VIA: DOCLINE
DOCLINE NO.: 27940523
OPAC NO.: AAAOANN

REG | Copy | Journal | NEED BEFORE: 2009-10-25

TITLE:	EXPERT REVIEW OF NEUROTHERAPEUTICS
PUBLISHER/PLACE:	Future Drugs Ltd. London :
VOLUME/ISSUE/PAGES:	2008 Jul;8(7):1101-13 1101-13
DATE:	2008
AUTHOR OF ARTICLE:	Kapczinski F;Frey B;Kauer-Sant'Anna M;Grassi-Oliveira R
TITLE OF ARTICLE:	BRAIN-DERIVED NEUROTROPHIC FACTOR AND NEUROPLASTIC
ISSN:	1473-7175
OTHER NUMBERS/LETTERS:	Unique ID.: 101129944 27940523 18590480
SOURCE:	PubMed
MAX COST:	$15.00
COPYRIGHT COMP.:	Guidelines
CALL NUMBER:	W1 EX520M (Gen); E-Journal w/ILL access
NOTES:	GMR-RL (Ariel 4.1.1) Please do NOT fax or send through U.S. Mail.

ILL Document Delivery

REG-14800223

REQUESTER INFO:	Henke, Amanda
DELIVERY:	Ariel: 192.236.50.225
REPLY:	Mail:

KEEP THIS RECEIPT TO RECONCILE WITH BILLING STATEMENT
For problems or questions, contact NLM at http://wwwcf.nlm.nih.gov/ill/ill_web_form.cfm or phone 301-496-5511.
Include LIBID and request number.

NLM Collection Access Section, Bethesda, MD

Expert Reviews

Brain-derived neurotrophic factor and neuroplasticity in bipolar disorder

Expert Rev. Neurother. 8(7), 1101–1113 (2008)

Flavio Kapczinski†, Benicio N Frey, Marcia Kauer-Sant'Anna and Rodrigo Grassi-Oliveira

†Author for correspondence
Bipolar Disorder Program & Molecular Psychiatry Unit, Hospital de Clinicas, Federal University – UFRGS, Porto Alegre, Brazil
kapcz@terra.com.br

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

 10.1586/14737175.8.7.1101 ISSN 1473-7175

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 PLCγ/PIP_2 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 amygdale [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 preclinical 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

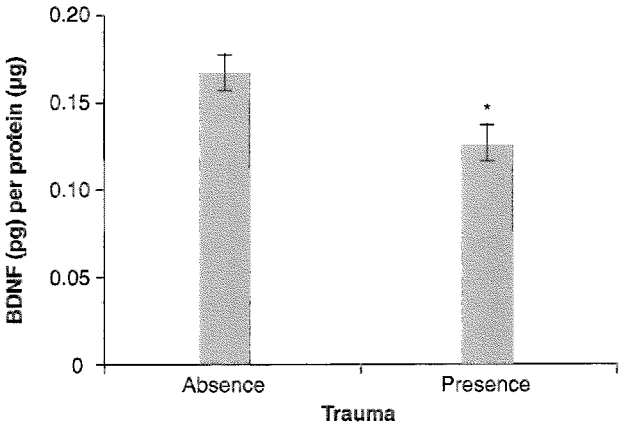


Figure 1. BDNF levels in the presence or absence of trauma in bipolar patients. *p = 0.002.
Reproduced with permission from [38] © (2007) Blackwell Munksgaard Publishing.

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].

