Published in final edited form as:

Neuropharmacology. 2014 January ; 76(0 0): . doi:10.1016/j.neuropharm.2013.04.011.

Synaptic regulation of affective behaviors; role of BDNF

Ipe Ninan

Department of Psychiatry, NYU School of Medicine, New York

Abstract

Brain derived neurotrophic factor (BDNF), a neurotrophin essential for nervous system development and synaptic plasticity, has been found to have a significant influence on affective behaviors. The notion that an impairment in BDNF signaling might be involved in affective disorders is originated primarily from the opposing effects of antidepressants and stress on BDNF signaling. Antidepressants enhance BDNF signaling and synaptic plasticity. On the other hand, negative environmental factors such as severe stress suppress BDNF signaling, impair synaptic activity and increase susceptibility to affective disorders. Postmortem studies provided strong support for decreased BDNF signaling in depressive disorders. Remarkably, studies in humans with a single nucleotide polymorphism in the BDNF gene, the BDNF Val66Met which affects regulated release of BDNF, showed profound deficits in hippocampal and prefrontal cortical (PFC) plasticity and cognitive behaviors. BDNF regulates synaptic mechanisms responsible for various cognitive processes including attenuation of aversive memories, a key process in the regulation of affective behaviors. The unique role of BDNF in cognitive and affective behaviors suggests that cognitive deficits due to altered BDNF signaling might underlie affective disorders. Understanding how BDNF modulates synapses in neural circuits relevant to affective behaviors, particularly the medial prefrontal cortical (mPFC)-hippocampus-amygdala pathway, and its interaction with development, sex, and environmental risk factors might shed light on potential therapeutic targets for affective disorders.

Keywords

BDNF; synaptic plasticity; medial prefrontal cortex; affective behaviors

INTRODUCTION

BDNF is a member of a small group of neurotrophic factors which includes nerve growth factor (NGF), neurotrophin 3 (NT3) and neurotrophin 4 (NT4). Neurotrophins bind to their receptors, p75 and tropomyosin-related kinase (Trk) receptors (Chao, 2003; Huang and Reichardt, 2003). While BDNF and NT4 bind to TrkB receptors, NGF and NT3 bind to TrkA and TrkC, respectively (Chao, 2003). p75 and Trk receptors have distinct downstream signaling mechanisms and therefore, separate physiological functions (Chao, 2003; Hempstead, 2002; Patapoutian and Reichardt, 2001). BDNF binding results in dimerization of TrkB receptor and activation of the internal kinase domain, which subsequently autophosphorylates specific tyrosine residues, Shc site (Y⁵¹⁵) and the phospholipase C- γ

© 2013 Elsevier Ltd. All rights reserved.

Corresponding author: Ipe Ninan, Department of Psychiatry, NYU School of Medicine, SKI 5-3, 540 1Ave, New York 10116, Ipe.Ninan@nyumc.org, Tel: +1 347 535 0710.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(PLC- γ) site (Y⁸¹⁶). While the Shc binding to TrkB couples the activated receptor to the Ras/extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 3-kinase (PI3K) signaling pathways, the PLC- γ interaction is responsible for the formation of the second messengers inositol triphosphate (IP₃) and diacylglycerol, Ca²⁺ release from intracellular Ca²⁺ stores and activation of protein kinase C (Ernfors and Bramham, 2003). These downstream signaling mechanisms have been implicated in BDNF-mediated modulation of synapses and behavior (Bekinschtein et al., 2008; Minichiello, 2009).

Multiple roles of BDNF in the development, stabilization and plasticity of synapses are largely facilitated by various levels of cellular and molecular regulation including transcriptional, translational, trafficking and secretion mechanisms in the nervous system (Park and Poo, 2012). Regulation of BDNF transcription by ion channels such as voltage-gated calcium channels and glutamate receptors plays an important role in synaptic plasticity (West et al., 2001). Among the several BDNF promoters identified, some are selectively activated by specific stimuli providing yet another level of molecular regulation of neuronal function and behavior (Cunha et al., 2010; Park and Poo, 2012). Region-specific segregation of *bdnf* transcripts is believed to play an important role in diverse functions of BDNF within a neuron (Baj et al., 2011). Furthermore, homeostatic synaptic plasticity involves local translation of BDNF (Jakawich et al., 2010). In contrast to the effect of BDNF, pro-BDNF, the precursor of BDNF, has been demonstrated to promote activity-dependent depression of synaptic strength by the activation of p75 receptors (Woo et al., 2005). Apart from the activity-dependent transcription and translation of BDNF, regulated release of BDNF is critical for plasticity and cognitive behaviors. The BDNF Val66Met, a common single nucleotide polymorphism in the *bdnf* gene leading to a valine (Val) to methionine (Met) substitution at codon 66 in the prodomain, causes an altered binding to sortilin, a Vps 10p domain protein, resulting in the impairment of regulated release of BDNF (Chen et al., 2005; Chen et al., 2006; Egan et al., 2003). Humans and rodents carrying the BDNF Val66Met exhibit profound impairments in synaptic and cognitive functions (Bath et al., 2012b; Egan et al., 2003; Ninan et al., 2010a; Pattwell et al., 2012a; Soliman et al., 2010). The tight link between these cellular mechanisms that regulate BDNF and synaptic functions strongly supports the essential role of BDNF in brain health.

BDNF has been studied extensively for its role in synaptic transmission and plasticity, majority of which have been undertaken in the hippocampus, a brain region critical for learning and memory and affective behaviors. Subsequently, these studies have been extended to various regions of the cortex and striatum. *In vitro* studies utilizing exogenous BDNF and transgenic approaches to alter BDNF signaling revealed that BDNF is essential for transmission and plasticity at both excitatory and inhibitory synapses in the cortex and hippocampus (Figurov et al., 1996; Gottschalk et al., 1998; Hong et al., 2008; Kang and Schuman, 1995; Korte et al., 1995; Patterson et al., 1996; Pattwell et al., 2012a; Sakata et al., 2009; Yamada et al., 2002; Yano et al., 2006). Consistently, behavioral studies have suggested that the altered BDNF signaling in hippocampus and cortex has significant impact on cognitive functions (Chen et al., 2006; Ninan et al., 2010a; Pattwell et al., 2012a; Soliman et al., 2010; Yu et al., 2009). These cognitive deficits due to altered BDNF signaling have been linked to impaired neurogenesis, synaptogenesis and synaptic plasticity. Congruent with the purported role of BDNF-dependent synaptic activity in higher-order cognitive functions, cognitive decline in neurodegenerative disorders is associated with impaired synaptic function and decreased BDNF signaling (Arancio and Chao, 2007; Nagahara and Tuszynski, 2011; Zuccato and Cattaneo, 2009). Although the enhancement of BDNF signaling in preclinical studies suggested its beneficial effects in neurodegenerative diseases (Nagahara et al., 2009; Simmons et al., 2009; Xie et al., 2010), the mechanism by which BDNF deficit causes early cognitive deficits and comorbid affective symptoms in neurodegenerative disorders is not well understood (Arancio and Chao, 2007). Despite the

large wealth of data supporting the role of BDNF in higher-order cognitive function and synaptic plasticity, efforts to utilize BDNF-TrkB signaling as a therapeutic target has not been successful. BDNF is expressed in several brain regions and exerts diverse functions depending upon cell type, brain areas and developmental stage. Given the region-specific differences in BDNF expression and synaptogenesis during development, future studies will be essential to understand how BDNF participates in the differential regulation of synapses in brain regions pertinent to affective behaviors particularly non-linear development of cortical synapses (Giedd et al., 1999; Gogtay et al., 2004; Kaufman et al., 2006; Kilb, 2012; Pattwell et al., 2012b; Spear, 2000). Furthermore, understanding how these development-dependent changes in synapses are affected by sex and environmental factors will shed light on the neurobiology of affective disorders. In this review, I will discuss the role of BDNF in affective disorders and how changes in BDNF signaling modulate synapses in brain regions relevant to affective behaviors.

Impairment of neurogenesis, synaptic and structural plasticity in affective disorders

The development and plasticity of synapses rely heavily on availability of BDNF which is affected by various environmental, genetic and epigenetic factors suggesting multiple roles for BDNF in the etiology of affective disorders. An opposite effect of severe stress and antidepressant treatment on BDNF signaling, a decrease and an increase respectively, implies a correlation between BDNF deficits and affective disorders (Altar, 1999; Duman et al., 1997; Nibuya et al., 1996). A decrease in serum BDNF level in depressed patients and its correlation with the severity of depressive symptoms has also been described (Karege et al., 2002; Shimizu et al., 2003). Studies on the effect of stress on BDNF levels were primarily focused on hippocampus which showed a suppression of BDNF (Smith et al., 1995; Ueyama et al., 1997). An enhanced BDNF level has been described in the mPFC and amygdala following stress (Bland et al., 2005; Fanous et al., 2010; Lakshminarasimhan and Chattarji, 2012). However, given the potential influence of the duration and severity of stress on BDNF levels in different brain regions, parallel measurements of BDNF and plasticity in the hippocampus, mPFC and amygdala using multiple stress paradigms will clarify whether stress induces a region-specific modification of BDNF levels and plasticity relevant to affective symptoms. Consistent with the role of BDNF in neuronal structural plasticity (Mamounas et al., 1995; Studer et al., 1995; Tanaka et al., 2008; Yamada et al., 2002), an increased atrophy of neurons following stress and improved neuronal morphology in response to antidepressant treatment were observed (Kitayama et al., 1997; Rajkowska, 2000; Watanabe et al., 1992a). Concurrent studies demonstrated antidepressant-like effects of centrally administered BDNF in rodents (Siuciak et al., 1997). Also, an increase in CREB activity produced antidepressant-like effects in animals possibly due to an enhanced BDNF expression (Chen et al., 2001a). Consistently, subsequent postmortem studies showed an enhanced BDNF signaling after antidepressant treatment (Chen et al., 2001b). Although several animal studies have shown an enhancement of BDNF-TrkB signaling in the mPFC, hippocampus and amygdala in response to antidepressant treatment, there are significant inconsistencies among different studies on the extent of BDNF modulation as well as region specificity (Balu et al., 2008; Hamilton et al., 2008; Karpova et al., 2011; Tardito et al., 2006). Type of antidepressants, dose, route of administration and the time of measurements might have contributed to this inconsistency in the data (Tardito et al., 2006). While the aforementioned studies supported the “neurotrophin hypothesis” of mood disorders, additional studies were undertaken to understand the possible mechanism by which BDNF regulates affective behaviors particularly modulation of adult neurogenesis, synaptic and structural plasticity (Figure 1).