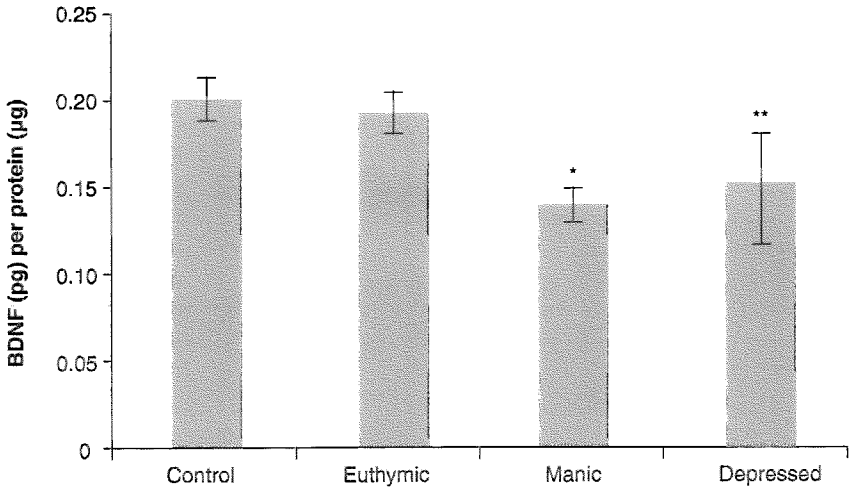


Figure 2. Serum BDNF levels in bipolar disorder patients and healthy controls. *p = 0.019; **p = 0.027.
Reproduced with permission from [20] © (2006) Elsevier.

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.

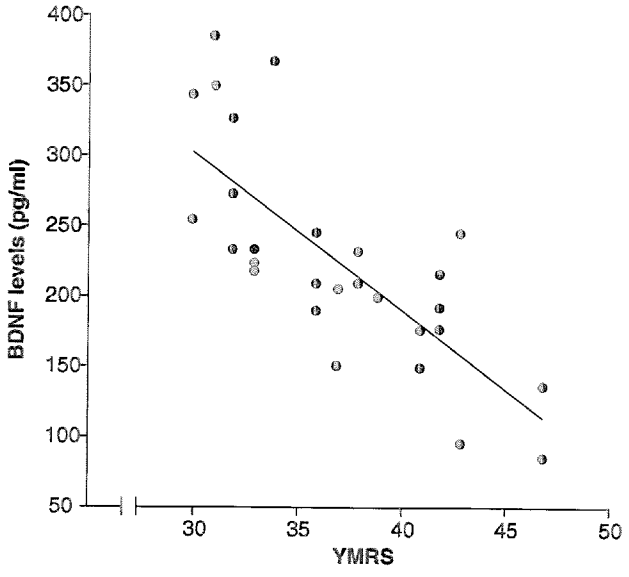
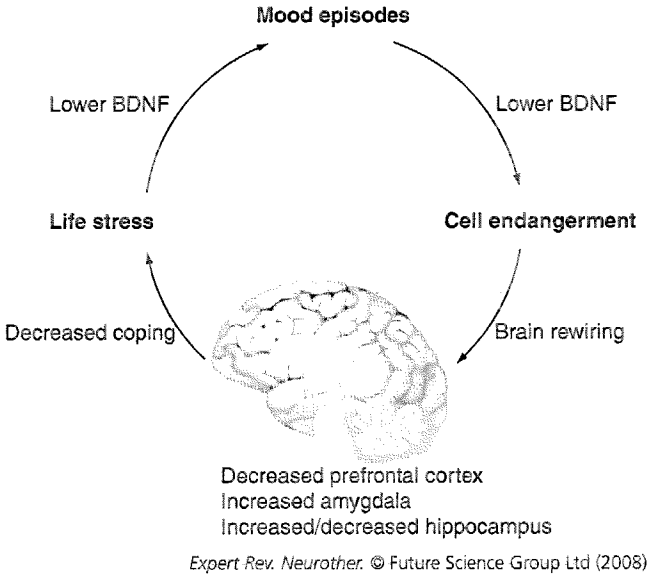


Figure 3. Correlation between YMRS values and plasma BDNF levels in unmedicated manic patients (p = 0.001; r = 0.78).
YMRS: Young Mania Rating Scale.
Reproduced with permission from [20] © (2007) Elsevier and Society of Biological Psychiatry.

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, postmortem 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}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.

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).



Expert Rev. Neurother. © Future Science Group Ltd (2008)

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

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 ^{1}H-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 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 ^{1}H-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

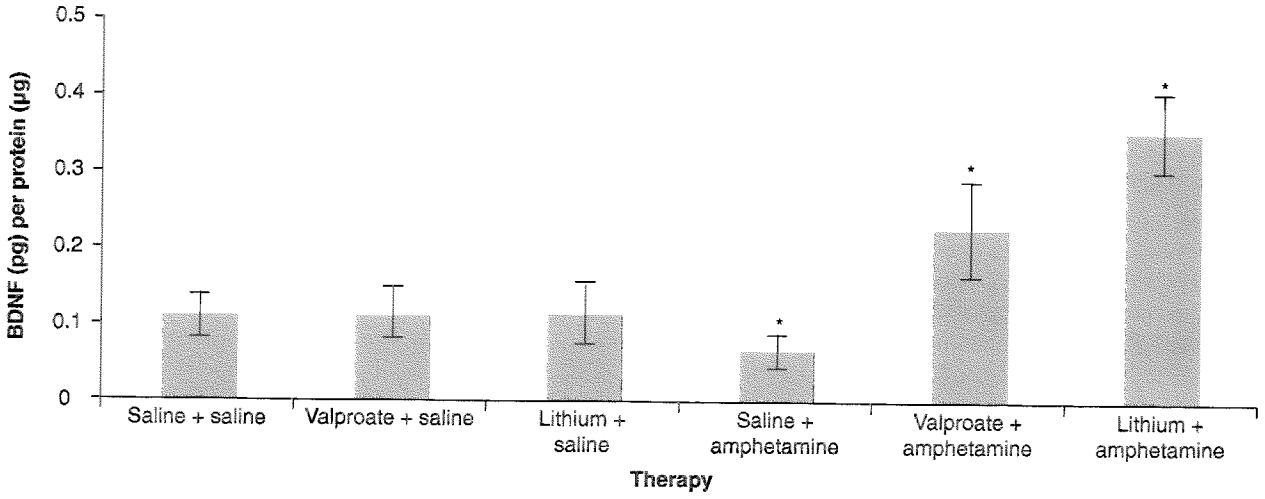


Figure 5. BDNF levels in rat hippocampus after 7 days of treatment with mood stabilizers and 7 days of mood stabilizers and amphetamine. *$p < 0.05.
Reproduced with permission from [107] © (2006) Elsevier.

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

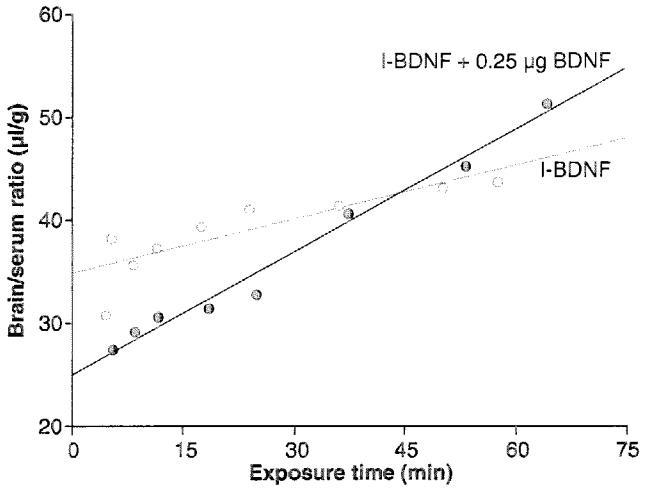


Figure 6. Influx of ^{125}I-BDNF after intravenous injection, with or without unlabeled BDNF in the injection solution.
There was a statistically significant difference between the two regression lines. I-BDNE: ^{125}I-BDNE only ($r^2 = 0.70$); I-BDNF + 0.25 mg BDNE ($r^2 = 0.98$).
Reproduced with permission from [113] © (1998) Elsevier.

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 lead 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 patents, 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.

Financial & competing interests disclosure

Flavio Kapczinski is a NARSAD Independent Investigator. His work is supported by the Stanley Medical Research Institute and CNPq, Brazil. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Kessler RC, McGonagle KA, Zhao S *et al.* Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch. Gen. Psychiatry* 51(1), 8–19 (1994).

2 Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361(6407), 31–39 (1993).

3 Kuipers SD, Bramham CR. Brain-derived neurotrophic factor mechanisms and function in adult synaptic plasticity: new insights and implications for therapy. *Curr. Opin. Drug Discov. Dev.* 9(5), 580–586 (2006).

4 Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nat. Neurosci.* 10(9), 1089–1093 (2007).

5 Timmusk T, Palm K, Metsis M *et al.* Multiple promoters direct tissue-specific expression of the rat BDNF gene. *Neuron* 10(3), 475–489 (1993).

6 Martinowich K, Hattori D, Wu H *et al.* DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. *Science* 302(5646), 890–893 (2003).

7 Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat. Neurosci.* 9(4), 519–525 (2006).

8 Yasuda S, Liang MH, Marinova Z, Yahyavi A, Chuang DM. The mood stabilizers lithium and valproate selectively activate the promoter IV of brain-derived neurotrophic factor in neurons. *Mol. Psychiatry* (2007) (Epub ahead of print).