Following the demonstration that antidepressants enhance adult neurogenesis in the hippocampus (Malberg et al., 2000), several groups have investigated whether BDNF is necessary for the antidepressant-mediated augmentation of neurogenesis. Studies using heterozygous BDNF null mice and mice overexpressing truncated TrkB (TrkB. T1) suggested that BDNF is necessary for long-term survival of newborn neurons induced by antidepressant treatment (Sairanen et al., 2005). These results were recently confirmed by an RNA interference approach (Taliaz et al., 2010). Consistent with the role of BDNF in antidepressant-mediated hippocampal neurogenesis, mice lacking TrkB in hippocampal neural progenitor cells failed to exhibit antidepressant-induced proliferation and neurogenesis (Li et al., 2008). In a completely different set of experiments to study learned safety as an approach to reduce depression-like behaviors, an enhanced survival of hippocampal neurons and BDNF expression have been observed in rodents that underwent safety learning (Pollak et al., 2008). Also, peripheral administration of BDNF produced anxiolytic and antidepressant effects and an increased hippocampal neurogenesis in mice (Schmidt and Duman, 2010). Administration of fluoxetine, a selective serotonin reuptake inhibitor, enhanced BDNF expression and neurogenesis in an animal model of Down syndrome (Ts65Dn mice) (Bianchi et al., 2010). Neurogenesis plays a critical role in fluoxetine-induced enhancement of long-term potentiation (LTP) in the dentate gyrus (Wang et al., 2008). However, a single nucleotide polymorphism in the BDNF gene, the Val66Met, interferes with fluoxetine-induced enhancement of hippocampal neurogenesis and LTP (Bath et al., 2012b). Interestingly, LTP itself enhances adult neurogenesis in the dentate gyrus (Bruehl-Jungman et al., 2006). Although these studies established the role of BDNF in antidepressant-induced neurogenesis, the molecular mechanism underlying BDNF-mediated adult neurogenesis remains to be elucidated.

Several lines of evidence from pharmacological, genetic and postmortem studies strongly suggest the involvement of synaptic dysfunction in affective disorders. BDNF regulates transmission at glutamatergic and GABAergic synapses by both pre- and post-synaptic mechanisms (Fortin et al., 2012; Minichiello, 2009). Therefore, it is conceivable that a decrease in BDNF signaling could profoundly alter neuronal function by interfering with synaptic function. Consistent with the putative role of both BDNF and NMDA receptors in plasticity and cognitive behaviors, BDNF modulates NMDA receptor activity and cognitive functions including fear extinction memory (Pattwell et al., 2012a; Peters et al., 2010). Decreased GluN2 subunits of NMDA receptors and PSD-95 were observed in the PFC of depressed subjects (Feyissa et al., 2009). A recent microarray and electron microscopic stereology study revealed significant downregulation of synaptic proteins in major depressive disorder (Kang et al., 2012). Similar to the studies in the PFC, diminished glutamate receptor signaling has been described in the hippocampus of depressed subjects (Duric et al., 2013). Decrease in GABA_A receptors and GABAergic neurons were also observed in depressed subjects compared to healthy controls (Rajkowska et al., 2007; Zhao et al., 2012). The BDNF Val66Met polymorphism that has been implicated in cognitive dysfunction, anxiety and depressive disorders (Chen et al., 2006; Egan et al., 2003; Verhagen et al., 2010), impairs NMDA and GABAergic transmission and synaptic plasticity in the mPFC (Pattwell et al., 2012a). Also, the BDNF Val66Met impairs fluoxetine-induced LTP in the dentate gyrus (Bath et al., 2012b). In addition to the demonstration of the role of BDNF in the effect of clinical antidepressants, recent studies to understand the fast antidepressant effect of ketamine, a non-competitive NMDA receptor antagonist (Berman et al., 2000), revealed that BDNF-dependent synaptic plasticity is involved in the antidepressant effect of low-dose ketamine (Autry et al., 2011; Li et al., 2010). Ketamine enhances mTOR and BDNF signaling and augments plasticity at excitatory synapses (Autry et al., 2011; Li et al., 2010). Consistent with the role of BDNF in ketamine's antidepressant effect, the BDNF Val66Met polymorphism interferes with ketamine-induced antidepressant and synaptogenic effects in the mPFC (Liu et al., 2012). Altogether these studies strongly

suggest the critical role of BDNF-dependent synaptic activity in the regulation of affective behaviors.

BDNF plays an important role in the formation, maturation and plasticity of pre- and post-synaptic compartments (Ji et al., 2005; Tanaka et al., 2008; Tyler and Pozzo-Miller, 2001). Susceptibility to affective disorders following a stressful event might involve decreased BDNF and associated changes in spine density and neuronal morphology (Blugeot et al., 2011). Anxiety and depression are associated with decreased spine density in the hippocampus (Soetanto et al., 2010). Severe stress decreases dendritic spines and causes atrophy of dendrites in the hippocampus and mPFC (Cook and Wellman, 2004; Radley et al., 2008; Sunanda et al., 1995; Watanabe et al., 1992b). It has been demonstrated that stressful events affect neuronal morphology in a region-specific fashion with significant atrophy of neurites in hippocampus and PFC while amygdala shows hypertrophy and increased neuronal activity (Blugeot et al., 2011; Vyas et al., 2002). Although these region-specific effects might depend upon the severity of stress, an increased vulnerability of the PFC and hippocampus to stress could result in a diminished top-down regulation of the amygdala, a potential causal mechanism in affective disorders (Sotres-Bayon et al., 2012). Consistent with the negative impact of severe stress and trauma on brain volume and structural changes (Bremner, 1999; Woon et al., 2010), depressive disorders are associated with significant alterations in brain volume and microstructural changes including decreased synaptic proteins (Charney and Manji, 2004; Kang et al., 2012; Licznarski and Duman, 2012). Subjects with major depression exhibited decrease in number of neurons and glial cells (Rajkowska et al., 1999). Diminished BDNF signaling has been linked to a decrease in brain volume (Egan et al., 2003; Montag et al., 2009). Reduction in dendritic spines, atrophy of neurites and cell death are likely to be responsible for stress-induced suppression of brain volume implying that environmental or genetic variations that affect the development and structural integrity of neurons could be susceptibility factors for affective disorders (Carballedo et al., 2012). However, hippocampal volume reductions could also occur after the onset of symptoms (McKinnon et al., 2009). Therapeutic approaches that benefit the management of affective disorders have been shown to improve structural plasticity in neurons. Electroconvulsive therapy (ECT), an effective treatment for depression, enhances BDNF signaling and reverses hippocampal volume loss in depression (Taylor, 2008). Similarly, antidepressants facilitate reversal of structural deficits associated with affective disorders (Hoexter et al., 2012; Kitayama et al., 1997; Rajkowska, 2000; Watanabe et al., 1992a). The recent demonstration that ketamine augments the formation of new dendritic spines in the PFC further supports the potential role of structural plasticity in the regulation of affective behaviors (Li et al., 2010). BDNF-dependent dendritic and spine morphogenesis, neurogenesis and prevention of cell death might play a role in the effect of ECT and antidepressants (Seil and Drake-Baumann, 2000; Vicario-Abejon et al., 1998) (McAllister et al., 1995; Park and Poo, 2012; Rex et al., 2007; Vicario-Abejon et al., 2002). Therefore, apart from being a biomarker in affective disorders, BDNF stands out as a clear target for behavioral and pharmacological manipulation for the management of affective symptoms.

Neural regulation of affective behaviors: synaptic plasticity and the role of BDNF

The recent neuroimaging studies and animal studies using both *in vivo* and *in vitro* approaches consolidated the idea that the mPFC-hippocampus-amygdala neural circuit regulates affective behaviors. Impairment in the mPFC-hippocampus-amygdala pathway might be a causal mechanism for high anxiety, a risk factor for depressive disorders (Sandi and Richter-Levin, 2009). In addition to environmental and genetic factors, sex and

development could influence synapses in the mPFC-hippocampus-amygdala neural circuit resulting in altered regulation of affective behaviors. Given the reciprocal interaction between synaptic activity and BDNF levels, it is conceivable that reduction in BDNF signaling due to severe stress or genetic factors such as the BDNF Val66Met polymorphism could alter mPFC-hippocampus-amygdala pathway. Emerging data suggest that BDNF in the mPFC and hippocampus augment top-down regulation of the amygdala (Heldt et al., 2007; Pattwell et al., 2012a; Peters et al., 2010; Soliman et al., 2010) (Figure. 2). Also, BDNF in the amygdala has been recently implicated in the consolidation of fear memory and augmentation of fear erasure (Chhatwal et al., 2006; Karpova et al., 2011; Rattiner et al., 2004). Therefore, elucidating the differential effects of BDNF on synapses in these key brain regions will be crucial to our understanding on the synaptic regulation of affective behaviors.