9 Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. *Nat. Rev. Neurosci.* 6(8), 603–614 (2005).

10 Chen ZY, Ieraci A, Teng H *et al.* Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. *J. Neurosci.* 25(26), 6156–6166 (2005).

11 Chen ZY, Jing D, Bath KG *et al.* Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* 314(5796), 140–143 (2006).

12 Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu. Rev. Neurosci.* 24, 677–736 (2001).

13 Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog. Neurobiol.* 76(2), 99–125 (2005).

14 Shaltiel G, Chen G, Manji HK. Neurotrophic signaling cascades in the pathophysiology and treatment of bipolar disorder. *Curr. Opin. Pharmacol.* 7(1), 22–26 (2007).

15 Blum R, Konnerth A. Neurotrophin-mediated rapid signaling in the central nervous system: mechanisms and functions. *Physiology* 20, 70–78 (2005).

16 Jovanovic JN, Czernik AJ, Fienberg AA, Greengard P, Sihra TS. Synapsins as mediators of BDNF-enhanced neurotransmitter release. *Nat. Neurosci.* 3(4), 323–329 (2000).

17 Levine ES, Crozier RA, Black IB, Plummer MR. Brain-derived neurotrophic factor modulates hippocampal synaptic transmission by increasing *N*-methyl-D-aspartic acid receptor activity. *Proc. Natl Acad. Sci. USA* 95(17), 10235–10239 (1998).

18 Castren E. Is mood chemistry? *Nat. Rev. Neurosci.* 6(3), 241–246 (2005).

19 Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.* 7(2), 137–151 (2006).

20 Cunha AB, Frey BN, Andreazza AC *et al.* Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. *Neurosci. Lett.* 398(3), 215–219 (2006).

21 Machado-Vieira R, Dietrich MO, Leke R *et al.* Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. *Biol. Psychiatry* 61(2), 142–144 (2007).

22 Manji HK, Quiroz JA, Sporn J *et al.* Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol. Psychiatry* 53(8), 707–742 (2003).

23 Manji HK, Duman RS. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. *Psychopharmacol. Bull.* 35(2), 5–49 (2001).

24 Strakowski SM, Adler CM, DelBello MP. Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? *Bipolar Disord.* 4(2), 80–88 (2002).

25 Martinez-Aran A, Vieta E, Reinares M *et al.* Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am. J. Psychiatry* 161(2), 262–270 (2004).

26 Thompson JM, Gallagher P, Hughes JH *et al.* Neurocognitive impairment in euthymic patients with bipolar affective disorder. *Br. J. Psychiatry* 186, 32–40 (2005).

27 Robinson LJ, Thompson JM, Gallagher P *et al.* A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J. Affect. Disord.* 93(1–3), 105–115 (2006).

28 Martinez-Aran A, Vieta E, Torrent C *et al.* Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord.* 9(1–2), 103–113 (2007).

29 Mueser KT, Rosenberg SD, Goodman LA, Trumbetta SL. Trauma, PTSD, and the course of severe mental illness: an interactive model. *Schizophr. Res.* 53(1–2), 123–143 (2002).

30 McCauley J, Kern DE, Kolodner K *et al.* Clinical characteristics of women with a history of childhood abuse: unhealed wounds. *JAMA* 277(17), 1362–1368 (1997).

31 Agid O, Kohn Y, Lerer B. Environmental stress and psychiatric illness. *Biomed. Pharmacother.* 54(3), 135–141 (2000).

32 Post RM, Leverich GS. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev. Psychopathol.* 18(4), 1181–1211 (2006).

33 Arnow BA. Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. *J. Clin. Psychiatry* 65(Suppl. 12), 10–15 (2004).

34 Gomez-Pinilla F, Vaynman S. A "deficient environment" in prenatal life may compromise systems important for cognitive function by affecting BDNF in the hippocampus. *Exp. Neurol.* 192(2), 235–243 (2005).

35 Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol. Psychiatry* 59(12), 1116–1127 (2006).

36 Savitz J, van der Merwe L, Stein DJ, Solms M, Ramesar R. Genotype and childhood sexual trauma moderate neurocognitive performance: a possible role for brain-derived neurotrophic factor and apolipoprotein E variants. *Biol. Psychiatry* 62(5), 391–399 (2007).