Role of BDNF in mPFC synaptic plasticity

Given the established role of mPFC in cognitive and affective behaviors, there has been significant interest in understanding specific mechanisms by which BDNF regulates mPFC synaptic plasticity. Several lines of evidence suggest that an altered BDNF signaling might be involved in maladaptive synapse development and plasticity in the PFC in response to environmental or genetic challenges (Kuipers et al., 2003). Downregulation of BDNF and impairment of plasticity in the mPFC after stress had been reported (Qi et al., 2009). The BDNF Val66Met has a significant effect on anatomy and neuronal morphology in the PFC (Pezawas et al., 2004). Also, the BDNF Val66Met affects functional connectivity in the PFC in a sex-dependent manner (Wei et al., 2012). To understand the synaptic basis of the effect of the BDNF Val66Met polymorphism on affective behaviors, we undertook electrophysiological experiments to study synaptic transmission and plasticity in the pyramidal neurons of the infralimbic mPFC. Although we did not observe any changes in glutamate release or AMPA receptor transmission, both NMDA receptor and GABAergic transmission were diminished in BDNF^{Met/Met} mice (Pattwell et al., 2012a). Consistent with the deficits in NMDA receptor transmission, we observed an impaired spike timing-dependent plasticity in the mPFC neurons. While acute application of BDNF to the brain slices was capable of reversing the deficits in NMDA receptors transmission and plasticity, both non-NMDA receptor transmission and GABAergic transmission remained unaffected in the presence of exogenous BDNF. Therefore, it is possible that genetic risk factors such as Val66Met polymorphism could exert their effects on synapses by disrupting not only synapse development but also acute modulation of synaptic transmission. These findings also suggest the possibility that synaptic deficits that are unrelated to development could be reversed by acute activation of BDNF-TrkB signaling. Ketamine, a non-competitive NMDA receptor antagonist with fast antidepressant activity, enhances BDNF signaling, synaptogenesis and plasticity in the mPFC (Autry et al., 2011; Li et al., 2010; Liu et al., 2012). A recent study demonstrated an impairment of ketamine-induced synaptogenesis in the mPFC as well as antidepressant effect in BDNF^{Met/Met} mice, further supporting the critical role of BDNF in mPFC plasticity and affective behaviors (Liu et al., 2012). An earlier study in promoter IV mutant BDNF (BDNF-KIV) mice described suppression of GABAergic transmission and an aberrant plasticity in the mPFC suggesting that decreased activity-dependent transcription of BDNF results in altered synaptic function (Sakata et al., 2009). Direct perfusion of BDNF into the IL-mPFC enhances fear extinction, a key mechanism involved in the regulation of affective behaviors (Peters et al., 2010). Interestingly, the effect of BDNF on fear extinction is NMDA receptor-dependent (Peters et al., 2010). Earlier studies have demonstrated that NMDA receptor-dependent burst firing in the mPFC is critical for fear extinction (Burgos-Robles et al., 2007). These findings are consistent with the effect of BDNF Val66Met polymorphism on NMDA receptor transmission and plasticity in the mPFC and deficits in fear extinction (Pattwell et al.,

2012a; Soliman et al., 2010). Similar to the effect on fear extinction, the BDNF Val66Met polymorphism also impairs extinction of conditioned taste aversion in mice (Yu et al., 2009). A correlated increase in c-fos activation after the extinction of conditioned taste aversion was observed in wild-type mice but not BDNF^{Met/Met} mice (Yu et al., 2009). Consistent with the deficits in NMDA receptor transmission in the mPFC of BDNF^{Met/Met} mice, D-cycloserine, a partial agonist at the glycine site on NMDA receptors, improved extinction of conditioned taste aversion in BDNF^{Met/Met} mice (Yu et al., 2009). BDNF has been shown to modulate phosphorylation, activity, expression and trafficking of NMDA receptors (Caldeira et al., 2007b; Carmignoto et al., 1997; Crozier et al., 2008; Levine et al., 1998; Lin et al., 1998; Suen et al., 1997). Apart from changes in transmission and plasticity at the mPFC, a smaller volume and lack of dendritic complexity was reported in the mPFC of BDNF^{Met/Met} mice (Yu et al., 2009). Although BDNF^{Met/Met} mice did not exhibit any deficits in cued fear or taste aversion memory, region-specific suppression of BDNF signaling in the prelimbic (PL) mPFC impairs consolidation of fear as well as appetitive and emotional aversive memory (Choi et al., 2012; Choi et al., 2010). Therefore, BDNF signaling regulates aversive memories by enhancing mPFC plasticity and top-down regulation of subcortical structures (Figure. 2). Since the BDNF-dependent mPFC plasticity is critical for the regulation of affective behaviors (Pattwell et al., 2012a; Pattwell et al., 2012b; Peters et al., 2010), identification of molecular targets that enhance BDNF signaling or its downstream mechanisms in the mPFC might facilitate effective strategies to improve the management of affective disorders.

Role of BDNF in hippocampal synaptic plasticity

A reciprocal interaction between BDNF levels and synaptic activity is believed to play an important role in hippocampal functions (Castren et al., 1993; Kang and Schuman, 1995; Zafra et al., 1991). The inhibition of glutamate receptors suppressed BDNF levels while an opposite effect was observed with the GABA receptor antagonists (Zafra et al., 1991). Activity-dependent plasticity relies on the availability of BDNF and the induction of LTP increases BDNF in the hippocampus (Castren et al., 1993; Figurov et al., 1996; Kang and Schuman, 1995; Korte et al., 1995; Patterson et al., 1996; Patterson et al., 1992). Activation of TrkB modulates pre-synaptic glutamate release in the hippocampus (Gottschalk et al., 1998; Yano et al., 2006). Post-synaptically BDNF promotes the expression and synaptic insertion of glutamate receptors (Caldeira et al., 2007a; Fortin et al., 2012; Slipczuk et al., 2009). Also, BDNF modulates NMDA receptor activity which is thought to play an important role in hippocampal plasticity (Lin et al., 1998; Xu et al., 2006). Activation of ERK, CREB and PLC γ signaling downstream of TrkB is necessary for BDNF-dependent synaptic plasticity in the hippocampus (Minichiello et al., 2002; Ying et al., 2002). Apart from the effect on glutamatergic synapses in the hippocampus, BDNF regulates GABAergic synapses which involve both pre- and post-synaptic mechanisms (Baldelli et al., 2005; Ohba et al., 2005; Sutachan et al., 2010). The effect of BDNF on hippocampal synapses involves synaptic remodeling and spine formation by the activation of multiple signaling mechanisms including cAMP, Vav family of Rac/RhoA guanine nucleotide exchange factors and Cdk5 (Hale et al., 2011; Ji et al., 2005; Lai et al., 2012). Consistent with the crucial role of BDNF in hippocampal synaptic plasticity, deficit in BDNF signaling results in cognitive impairment (Mizuno et al., 2000; Mu et al., 1999). Hippocampus-dependent learning and memory are essential for the regulation of affective behaviors. Ability to discriminate between contextual information related to safety and danger depends on hippocampal function and is believed to play an important role in attenuating fear memory and anxiety-like behaviors. Both the pattern separation and completion, two important hippocampus-dependent cognitive processes rely on neurogenesis and NMDA receptor transmission (McHugh et al., 2007; Nakashiba et al., 2012; Sahay et al., 2011). Consistent with the effect of BDNF on neurogenesis and synaptic plasticity (Caldeira et al., 2007b; Carmignoto et al.,

1997; Crozier et al., 2008; Levine et al., 1998; Li et al., 2008; Lin et al., 1998; Sairanen et al., 2005; Suen et al., 1997; Taliaz et al., 2010), BDNF infusion into the hippocampus enhances fear extinction (Peters et al., 2010). It is plausible that BDNF signaling in the ventral hippocampus has a direct role in fear extinction and regulation of anxiety behaviors by facilitating feed-forward inhibition of the PL-mPFC (Adhikari et al., 2011; Sotres-Bayon et al., 2012). Also, BDNF might facilitate stress regulation by promoting hippocampal neurogenesis (Snyder et al., 2011). Antidepressants that enhance BDNF signaling and adult neurogenesis facilitate recovery from the effects of stress (Surget et al., 2011). The rapid antidepressant activity of ketamine involves facilitation of AMPA receptor transmission in the hippocampus by a BDNF-dependent mechanism (Autry et al., 2011). Congruent with the role of hippocampal BDNF in contextual memory and adult neurogenesis (Chen et al., 2006; Sairanen et al., 2005), the BDNF Val66Met polymorphism impairs contextual fear memory, fear extinction, and adult neurogenesis (Bath et al., 2012b; Ninan et al., 2010b; Pattwell et al., 2012a; Soliman et al., 2010). Also, the BDNF Val66Met interferes with antidepressant-induced neurogenesis and plasticity in the dentate gyrus (Bath et al., 2012b). These studies strongly suggest that BDNF could regulate affective behaviors by diverse mechanisms including modulation of neurogenesis, synaptic and structural plasticity in the hippocampus.

Role of BDNF in amygdala synaptic plasticity

The amygdala, a key brain region necessary for vigilance and attention, is perhaps the least understood subcortical structure in terms of its complex neuronal architecture particularly distinct clusters of GABAergic neurons and the regulation of plasticity at several synaptic circuits. Consistent with the high expression of BDNF in the amygdala, BDNF release and activation of TrkB receptors in the amygdala are tightly linked to fear memory (Conner et al., 1997; Rattiner et al., 2004; Yan et al., 1997). The role of BDNF in the amygdala function is further supported by the demonstration of the downstream signaling mechanisms including MAPK and PI3K pathways in the amygdala-dependent learning (Ou and Gean, 2006). In addition to the acquisition of fear memory, amygdala BDNF is necessary for consolidation of extinction memory (Chhatwal et al., 2006). Consistently, decreased level of BDNF in the amygdala is associated with increased anxiety-like behaviors (Pandey et al., 2006). Several studies have suggested the direct role of amygdala BDNF signaling in the regulation of affective behaviors. Mice that are deficient in TrkB. T1 show morphological abnormalities in the amygdala and increased anxiety-like behaviors (Carim-Todd et al., 2009). The human carriers of the BDNF Val66Met polymorphism show reduction in amygdala volume and impairment in fear acquisition (Hajcak et al., 2009; Lonsdorf et al., 2010; Montag et al., 2009). The Val66Met carriers who were exposed to early life stress showed reduced amygdala volume and increased depressive behaviors (Gatt et al., 2009). Although the mechanism is unclear, the BDNF Val66Met causes increased activity in the amygdala in response to emotional stimuli (Montag et al., 2008). Apart from potential deficits within the amygdala, it is plausible that a deficit in mPFC-mediated top-down regulation of the amygdala causes an altered response to emotional demands. In contrast to several studies that tested the effect of antidepressants in hippocampus, only few studies were undertaken to examine whether antidepressant effects involve plasticity in the amygdala. It has been suggested that antidepressants increase amygdala volume, rendering it less susceptible to stress and affective disorders possibly by a BDNF-dependent mechanism (Hamilton et al., 2008). Also, fluoxetine augments fear erasure by enhancing synaptic plasticity in the amygdala in a BDNF-dependent fashion (Karpova et al., 2011). This effect of fluoxetine involved reactivation of juvenile-like plasticity in the basolateral amygdala (Karpova et al., 2011). Similar to the role of BDNF in the mPFC- and hippocampus-dependent cognitive functions, BDNF in the amygdala is critical for acquisition and consolidation of fear memory and fear extinction (Chhatwal et al., 2006; Rattiner et al., 2004). Although these studies demonstrate that BDNF is necessary for amygdala-dependent

cognitive behaviors, given the complex neuronal and synaptic network in the amygdala, a significant challenge is to elucidate the role of BDNF in plasticity at its inputs, outputs and synaptic networks comprised of distinct classes of GABAergic and glutamatergic neurons within several anatomically and functionally distinct nuclei. Another major area remains to be explored is the sexual dimorphism in the amygdala neuronal circuits (Cooke and Woolley, 2005; Hermel et al., 2006; Kerchner et al., 1995; Morris et al., 2008a; Morris et al., 2008b). The critical role of BDNF-TrkB signaling in the effect of estradiol on nervous system suggest that BDNF might be involved in sex-dependent modification of amygdala function (Autry et al., 2009; Becker et al., 2007; Bus et al.; Kramar et al., 2012; Monteggia et al., 2007; Murphy et al., 1998; Sohrabji et al., 1995).

Pharmacological and behavioral enhancement of BDNF signaling

Although various experimental approaches including infusion of BDNF and genetic methods to enhance BDNF signaling to elicit nootropic and neuroprotective effects have been successful in animal studies, a safe, effective and feasible approach to enhance BDNF-TrkB signaling for the purpose of alleviating cognitive and affective disorders in humans is not yet successful. Biochemical, electrophysiological and behavioral studies on several classes of molecular targets provided promising preliminary data suggesting the possibility of enhancing BDNF-TrkB signaling by alternate pharmacological approaches. Pharmacological agents such as ampakines, Sphingosine-1 phosphate receptor agonist, estrogen receptor agonists, molecules that act as TrkB agonists and antidepressants enhanced cognitive behaviors and synaptic function by augmenting BDNF signaling. Apart from pharmacological agents, positive behavioral experiences such as environmental enrichment and physical exercise have been demonstrated to enhance BDNF signaling and synaptic function.

Ampakines

Ampakines are a diverse class of molecules that enhance AMPA receptor transmission (Lynch, 2006). Consistent with the effect on synaptic transmission, ampakines have been shown to promote cognitive functions (Hampson et al., 1998a, b). The region-specific and context-dependent effects of ampakines make them an attractive target for the development of therapeutic approaches for neuropsychiatric disorders (Lauterborn et al., 2003; Lynch, 2006; Xia and Arai, 2005; Xia et al., 2005). Consistent with the cognitive model of depression (Disner et al., 2011), some of the ampakines with nootropic effects also show antidepressant-like effects (Knapp et al., 2002). Following the demonstration of the beneficial effects of an ampakine CX516 in learning and memory in animal studies, a combination of antipsychotic drug and CX516 was tested in schizophrenia which showed promising effects on attention and memory (Goff et al., 2001). Superior memory performance in healthy volunteers after treatment with farampator suggested the beneficial effects of ampakines in cognitive and affective disorders (Wezenberg et al., 2007). A remarkable finding that ampakines increase neurotrophin signaling and the demonstration that these effects might benefit management of excitotoxicity and Parkinson's disease fueled studies to understand how ampakines modulate neurogenesis and plasticity (Dicou et al., 2003; Lauterborn et al., 2000; Murray et al., 2003). Ampakines enhance BDNF mRNA and protein levels in the hippocampus and facilitate BDNF release (Jourdi et al., 2009; Lauterborn et al., 2000). Ampakine CX546 enhances neurogenesis in SVZ cell cultures (Schitine et al., 2012). Also, LY451646 increases cell proliferation in adult rat hippocampus (Bai et al., 2003). Ampakines facilitate spine actin polymerization, LTP and improve cognitive functions in an animal model of Angelman syndrome (Baudry et al., 2012). Similarly, upregulation of BDNF by ampakines improves synaptic plasticity and memory in a knockin mouse model of Huntington's disease (Simmons et al., 2009). The effects of

ampakines on BDNF signaling, synaptic plasticity and cognitive functions offer promising avenues for future pharmacological interventions in cognitive and affective disorders based on a glutamate receptor-based enhancement of BDNF signaling (Castren et al., 1993; Kang and Schuman, 1995; Zafra et al., 1991).

Sphingosine-1 phosphate receptor modulation

A recent study demonstrated that Sphingosine-1 phosphate receptor agonist, fingolimod, an approved drug for multiple sclerosis, enhances BDNF mRNA and protein levels in the cortex, hippocampus and striatum in an activity- and MAPK pathway-dependent fashion (Deogracias et al., 2012). It also mimicked the effect of BDNF on excitatory and inhibitory synaptic transmission, an enhancement of spontaneous excitatory synaptic transmission and a suppression of spontaneous inhibitory synaptic transmission, respectively (Deogracias et al., 2012; Pattwell et al., 2012a). In addition, the increase in BDNF levels was associated with a reversal of motor deficits in a mouse model of Rett syndrome suggesting the potential use of sphingosine-1 phosphate receptor activation in synaptic deficits (Deogracias et al., 2012). Given these exciting findings, a further evaluation of sphingosine-1 phosphate receptors as a target to enhance BDNF signaling and its beneficial effects in cognitive and affective behaviors is warranted.

Estrogen receptor agonists

Estrogens exert some of their biological effects through BDNF which involve increased BDNF transcription (Sohrabji et al., 1995). Additional studies suggested that the activation of estrogen receptors might reverse neuronal loss and memory impairment in Alzheimer's disease by enhancing neurotrophin signaling (Simpkins et al., 1997). Consistent with the promising effects of estrogen on cognitive behaviors, it has been shown that estrogen facilitates dendritic spine formation through BDNF signaling (Murphy et al., 1998). Furthermore, an estradiol-mediated enhancement of synaptic plasticity via a BDNF-dependent mechanism has been demonstrated (Kramar et al., 2012). An impairment in estradiol-dependent modulation of BDNF signaling might play a role in the incidence of neuropsychiatric and neurodegenerative disorders (Scharfman and Maclusky, 2005). In addition, deficit in BDNF signaling results in sex-specific increase in depression-like behaviors suggesting that BDNF is necessary for estradiol-dependent regulation of affective behaviors (Autry et al., 2009; Becker et al., 2007; Bus et al.; Monteggia et al., 2007). The BDNF Val66Met polymorphism affects PFC activity and anxiety-like behaviors in a sex-dependent manner (Bath et al., 2012a; Wei et al., 2012). The incidence of affective disorders in women is significantly higher than men (Becker et al., 2007; Hankin and Abramson, 1999; Zender and Olshansky, 2009). Also, a gender difference exists in the severity of the affective symptoms and the quality of life between affected women and men (Breslau et al., 1997; Holbrook et al., 2002; Seedat et al., 2005). Since the gender difference in affective symptoms emerges after puberty, it is believed that variations in estradiol levels might play a role in affective disorders (Angold et al., 1998; Becker et al., 2007; Solomon and Herman, 2009). Higher estradiol levels are associated with reduced anxiety-like symptoms and increased fear extinction, while reduced estradiol levels are associated with high incidence of anxiety-like disorders and suppressed fear extinction (Altshuler et al., 1998; Harsh et al., 2009; Lebron-Milad and Milad, 2012; Schmidt and Rubinow, 2009; Schnatz et al., 2010). The notion that estrogen receptor signaling might be critical for the regulation of affective behaviors is supported by the recent finding that estrogen receptor β agonists facilitate fear extinction and exert anxiolytic effects (Lund et al., 2005; Zeidan et al., 2011). The activation of estrogen receptors enhances BDNF signaling (Blurton-Jones and Tuszynski, 2006). Given the abundant expression of estrogen receptor β in the mPFC, modulation of these receptors might facilitate cognitive behaviors such as fear extinction by enhancing BDNF signaling

(Kritzer, 2002; Shughrue et al., 1997). Also, understanding the role of BDNF in estradiol-mediated regulation of synapses in the mPFC-hippocampus-amygdala pathway might shed light on increased incidence of affective symptoms in women and identification of therapeutic targets downstream of estrogen receptors.