37 Kaufman J, Yang BZ, Douglas-Palumberi H *et al.* Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biol. Psychiatry* 59(8), 673–680 (2006).

38 Kauer-Sant'anna M, Tramontina JF, Andreazza AC *et al.* Traumatic life events in bipolar disorder: impact on BDNF levels and psychopatology. *Bipolar Disord.* 9(Suppl. 1), 128–135 (2007).

39 Breslau N, Lucia VC, Alvarado GF. Intelligence and other predisposing factors in exposure to trauma and posttraumatic stress disorder: a follow-up study at age 17 years. *Arch. Gen. Psychiatry* 63(11), 1238–1245 (2006).

40 Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. *Behav. Pharmacol.* 18(5–6), 391–418 (2007).

41 Duval F, Crocq MA, Guillon MS *et al.* Increased adrenocorticotropin suppression following dexamethasone administration in sexually abused adolescents with posttraumatic stress disorder. *Psychoneuroendocrinology* 29(10), 1281–1289 (2004).

42 Grassi-Oliveira R, Ohashi K, Polcari A *et al.* Harsh corporal punishment associated with enduring alterations in hormonal and cardiac response to stress challenge. *Biol. Psychiatry* 61, 45S (2007).

43 Schule C, Zill P, Baghai TC *et al.* Brain-derived neurotrophic factor Val66Met polymorphism and dexamethasone/CRH test results in depressed patients. *Psychoneuroendocrinology* 31(8), 1019–1025 (2006).

44 McEwen BS. Effects of adverse experiences for brain structure and function. *Biol. Psychiatry* 48(8), 721–731 (2000).

45 Maroun M. Stress reverses plasticity in the pathway projecting from the ventromedial prefrontal cortex to the basolateral amygdala. *Eur J. Neurosci.* 24(10), 2917–2922 (2006).

46 Jay TM, Rocher C, Hotte M, Naudon L, Gurden H, Spedding M. Plasticity at hippocampal to prefrontal cortex synapses is impaired by loss of dopamine and stress: importance for psychiatric diseases. *Neurotox. Res.* 6(3), 233–244 (2004).

47 Brown SM, Henning S, Wellman CL. Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex. *Cereb. Cortex* 15(11), 1714–1722 (2005).

48 Czeh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. *Neuropsychopharmacology* 31(8), 1616–1626 (2006).

49 Vyas A, Bernal S, Chattarji S. Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Res.* 965(1–2), 290–294 (2003).

50 McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism* 54(5 Suppl. 1), 20–23 (2005).

51 Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J. Neurosci.* 15(3 Pt 1), 1768–1777 (1995).

52 Ueyama T, Kawai Y, Nemoto K, Sekimoto M, Tone S, Senba E. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. *Neurosci. Res.* 28(2), 103–110 (1997).

53 Vythilingam M, Heim C, Newport J *et al.* Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am. J. Psychiatry* 159(12), 2072–2080 (2002).

54 Rattiner LM, Davis M, Ressler KJ. Brain-derived neurotrophic factor in amygdala-dependent learning. *Neuroscientist* 11(4), 323–333 (2005).

55 Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol. Psychiatry* 59(12), 1136–1143 (2006).

56 Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. *J. Psychiatr. Res.* 41(12), 979–990 (2007).

57 Rybakowski JK, Borkowska A, Czerski PM, Skibinska M, Hauser J. Polymorphism of the brain-derived neurotrophic factor gene and performance on a cognitive prefrontal test in bipolar patients. *Bipolar Disord.* 5(6), 468–472 (2003).

58 Green EK, Raybould R, Macgregor S *et al.* Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder: case-control study of over 3000 individuals from the UK. *Br. J. Psychiatry* 188, 21–25 (2006).

59 Muller DJ, de Luca V, Sicard T, King N, Strauss J, Kennedy JL. Brain-derived neurotrophic factor (BDNF) gene and rapid-cycling bipolar disorder: family-based association study. *Br. J. Psychiatry* 189, 317–323 (2006).

60 Tramontina J, Frey BN, Andreazza AC, Zandona M, Santin A, Kapczinski F. Val66met polymorphism and serum brain-derived neurotrophic factor levels in bipolar disorder. *Mol. Psychiatry* 12(3), 230–231 (2007).

61 Rosa AR, Frey BN, Andreazza AC *et al.* Increased serum glial cell line-derived neurotrophic factor immunocontent during manic and depressive episodes in individuals with bipolar disorder. *Neurosci. Lett.* 407(2), 146–150 (2006).