TrkB agonists

Despite the putative role of BDNF-TrkB signaling in the regulation of cognitive and affective behaviors, there has been limited success in developing direct activators of TrkB that mimics the function of BDNF. Recently, a novel pharmacological agent, 7,8-Dihydroxyflavone, developed as a TrkB agonist (Jang et al., 2010). Systemic administration of 7,8-Dihydroxyflavone reversed learning deficits in BDNF knockout mice (Choi et al., 2010). 7,8-Dihydroxyflavone also enhanced both the acquisition and extinction of fear memory and reversed memory deficit due to immobilization stress (Andero et al., 2011) (Andero et al., 2012). A synthetic 4'-dimethyl amino-7,8-dihydroxyflavone derivative promoted neurogenesis and exhibited antidepressant-like properties (Liu et al., 2010). In an animal model for Alzheimer's disease, 5XFAD transgenic mice that co-overexpress human APP and presenilin 1 (PS1) harboring five familial AD mutations, 7,8-Dihydroxyflavone reversed cognitive deficits (Devi and Ohno, 2012). Also, 7,8-dihydroxyflavone enhanced synaptic plasticity, modified dendritic spines in the hippocampus and improved spatial memory in aged rats (Zeng et al., 2012). These promising early results are expected to trigger development of small molecules to activate TrkB receptors for potential clinical use.

Effect of exercise and environmental enrichment on BDNF signaling

The finding that physical exercise could increase BDNF mRNA levels in the cortex and hippocampus provided new insights into relationship between physical activity and brain health (Neeper et al., 1996). Physical exercise increases BDNF levels and improves cognitive and affective behaviors (Laske et al., 2010). The potential benefits of a combination of physical activity and antidepressant treatment were also suggested (Russo-Neustadt et al., 2000). Voluntary wheel running increased BDNF levels in mice (Johnson et al., 2003). Exercise-induced enhancement of CREB under the control of BDNF in the hippocampus improves synaptic function and enhances learning and memory (Vaynman et al., 2004). Increase in BDNF levels in the striatum and associated improvement in depression-like symptoms were reported subsequently (Marais et al., 2009). Running-induced improvement in cognitive function and mood behavior involved hippocampal neurogenesis and dendritic plasticity (Yau et al., 2011). Consistent with these animal studies, human data strongly suggest that physical exercise improves depressive symptoms (Silveira et al., 2013). Also, recent evidence indicate the beneficial effects of physical exercise on cognitive functions (Guiney and Machado, 2013). Given the potential benefits, physical activity-dependent enhancement of BDNF signaling is expected to have a role in the management of affective disorders.

Congruent with the beneficial effects of enhanced BDNF signaling in cognitive functions, enriched environment augments cognitive functions via BDNF signaling in the hippocampus (Falkenberg et al., 1992). The neuroprotective effects of environmental enrichment involve increased pCREB activity and BDNF (Young et al., 1999). Also, environmental enrichment improved deficits in a mouse model of Huntington's disease by rescuing BDNF levels (Spires et al., 2004). Consistent with the increase in BDNF levels, environmentally enriched animals showed improved neurogenesis (Rossi et al., 2006). Environmental enrichment reverses deficits in neurogenesis and depression-like behaviors in mice lacking expression of BDNF through promoter IV (BDNF-KIV mice) (Jha et al., 2011). Also, environmental enrichment in adulthood promotes amblyopia recovery by reducing intracortical inhibition

via BDNF (Sale et al., 2007). Although the mechanism by which BDNF mediates the beneficial effects of environmental enrichment is unknown, a recent study demonstrated that kinesin superfamily motor protein 1A (KIF1A) is necessary for hippocampal synaptogenesis and cognitive functions after environmental enrichment (Kondo et al., 2012). Acting downstream of BDNF, KIF1A enhances synaptogenesis by augmenting the transport of pre-synaptic vesicle associated proteins (Kondo et al., 2012). It is possible that KIF1A affects synaptogenesis by regulating the BDNF transport as well (Lo et al., 2011). Unlike the animal studies which mostly involve manipulation of housing conditions, translation of this approach to humans might require an individualized approach based on cognitive and affective repertoire. Nevertheless the aforementioned studies provide strong scientific support for employing behavioral modifications such as physical exercise and environmental enrichment in facilitating the management of affective symptoms.

Conclusion

Extensive studies over nearly two decades have established the critical role of BDNF in the regulation of synaptic development and plasticity. Consistent with its effects on synapses, behavioral studies utilizing various genetic and pharmacological approaches confirmed that BDNF regulates cognitive and affective behaviors. Despite the strong support for the potential role of BDNF signaling in affective disorders, there have been many reports incongruent with the neurotrophin hypothesis of mood disorders. This includes the lack of effect of antidepressants on BDNF and the absence of anxiety and depression-like symptoms in animals with altered BDNF signaling (Groves, 2007). Differences in the duration and dose of antidepressant treatment, animal strain, and the nature of genetic manipulation could contribute to these discrepancies. However, it is also important to emphasize the region-specific effects of BDNF and its impact on affective behaviors. For example, BDNF modulates midbrain-ventral striatum pathway and exacerbates affective symptoms (Nestler and Carlezon, 2006). Therefore, comprehensive studies will be necessary to reconcile the impact of BDNF signaling on various brain regions and affective behaviors. The development of pharmacological approaches to modulate BDNF signaling for clinical use is still in experimental stages. Non-selective expression of BDNF in various brain areas and its diverse functions depending upon cell types and brain areas pose significant challenges to therapeutic development. The finding that TrkB receptors could be activated in a neurotrophin-independent manner provided new clues for potential pharmacological approaches to enhance TrkB signaling (Lee and Chao, 2001). A deeper understanding of the role of BDNF in neural circuits involved in cognitive and affective behaviors could be achieved by studying behaviors in response to region-specific manipulation of BDNF signaling. Future studies will be necessary to understand whether and how BDNF mediates a temporal regulation of synapse development particularly in the PFC, hippocampus, amygdala and midbrain-ventral striatum pathway. Given the significant influence of age, gender and environment on affective behaviors, it will be critical to understand how sex hormones and environment shape synaptic function by their interaction with BDNF during various stages of development.

Acknowledgments

This work was supported by funding from the National Institutes of Health (RO1 MH96899).

References

- Adhikari A, Topiwala MA, Gordon JA. Single units in the medial prefrontal cortex with anxiety-related firing patterns are preferentially influenced by ventral hippocampal activity. *Neuron*. 2011; 71:898–910. [PubMed: 21903082]

- Altar CA. Neurotrophins and depression. *Trends Pharmacol Sci.* 1999; 20:59–61. [PubMed: 10101965]
- Altshuler LL, Hendrick V, Cohen LS. Course of mood and anxiety disorders during pregnancy and the postpartum period. *J Clin Psychiatry.* 1998; 59(Suppl 2):29–33. [PubMed: 9559757]
- Andero R, Daviu N, Escorihuela RM, Nadal R, Armario A. 7,8-dihydroxyflavone, a TrkB receptor agonist, blocks long-term spatial memory impairment caused by immobilization stress in rats. *Hippocampus.* 2012; 22:399–408. [PubMed: 21136519]
- Andero R, Heldt SA, Ye K, Liu X, Armario A, Ressler KJ. Effect of 7,8-dihydroxyflavone, a small-molecule TrkB agonist, on emotional learning. *Am J Psychiatry.* 2011; 168:163–172. [PubMed: 21123312]
- Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychol Med.* 1998; 28:51–61. [PubMed: 9483683]
- Arancio O, Chao MV. Neurotrophins, synaptic plasticity and dementia. *Curr Opin Neurobiol.* 2007; 17:325–330. [PubMed: 17419049]
- Autry AE, Adachi M, Cheng P, Monteggia LM. Gender-specific impact of brain-derived neurotrophic factor signaling on stress-induced depression-like behavior. *Biol Psychiatry.* 2009; 66:84–90. [PubMed: 19358977]
- Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature.* 2011; 475:91–95. [PubMed: 21677641]
- Bai F, Bergeron M, Nelson DL. Chronic AMPA receptor potentiator (LY451646) treatment increases cell proliferation in adult rat hippocampus. *Neuropharmacology.* 2003; 44:1013–1021. [PubMed: 12763094]
- Baj G, Leone E, Chao MV, Tongiorgi E. Spatial segregation of BDNF transcripts enables BDNF to differentially shape distinct dendritic compartments. *Proc Natl Acad Sci U S A.* 2011; 108:16813–16818. [PubMed: 21933955]
- Baldelli P, Hernandez-Guijo JM, Carabelli V, Carbone E. Brain-derived neurotrophic factor enhances GABA release probability and nonuniform distribution of N- and P/Q-type channels on release sites of hippocampal inhibitory synapses. *J Neurosci.* 2005; 25:3358–3368. [PubMed: 15800191]
- Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I. Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. *Brain Res.* 2008; 1211:37–43. [PubMed: 18433734]
- Bath KG, Chuang J, Spencer-Segal JL, Amso D, Altemus M, McEwen BS, Lee FS. Variant brain-derived neurotrophic factor (Valine66Methionine) polymorphism contributes to developmental and estrous stage-specific expression of anxiety-like behavior in female mice. *Biol Psychiatry.* 2012a; 72:499–504. [PubMed: 22552045]
- Bath KG, Jing DQ, Dincheva I, Neeb CC, Pattwell SS, Chao MV, Lee FS, Ninan I. BDNF Val66Met Impairs Fluoxetine-Induced Enhancement of Adult Hippocampus Plasticity. *Neuropsychopharmacology.* 2012b
- Baudry M, Kramar E, Xu X, Zadran H, Moreno S, Lynch G, Gall C, Bi X. Ampakines promote spine actin polymerization, long-term potentiation, and learning in a mouse model of Angelman syndrome. *Neurobiol Dis.* 2012; 47:210–215. [PubMed: 22525571]
- Becker JB, Monteggia LM, Perrot-Sinal TS, Romeo RD, Taylor JR, Yehuda R, Bale TL. Stress and disease: is being female a predisposing factor? *J Neurosci.* 2007; 27:11851–11855. [PubMed: 17978023]
- Bekinschtein P, Cammarota M, Izquierdo I, Medina JH. BDNF and memory formation and storage. *Neuroscientist.* 2008; 14:147–156. [PubMed: 17911219]
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry.* 2000; 47:351–354. [PubMed: 10686270]
- Bianchi P, Ciani E, Guidi S, Trazzi S, Felice D, Grossi G, Fernandez M, Giuliani A, Calza L, Bartesaghi R. Early pharmacotherapy restores neurogenesis and cognitive performance in the Ts65Dn mouse model for Down syndrome. *J Neurosci.* 2010; 30:8769–8779. [PubMed: 20592198]

- Bland ST, Schmid MJ, Der-Avakian A, Watkins LR, Spencer RL, Maier SF. Expression of c-fos and BDNF mRNA in subregions of the prefrontal cortex of male and female rats after acute uncontrollable stress. *Brain Res.* 2005; 1051:90–99. [PubMed: 15993862]
- Blugeot A, Rivat C, Bouvier E, Molet J, Mouchard A, Zeau B, Bernard C, Benoliel JJ, Becker C. Vulnerability to depression: from brain neuroplasticity to identification of biomarkers. *J Neurosci.* 2011; 31:12889–12899. [PubMed: 21900567]
- Blurton-Jones M, Tuszynski MH. Estradiol-induced modulation of estrogen receptor-beta and GABA within the adult neocortex: a potential transsynaptic mechanism for estrogen modulation of BDNF. *J Comp Neurol.* 2006; 499:603–612. [PubMed: 17029253]
- Bremner JD. Does stress damage the brain? *Biol Psychiatry.* 1999; 45:797–805. [PubMed: 10202566]
- Breslau N, Davis GC, Andreski P, Peterson EL, Schultz LR. Sex differences in posttraumatic stress disorder. *Arch Gen Psychiatry.* 1997; 54:1044–1048. [PubMed: 9366662]
- Bruel-Jungerman E, Davis S, Rampon C, Laroche S. Long-term potentiation enhances neurogenesis in the adult dentate gyrus. *J Neurosci.* 2006; 26:5888–5893. [PubMed: 16738230]
- Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. *Neuron.* 2007; 53:871–880. [PubMed: 17359921]
- Bus BA, Tendolkar I, Franke B, de Graaf J, Heijer MD, Buitelaar JK, Oude Voshaar RC. Serum brain-derived neurotrophic factor: Determinants and relationship with depressive symptoms in a community population of middle-aged and elderly people. *World J Biol Psychiatry.*
- Caldeira MV, Melo CV, Pereira DB, Carvalho R, Correia SS, Backos DS, Carvalho AL, Esteban JA, Duarte CB. Brain-derived neurotrophic factor regulates the expression and synaptic delivery of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits in hippocampal neurons. *J Biol Chem.* 2007a; 282:12619–12628. [PubMed: 17337442]
- Caldeira MV, Melo CV, Pereira DB, Carvalho RF, Carvalho AL, Duarte CB. BDNF regulates the expression and traffic of NMDA receptors in cultured hippocampal neurons. *Mol Cell Neurosci.* 2007b; 35:208–219. [PubMed: 17428676]
- Carballedo A, Lisiecka D, Fagan A, Saleh K, Ferguson Y, Connolly G, Meaney J, Frodl T. Early life adversity is associated with brain changes in subjects at family risk for depression. *World J Biol Psychiatry.* 2012; 13:569–578. [PubMed: 22515408]
- Carim-Todd L, Bath KG, Fulgenzi G, Yanpallear S, Jing D, Barrick CA, Becker J, Buckley H, Dorsey SG, Lee FS, Tessarollo L. Endogenous truncated TrkB. T1 receptor regulates neuronal complexity and TrkB kinase receptor function in vivo. *J Neurosci.* 2009; 29:678–685. [PubMed: 19158294]
- Carmignoto G, Pizzorusso T, Tia S, Vicini S. Brain-derived neurotrophic factor and nerve growth factor potentiate excitatory synaptic transmission in the rat visual cortex. *J Physiol.* 1997; 498 (Pt 1):153–164. [PubMed: 9023775]
- Castren E, Pitkanen M, Sirvio J, Parsadanian A, Lindholm D, Thoenen H, Riekkinen PJ. The induction of LTP increases BDNF and NGF mRNA but decreases NT-3 mRNA in the dentate gyrus. *Neuroreport.* 1993; 4:895–898. [PubMed: 8396461]
- Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci.* 2003; 4:299–309. [PubMed: 12671646]
- Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. *Sci STKE.* 2004;re5. [PubMed: 15039492]
- Chen AC, Shirayama Y, Shin KH, Neve RL, Duman RS. Expression of the cAMP response element binding protein (CREB) in hippocampus produces an antidepressant effect. *Biol Psychiatry.* 2001a; 49:753–762. [PubMed: 11331083]
- Chen B, Dowlatsahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry.* 2001b; 50:260–265. [PubMed: 11522260]
- Chen ZY, Ieraci A, Teng H, Dall H, Meng CX, Herrera DG, Nykjaer A, Hempstead BL, Lee FS. Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. *J Neurosci.* 2005; 25:6156–6166. [PubMed: 15987945]

- Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS, Hempstead BL, Lee FS. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science*. 2006; 314:140–143. [PubMed: 17023662]
- Chhatwal JP, Stanek-Rattiner L, Davis M, Ressler KJ. Amygdala BDNF signaling is required for consolidation but not encoding of extinction. *Nat Neurosci*. 2006; 9:870–872. [PubMed: 16783370]
- Choi DC, Gourley SL, Ressler KJ. Prelimbic BDNF and TrkB signaling regulates consolidation of both appetitive and aversive emotional learning. *Transl Psychiatry*. 2012; 2:e205. [PubMed: 23250006]
- Choi DC, Maguschak KA, Ye K, Jang SW, Myers KM, Ressler KJ. Prelimbic cortical BDNF is required for memory of learned fear but not extinction or innate fear. *Proc Natl Acad Sci U S A*. 2010; 107:2675–2680. [PubMed: 20133801]
- Conner JM, Lauterborn JC, Yan Q, Gall CM, Varon S. Distribution of brain-derived neurotrophic factor (BDNF) protein and mRNA in the normal adult rat CNS: evidence for anterograde axonal transport. *J Neurosci*. 1997; 17:2295–2313. [PubMed: 9065491]
- Cook SC, Wellman CL. Chronic stress alters dendritic morphology in rat medial prefrontal cortex. *J Neurobiol*. 2004; 60:236–248. [PubMed: 15266654]
- Cooke BM, Woolley CS. Sexually dimorphic synaptic organization of the medial amygdala. *J Neurosci*. 2005; 25:10759–10767. [PubMed: 16291949]
- Crozier RA, Bi C, Han YR, Plummer MR. BDNF modulation of NMDA receptors is activity dependent. *J Neurophysiol*. 2008; 100:3264–3274. [PubMed: 18842955]
- Cunha C, Brambilla R, Thomas KL. A simple role for BDNF in learning and memory? *Front Mol Neurosci*. 2010; 3:1. [PubMed: 20162032]
- Deogracias R, Yazdani M, Dekkers MP, Guy J, Ionescu MC, Vogt KE, Barde YA. Fingolimod, a sphingosine-1 phosphate receptor modulator, increases BDNF levels and improves symptoms of a mouse model of Rett syndrome. *Proc Natl Acad Sci U S A*. 2012; 109:14230–14235. [PubMed: 22891354]
- Devi L, Ohno M. 7,8-dihydroxyflavone, a small-molecule TrkB agonist, reverses memory deficits and BACE1 elevation in a mouse model of Alzheimer's disease. *Neuropsychopharmacology*. 2012; 37:434–444. [PubMed: 21900882]
- Dicou E, Rangon CM, Guimiot F, Spedding M, Gressens P. Positive allosteric modulators of AMPA receptors are neuroprotective against lesions induced by an NMDA agonist in neonatal mouse brain. *Brain Res*. 2003; 970:221–225. [PubMed: 12706264]
- Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci*. 2011; 12:467–477. [PubMed: 21731066]
- Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. *Arch Gen Psychiatry*. 1997; 54:597–606. [PubMed: 9236543]
- Duric V, Banasr M, Stockmeier CA, Simen AA, Newton SS, Overholser JC, Jurjus GJ, Dieter L, Duman RS. Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. *Int J Neuropsychopharmacol*. 2013; 16:69–82. [PubMed: 22339950]
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003; 112:257–269. [PubMed: 12553913]
- Ernfors P, Bramham CR. The coupling of a trkB tyrosine residue to LTP. *Trends Neurosci*. 2003; 26:171–173. [PubMed: 12689763]
- Falkenberg T, Mohammed AK, Henriksson B, Persson H, Winblad B, Lindefors N. Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. *Neurosci Lett*. 1992; 138:153–156. [PubMed: 1407655]
- Fanous S, Hammer RP Jr, Nikulina EM. Short- and long-term effects of intermittent social defeat stress on brain-derived neurotrophic factor expression in mesocorticolimbic brain regions. *Neuroscience*. 2010; 167:598–607. [PubMed: 20206238]