62 Walz JC, Andreazza AC, Frey BN *et al.* Serum neurotrophin-3 is increased during manic and depressive episodes in bipolar disorder. *Neurosci. Lett.* 415(1), 87–89 (2007).

63 Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol. Psychiatry* 49(9), 741–752 (2001).

64 McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann. NY Acad. Sci.* 1032, 1–7 (2004).

65 Phillips ML, Vieta E. Identifying functional neuroimaging biomarkers of bipolar disorder: toward DSM-V. *Schizophr. Bull.* 33(4), 893–904 (2007).

66 Yurgelun-Todd DA, Gruber SA, Kanayama G, Killgore WD, Baird AA, Young AD. fMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord.* 2(3 Pt 2), 237–248 (2000).

67 Malhi GS, Lagopoulos J, Owen AM, Yatham LN. Bipolaroids: functional imaging in bipolar disorder. *Acta Psychiatr. Scand. Suppl.* (422), 46–54 (2004).

68 Chen CH, Lennox B, Jacob R *et al.* Explicit and implicit facial affect recognition in manic and depressed States of bipolar disorder: a functional magnetic resonance imaging study. *Biol. Psychiatry* 59(1), 31–39 (2006).

69 Kauer-Sant'anna M, Yatham LN, Tramontina J et al. Emotional memory in bipolar disorder. *Br. J. Psychiatry* 192, 458–463 (2008).

70 Cahill L, Prins B, Weber M, McGaugh JL. β-adrenergic activation and memory for emotional events. *Nature* 371(6499), 702–704 (1994).

71 Romeo RD, McEwen BS. Stress and the adolescent brain. *Ann. NY Acad. Sci.* 1094, 202–214 (2006).

72 Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc. Natl Acad. Sci. USA* 95(22), 13290–13295 (1998).

73 Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr. Res.* 67(2–3), 269–275 (2004).

74 Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol. Psychiatry* 48(8), 766–777 (2000).

75 Cecil KM, DelBello MP, Morey R, Strakowski SM. Frontal lobe differences in bipolar disorder as determined by proton MR spectroscopy. *Bipolar Disord.* 4(6), 357–365 (2002).

76 Winsberg ME, Sachs N, Tate DL, Adalsteinsson E, Spielman D, Ketter TA. Decreased dorsolateral prefrontal N-acetyl aspartate in bipolar disorder. *Biol. Psychiatry* 47(6), 475–481 (2000).

77 Compas BE. Psychobiological processes of stress and coping: implications for resilience in children and adolescents – comments on the papers of Romeo & McEwen and Fisher *et al. Ann. NY Acad. Sci.* 1094, 226–234 (2006).

78 Frey BN, Andreazza AC, Nery FG *et al.* The role of hippocampus in the pathophysiology of bipolar disorder. *Behav. Pharmacol.* 18(5–6), 419–430 (2007).

79 Frazier JA, Breeze JL, Makris N *et al.* Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. *Bipolar Disord.* 7(6), 555–569 (2005).

80 Lupien SJ, Evans A, Lord C *et al.* Hippocampal volume is as variable in young as in older adults: implications for the notion of hippocampal atrophy in humans. *Neuroimage* 34(2), 479–485 (2007).

81 Zammit S, Allebeck P, David AS *et al.* A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch. Gen. Psychiatry* 61(4), 354–360 (2004).

82 Reichenberg A, Weiser M, Rapp MA *et al.* Elaboration on premorbid intellectual performance in schizophrenia: premorbid intellectual decline and risk for schizophrenia. *Arch. Gen. Psychiatry* 62(12), 1297–1304 (2005).

83 Patterson SL, Pittenger C, Morozov A *et al.* Some forms of cAMP-mediated long-lasting potentiation are associated with release of BDNF and nuclear translocation of phospho-MAP kinase. *Neuron* 32(1), 123–140 (2001).

84 Minichiello L, Korte M, Wolfer D *et al.* Essential role for TrkB receptors in hippocampus-mediated learning. *Neuron* 24(2), 401–414 (1999).

85 Egan MF, Kojima M, Callicott JH *et al.* The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112(2), 257–269 (2003).

86 Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am. J. Hum. Genet.* 71(3), 651–655 (2002).