- Feyissa AM, Chandran A, Stockmeier CA, Karolewicz B. Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33:70–75. [PubMed: 18992785]
- Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature*. 1996; 381:706–709. [PubMed: 8649517]
- Fortin DA, Srivastava T, Dwarakanath D, Pierre P, Nygaard S, Derkach VA, Soderling TR. Brain-derived neurotrophic factor activation of CaM-kinase kinase via transient receptor potential canonical channels induces the translation and synaptic incorporation of GluA1-containing calcium-permeable AMPA receptors. *J Neurosci*. 2012; 32:8127–8137. [PubMed: 22699894]
- Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, Gordon E, Kemp AH, Williams LM. Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Mol Psychiatry*. 2009; 14:681–695. [PubMed: 19153574]
- Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 1999; 2:861–863. [PubMed: 10491603]
- Goff DC, Leahy L, Berman I, Posever T, Herz L, Leon AC, Johnson SA, Lynch G. A placebo-controlled pilot study of the ampakine CX516 added to clozapine in schizophrenia. *J Clin Psychopharmacol*. 2001; 21:484–487. [PubMed: 11593073]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF 3rd, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A*. 2004; 101:8174–8179. [PubMed: 15148381]
- Gottschalk W, Pozzo-Miller LD, Figurov A, Lu B. Presynaptic modulation of synaptic transmission and plasticity by brain-derived neurotrophic factor in the developing hippocampus. *J Neurosci*. 1998; 18:6830–6839. [PubMed: 9712654]
- Groves JO. Is it time to reassess the BDNF hypothesis of depression? *Mol Psychiatry*. 2007; 12:1079–1088. [PubMed: 17700574]
- Guiney H, Machado L. Benefits of regular aerobic exercise for executive functioning in healthy populations. *Psychon Bull Rev*. 2013; 20:73–86. [PubMed: 23229442]
- Hajcak G, Castille C, Olvet DM, Dunning JP, Roohi J, Hatchwell E. Genetic variation in brain-derived neurotrophic factor and human fear conditioning. *Genes Brain Behav*. 2009; 8:80–85. [PubMed: 19220486]
- Hale CF, Dietz KC, Varela JA, Wood CB, Zirlin BC, Leverich LS, Greene RW, Cowan CW. Essential role for vav Guanine nucleotide exchange factors in brain-derived neurotrophic factor-induced dendritic spine growth and synapse plasticity. *J Neurosci*. 2011; 31:12426–12436. [PubMed: 21880903]
- Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Mol Psychiatry*. 2008; 13:993–1000. [PubMed: 18504424]
- Hampson RE, Rogers G, Lynch G, Deadwyler SA. Facilitative effects of the ampakine CX516 on short-term memory in rats: correlations with hippocampal neuronal activity. *J Neurosci*. 1998a; 18:2748–2763. [PubMed: 9502832]
- Hampson RE, Rogers G, Lynch G, Deadwyler SA. Facilitative effects of the ampakine CX516 on short-term memory in rats: enhancement of delayed-nonmatch-to-sample performance. *J Neurosci*. 1998b; 18:2740–2747. [PubMed: 9502831]
- Hankin BL, Abramson LY. Development of gender differences in depression: description and possible explanations. *Ann Med*. 1999; 31:372–379. [PubMed: 10680851]
- Harsh V, Meltzer-Brody S, Rubinow DR, Schmidt PJ. Reproductive aging, sex steroids, and mood disorders. *Harv Rev Psychiatry*. 2009; 17:87–102. [PubMed: 19373618]
- Heldt SA, Stanek L, Chhatwal JP, Ressler KJ. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Mol Psychiatry*. 2007; 12:656–670. [PubMed: 17264839]

- Hempstead BL. The many faces of p75NTR. *Curr Opin Neurobiol.* 2002; 12:260–267. [PubMed: 12049931]
- Hermel EE, Ilha J, Xavier LL, Rasia-Filho AA, Achaval M. Influence of sex and estrous cycle, but not laterality, on the neuronal somatic volume of the posterodorsal medial amygdala of rats. *Neurosci Lett.* 2006; 405:153–158. [PubMed: 16860473]
- Hoexter MQ, de Souza Duran FL, D'Alcanta CC, Dougherty DD, Shavitt RG, Lopes AC, Diniz JB, Deckersbach T, Batistuzzo MC, Bressan RA, Miguel EC, Busatto GF. Gray matter volumes in obsessive-compulsive disorder before and after fluoxetine or cognitive-behavior therapy: a randomized clinical trial. *Neuropsychopharmacology.* 2012; 37:734–745. [PubMed: 22030709]
- Holbrook TL, Hoyt DB, Stein MB, Sieber WJ. Gender differences in long-term posttraumatic stress disorder outcomes after major trauma: women are at higher risk of adverse outcomes than men. *J Trauma.* 2002; 53:882–888. [PubMed: 12435938]
- Hong EJ, McCord AE, Greenberg ME. A biological function for the neuronal activity-dependent component of Bdnf transcription in the development of cortical inhibition. *Neuron.* 2008; 60:610–624. [PubMed: 19038219]
- Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. *Annu Rev Biochem.* 2003; 72:609–642. [PubMed: 12676795]
- Jakawich SK, Nasser HB, Strong MJ, McCartney AJ, Perez AS, Rakesh N, Carruthers CJ, Sutton MA. Local presynaptic activity gates homeostatic changes in presynaptic function driven by dendritic BDNF synthesis. *Neuron.* 2010; 68:1143–1158. [PubMed: 21172615]
- Jang SW, Liu X, Yepes M, Shepherd KR, Miller GW, Liu Y, Wilson WD, Xiao G, Blanchi B, Sun YE, Ye K. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. *Proc Natl Acad Sci U S A.* 2010; 107:2687–2692. [PubMed: 20133810]
- Jha S, Dong B, Sakata K. Enriched environment treatment reverses depression-like behavior and restores reduced hippocampal neurogenesis and protein levels of brain-derived neurotrophic factor in mice lacking its expression through promoter IV. *Transl Psychiatry.* 2011; 1:e40. [PubMed: 22832656]
- Ji Y, Pang PT, Feng L, Lu B. Cyclic AMP controls BDNF-induced TrkB phosphorylation and dendritic spine formation in mature hippocampal neurons. *Nat Neurosci.* 2005; 8:164–172. [PubMed: 15665879]
- Johnson RA, Rhodes JS, Jeffrey SL, Garland T Jr, Mitchell GS. Hippocampal brain-derived neurotrophic factor but not neurotrophin-3 increases more in mice selected for increased voluntary wheel running. *Neuroscience.* 2003; 121:1–7. [PubMed: 12946694]
- Jourdi H, Hsu YT, Zhou M, Qin Q, Bi X, Baudry M. Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation. *J Neurosci.* 2009; 29:8688–8697. [PubMed: 19587275]
- Kang H, Schuman EM. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. *Science.* 1995; 267:1658–1662. [PubMed: 7886457]
- Kang HJ, Voleti B, Hajszan T, Rajkowska G, Stockmeier CA, Licznerski P, Lepack A, Majik MS, Jeong LS, Banasr M, Son H, Duman RS. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nat Med.* 2012; 18:1413–1417. [PubMed: 22885997]
- Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res.* 2002; 109:143–148. [PubMed: 11927139]
- Karpova NN, Pickenhagen A, Lindholm J, Tiraboschi E, Kuleshkaya N, Agustsdottir A, Antila H, Popova D, Akamine Y, Bahi A, Sullivan R, Hen R, Drew LJ, Castren E. Fear erasure in mice requires synergy between antidepressant drugs and extinction training. *Science.* 2011; 334:1731–1734. [PubMed: 22194582]
- Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, Houshyar S, Krystal JH, Gelernter J. Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biol Psychiatry.* 2006; 59:673–680. [PubMed: 16458264]
- Kerchner M, Malsbury CW, Ward OB, Ward IL. Sexually dimorphic areas in the rat medial amygdala: resistance to the demasculinizing effect of prenatal stress. *Brain Res.* 1995; 672:251–260. [PubMed: 7749746]

- Kilb W. Development of the GABAergic system from birth to adolescence. *Neuroscientist*. 2012; 18:613–630. [PubMed: 21952258]
- Kitayama I, Yaga T, Kayahara T, Nakano K, Murase S, Otani M, Nomura J. Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. *Biol Psychiatry*. 1997; 42:687–696. [PubMed: 9325562]
- Knapp RJ, Goldenberg R, Shuck C, Cecil A, Watkins J, Miller C, Crites G, Malatynska E. Antidepressant activity of memory-enhancing drugs in the reduction of submissive behavior model. *Eur J Pharmacol*. 2002; 440:27–35. [PubMed: 11959085]
- Kondo M, Takei Y, Hirokawa N. Motor protein KIF1A is essential for hippocampal synaptogenesis and learning enhancement in an enriched environment. *Neuron*. 2012; 73:743–757. [PubMed: 22365548]
- Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proc Natl Acad Sci U S A*. 1995; 92:8856–8860. [PubMed: 7568031]
- Kramar EA, Babayan AH, Gall CM, Lynch G. Estrogen promotes learning-related plasticity by modifying the synaptic cytoskeleton. *Neuroscience*. 2012
- Kritzer MF. Regional, laminar, and cellular distribution of immunoreactivity for ER alpha and ER beta in the cerebral cortex of hormonally intact, adult male and female rats. *Cereb Cortex*. 2002; 12:116–128. [PubMed: 11739260]
- Kuipers SD, Trentani A, Den Boer JA, Ter Horst GJ. Molecular correlates of impaired prefrontal plasticity in response to chronic stress. *J Neurochem*. 2003; 85:1312–1323. [PubMed: 12753089]
- Lai KO, Wong AS, Cheung MC, Xu P, Liang Z, Lok KC, Xie H, Palko ME, Yung WH, Tessarollo L, Cheung ZH, Ip NY. TrkB phosphorylation by Cdk5 is required for activity-dependent structural plasticity and spatial memory. *Nat Neurosci*. 2012; 15:1506–1515. [PubMed: 23064382]
- Lakshminarasimhan H, Chattarji S. Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. *PLoS One*. 2012; 7:e30481. [PubMed: 22272355]
- Laske C, Banschbach S, Stransky E, Bosch S, Straten G, Machann J, Fritsche A, Hipp A, Niess A, Eschweiler GW. Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression. *Int J Neuropsychopharmacol*. 2010; 13:595–602. [PubMed: 20067661]
- Lauterborn JC, Lynch G, Vanderklis P, Arai A, Gall CM. Positive modulation of AMPA receptors increases neurotrophin expression by hippocampal and cortical neurons. *J Neurosci*. 2000; 20:8–21. [PubMed: 10627576]
- Lauterborn JC, Truong GS, Baudry M, Bi X, Lynch G, Gall CM. Chronic elevation of brain-derived neurotrophic factor by ampakines. *J Pharmacol Exp Ther*. 2003; 307:297–305. [PubMed: 12893840]
- Lebron-Milad K, Milad MR. Sex differences, gonadal hormones and the fear extinction network: implications for anxiety disorders. *Biol Mood Anxiety Disord*. 2012; 2:3. [PubMed: 22738383]
- Lee FS, Chao MV. Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc Natl Acad Sci U S A*. 2001; 98:3555–3560. [PubMed: 11248116]
- 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 U S A*. 1998; 95:10235–10239. [PubMed: 9707630]
- Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010; 329:959–964. [PubMed: 20724638]
- Li Y, Luikart BW, Birnbaum S, Chen J, Kwon CH, Kernie SG, Bassel-Duby R, Parada LF. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. *Neuron*. 2008; 59:399–412. [PubMed: 18701066]
- Licznerski P, Duman RS. Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. *Neuroscience*. 2012