87 Sklar P, Gabriel SB, McInnis MG *et al.* Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. *Mol. Psychiatry* 7(6), 579–593 (2002).

88 Geller B, Badner JA, Tillman R, Christian SL, Bolhofner K, Cook EH Jr. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. *Am. J. Psychiatry* 161(9), 1698–1700 (2004).

89 Oswald P, Del-Favero J, Massat I *et al.* Non-replication of the brain-derived neurotrophic factor (BDNF) association in bipolar affective disorder: a Belgian patient-control study. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 129(1), 34–35 (2004).

90 Skibinska M, Hauser J, Czerski PM *et al.* Association analysis of brain-derived neurotrophic factor (BDNF) gene Val66Met polymorphism in schizophrenia and bipolar affective disorder. *World J. Biol. Psychiatry* 5(4), 215–220 (2004).

91 Rybakowski JK, Suwalska A, Skibinska M *et al.* Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. *Pharmacopsychiatry* 38(4), 166–170 (2005).

92 Rybakowski JK, Borkowska A, Skibinska M, Hauser J. Illness-specific association of val66met BDNF polymorphism with performance on Wisconsin Card Sorting Test in bipolar mood disorder. *Mol. Psychiatry* 11(2), 122–124 (2006).

93 Matsuo K, Walls-Bass C, Nicoletti M *et al.* Brain-derived neurotrophic factor val66met polymorphism and morphometric abnormality in bipolar disorder patients. *Biol. Psychiatry* 61(Suppl. 1), S141 (2007).

94 Frey BN, Walss-Bass C, Stanley JA *et al.* Brain-derived neurotrophic factor val66met polymorphism affects prefrontal energy metabolism in bipolar disorder. *Neuroreport* 18(15), 1567–1570 (2007).

95 Hariri AR, Goldberg TE, Mattay VS *et al.* Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J. Neurosci.* 23(17), 6690–6694 (2003).

96 Szeszko PR, Lipsky R, Mentschel C *et al.* Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Mol. Psychiatry* 10(7), 631–636 (2005).

97 Pezawas L, Verchinski BA, Mattay VS *et al.* The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J. Neurosci.* 24(45), 10099–10102 (2004).

98 Nemoto K, Ohnishi T, Mori T *et al.* The Val66Met polymorphism of the brain-derived neurotrophic factor gene affects age-related brain morphology. *Neurosci. Lett.* 397(1–2), 25–29 (2006).

99 Bath KG, Lee FS. Variant BDNF (Val66Met) impact on brain structure and function. *Cogn. Affect. Behav. Neurosci.* 6(1), 79–85 (2006).

100 Aicardi G, Argilli E, Cappello S *et al.* Induction of long-term potentiation and depression is reflected by corresponding changes in secretion of endogenous brain-derived neurotrophic factor. *Proc. Natl Acad. Sci. USA* 101(44), 15788–15792 (2004).

101 von Bohlen und Halbach O, Krause S, Medina D, Sciarretta C, Minichiello L, Unsicker K. Regional- and age-dependent reduction in trkB receptor expression in the hippocampus is associated with altered spine morphologies. *Biol. Psychiatry* 59(9), 793–800 (2006).

102 Castren E, Voikar V, Rantamaki T. Role of neurotrophic factors in depression. *Curr. Opin. Pharmacol.* 7(1), 18–21 (2007).

103 Coyle JT, Duman RS. Finding the intracellular signaling pathways affected by mood disorder treatments. *Neuron* 38(2), 157–160 (2003).

104 Saarelainen T, Hendolin P, Lucas G *et al.* Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J. Neurosci.* 23(1), 349–357 (2003).

105 Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J. Neurosci.* 22(8), 3251–3261 (2002).

106 Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. *Psychopharmacology (Berl.)* 158(1), 100–106 (2001).

107 Frey BN, Andreazza AC, Cereser KM *et al.* Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania. *Life Sci.* 79(3), 281–286 (2006).

108 Eisch AJ, Bolanos CA, de Wit J *et al.* Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: a role in depression. *Biol. Psychiatry* 54(10), 994–1005 (2003).

109 Berton O, McClung CA, Dileone RJ *et al.* Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 311(5762), 864–868 (2006).

110 Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. *Biol. Psychiatry* 57(9), 1068–1072 (2005).

111 Noga O, Englmann C, Hanf G, Grutzkau A, Seybold J, Kunkel G. The production, storage and release of the neurotrophins nerve growth factor, brain-derived neurotrophic factor and neurotrophin-3 by human peripheral eosinophils in allergics and non-allergics. *Clin. Exp. Allergy* 33(5), 649–654 (2003).

112 Nakahashi T, Fujimura H, Altar CA *et al.* Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor. *FEBS Lett.* 470(2), 113–117 (2000).

113 Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology* 37(12), 1553–1561 (1998).

114 Karege F, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. *Neurosci. Lett.* 328(3), 261–264 (2002).

115 Dawood T, Anderson J, Barton D *et al.* Reduced overflow of BDNF from the brain is linked with suicide risk in depressive illness. *Mol. Psychiatry* 12(11), 981–983 (2007).

116 Lang UE, Hellweg R, Seifert F, Schubert F, Gallinat J. Correlation between serum brain-derived neurotrophic factor level and an *in vivo* marker of cortical integrity. *Biol. Psychiatry* 62(5), 530–535 (2007).

117 Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol. Psychiatry* 50(4), 260–265 (2001).

118 Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet* 356(9237), 1241–1242 (2000).

119 Sassi RB, Nicoletti M, Brambilla P *et al.* Increased gray matter volume in lithium-treated bipolar disorder patients. *Neurosci. Lett.* 329(2), 243–245 (2002).

120 Bearden CE, Thompson PM, Dalwani M *et al.* Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biol. Psychiatry* 62(1), 7–16 (2007).

121 Bearden CE, Thompson PM, Dutton RA *et al.* Three-dimensional mapping of hippocampal anatomy in unmedicated and lithium-treated patients with bipolar disorder. *Neuropsychopharmacology* 33(6), 1229–1238 (2008).

122 Yucel K, McKinnon MC, Taylor VH *et al.* Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. *Psychopharmacology (Berl.)* 195(3), 357–367 (2007).

123 Yucel K, Taylor VH, McKinnon MC *et al.* Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology* 33(2), 361–367 (2008).

124 Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci.* 15(11), 7539–7547 (1995).

125 Zarate CA Jr, Singh JB, Carlson PJ *et al.* Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study. *Bipolar Disord.* 9(6), 561–570 (2007).

126 Zarate CA Jr, Quiroz JA, Singh JB *et al.* An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol. Psychiatry* 57(4), 430–432 (2005).

127 Zai G, Mundo E, Strauss J, Wong GW, Kennedy JL. Brain-derived neurotrophic factor (BDNF) gene not associated with antidepressant-induced mania. *Bipolar Disord.* 9(5), 521–525 (2007).

128 Mondimore FM. Kraepelin and manic-depressive insanity: an historical perspective. *Int. Rev. Psychiatry* 17(1), 49–52 (2005).

129 McGrath JJ, Feron FP, Burne TH, Mackay-Sim A, Eyles DW. The neurodevelopmental hypothesis of schizophrenia: a review of recent developments. *Ann. Med.* 35(2), 86–93 (2003).

130 Kapczinski F, Vieta E, Andreazza AC *et al.* Allostatic load in bipolar disorder: implications for pathophysiology and treatment. *Neurosci. Biobehav Rev.* 32(4), 675–692 (2008).

131 Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am. J. Psychiatry* 149(8), 999–1010 (1992).

132 Post RM. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. *Neurosci. Biobehav. Rev.* 31(6), 858–873 (2007).

133 Gama CS, Andreazza AC, Kunz M, Berk M, Belmonte-de-Abreu PS, Kapczinski F. Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder. *Neurosci. Lett.* 420(1), 45–48 (2007).

134 Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. *J. Affect. Disord.* 100(1–3), 279–281 (2007).

135 Vieta E, Phillips ML. Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. *Schizophr. Bull.* 33(4), 886–892 (2007).

Affiliations

- Flavio Kapczinski, MD, PhD
Bipolar Disorder Program & Molecular Psychiatry Unit, Hospital de Clínicas, Federal University – UFRGS, Porto Alegre, Brazil
kapcz@terra.com.br
- Benicio N Frey, MD, PhD
Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, ON L8P 3B6, Canada
- Marcia Kauer-Sant'Anna, MD, PhD
Mood Disorders Centre, University of British Columbia, Vancouver, Canada
- Rodrigo Grassi-Oliveira, MS, MD, PhD
Psychology Department, Pontifical University of Rio Grande do Sul, Porto Alegre, RS, Brazil