- Lin SY, Wu K, Levine ES, Mount HT, Suen PC, Black IB. BDNF acutely increases tyrosine phosphorylation of the NMDA receptor subunit 2B in cortical and hippocampal postsynaptic densities. *Brain Res Mol Brain Res*. 1998; 55:20–27. [PubMed: 9645956]
- Liu RJ, Lee FS, Li XY, Bambico F, Duman RS, Aghajanian GK. Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. *Biol Psychiatry*. 2012; 71:996–1005. [PubMed: 22036038]
- Liu X, Chan CB, Jang SW, Pradoldej S, Huang J, He K, Phun LH, France S, Xiao G, Jia Y, Luo HR, Ye K. A Synthetic 7,8-Dihydroxyflavone Derivative Promotes Neurogenesis and Exhibits Potent Antidepressant Effect. *J Med Chem*. 2010
- Lo KY, Kuzmin A, Unger SM, Petersen JD, Silverman MA. KIF1A is the primary anterograde motor protein required for the axonal transport of dense-core vesicles in cultured hippocampal neurons. *Neurosci Lett*. 2011; 491:168–173. [PubMed: 21256924]
- Lonsdorf TB, Weike AI, Golkar A, Schalling M, Hamm AO, Ohman A. Amygdala-dependent fear conditioning in humans is modulated by the BDNF Val66met polymorphism. *Behav Neurosci*. 2010; 124:9–15. [PubMed: 20141276]
- Lund TD, Rovis T, Chung WC, Handa RJ. Novel actions of estrogen receptor-beta on anxiety-related behaviors. *Endocrinology*. 2005; 146:797–807. [PubMed: 15514081]
- Lynch G. Glutamate-based therapeutic approaches: ampakines. *Curr Opin Pharmacol*. 2006; 6:82–88. [PubMed: 16361116]
- Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci*. 2000; 20:9104–9110. [PubMed: 11124987]
- Mamounas LA, Blue ME, Siuciak JA, Altar CA. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *J Neurosci*. 1995; 15:7929–7939. [PubMed: 8613731]
- Marais L, Stein DJ, Daniels WM. Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats. *Metab Brain Dis*. 2009; 24:587–597. [PubMed: 19844781]
- McAllister AK, Lo DC, Katz LC. Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron*. 1995; 15:791–803. [PubMed: 7576629]
- McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, Lowell BB, Fanselow MS, Wilson MA, Tonegawa S. Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. *Science*. 2007; 317:94–99. [PubMed: 17556551]
- McKinnon MC, Yucel K, Nazarov A, MacQueen GM. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *J Psychiatry Neurosci*. 2009; 34:41–54. [PubMed: 19125212]
- Minichiello L. TrkB signalling pathways in LTP and learning. *Nat Rev Neurosci*. 2009; 10:850–860. [PubMed: 19927149]
- Minichiello L, Calella AM, Medina DL, Bonhoeffer T, Klein R, Korte M. Mechanism of TrkB-mediated hippocampal long-term potentiation. *Neuron*. 2002; 36:121–137. [PubMed: 12367511]
- Mizuno M, Yamada K, Olariu A, Nawa H, Nabeshima T. Involvement of brain-derived neurotrophic factor in spatial memory formation and maintenance in a radial arm maze test in rats. *J Neurosci*. 2000; 20:7116–7121. [PubMed: 10995859]
- Montag C, Reuter M, Newport B, Elger C, Weber B. The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: evidence from a genetic imaging study. *Neuroimage*. 2008; 42:1554–1559. [PubMed: 18603005]
- Montag C, Weber B, Fliessbach K, Elger C, Reuter M. The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression. *Psychol Med*. 2009; 39:1831–1839. [PubMed: 19335934]
- Monteggia LM, Luikart B, Barrot M, Theobald D, Malkovska I, Nef S, Parada LF, Nestler EJ. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. *Biol Psychiatry*. 2007; 61:187–197. [PubMed: 16697351]
- Morris JA, Jordan CL, Breedlove SM. Sexual dimorphism in neuronal number of the posterodorsal medial amygdala is independent of circulating androgens and regional volume in adult rats. *J Comp Neurol*. 2008a; 506:851–859. [PubMed: 18076082]

- Morris JA, Jordan CL, King ZA, Northcutt KV, Breedlove SM. Sexual dimorphism and steroid responsiveness of the posterodorsal medial amygdala in adult mice. *Brain Res.* 2008b; 1190:115–121. [PubMed: 18054901]
- Mu JS, Li WP, Yao ZB, Zhou XF. Deprivation of endogenous brain-derived neurotrophic factor results in impairment of spatial learning and memory in adult rats. *Brain Res.* 1999; 835:259–265. [PubMed: 10415381]
- Murphy DD, Cole NB, Segal M. Brain-derived neurotrophic factor mediates estradiol-induced dendritic spine formation in hippocampal neurons. *Proc Natl Acad Sci U S A.* 1998; 95:11412–11417. [PubMed: 9736750]
- Murray TK, Whalley K, Robinson CS, Ward MA, Hicks CA, Lodge D, Vandergriff JL, Baumbarger P, Siuda E, Gates M, Ogden AM, Skolnick P, Zimmerman DM, Nisenbaum ES, Bleakman D, O'Neill MJ. LY503430, a novel alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor potentiator with functional, neuroprotective and neurotrophic effects in rodent models of Parkinson's disease. *J Pharmacol Exp Ther.* 2003; 306:752–762. [PubMed: 12730350]
- Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, Wang L, Blesch A, Kim A, Conner JM, Rockenstein E, Chao MV, Koo EH, Geschwind D, Masliah E, Chiba AA, Tuszynski MH. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nat Med.* 2009; 15:331–337. [PubMed: 19198615]
- Nagahara AH, Tuszynski MH. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nat Rev Drug Discov.* 2011; 10:209–219. [PubMed: 21358740]
- Nakashiba T, Cushman JD, Pelkey KA, Renaudineau S, Buhl DL, McHugh TJ, Rodriguez Barrera V, Chittajallu R, Iwamoto KS, McBain CJ, Fanselow MS, Tonegawa S. Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell.* 2012; 149:188–201. [PubMed: 22365813]
- Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res.* 1996; 726:49–56. [PubMed: 8836544]
- Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry.* 2006; 59:1151–1159. [PubMed: 16566899]
- Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci.* 1996; 16:2365–2372. [PubMed: 8601816]
- Ninan I, Bath KG, Dagar K, Perez-Castro R, Plummer MR, Lee FS, Chao MV. The BDNF Val66Met polymorphism impairs NMDA receptor-dependent synaptic plasticity in the hippocampus. *J Neurosci.* 2010a; 30:8866–8870. [PubMed: 20592208]
- Ninan I, Bath KG, Dagar K, Perez-Castro R, Plummer MR, Lee FS, Chao MV. The BDNF Val66Met polymorphism impairs NMDA receptor-dependent synaptic plasticity in the hippocampus. *J Neurosci.* 2010b; 30:8866–8870. [PubMed: 20592208]
- Ohba S, Ikeda T, Ikegaya Y, Nishiyama N, Matsuki N, Yamada MK. BDNF locally potentiates GABAergic presynaptic machineries: target-selective circuit inhibition. *Cereb Cortex.* 2005; 15:291–298. [PubMed: 15238431]
- Ou LC, Gean PW. Regulation of amygdala-dependent learning by brain-derived neurotrophic factor is mediated by extracellular signal-regulated kinase and phosphatidylinositol-3-kinase. *Neuropsychopharmacology.* 2006; 31:287–296. [PubMed: 16034442]
- Pandey SC, Zhang H, Roy A, Misra K. Central and medial amygdaloid brain-derived neurotrophic factor signaling plays a critical role in alcohol-drinking and anxiety-like behaviors. *J Neurosci.* 2006; 26:8320–8331. [PubMed: 16899727]
- Pare D, Quirk GJ, Ledoux JE. New vistas on amygdala networks in conditioned fear. *J Neurophysiol.* 2004; 92:1–9. [PubMed: 15212433]
- Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci.* 2012; 14:7–23. [PubMed: 23254191]
- Patapoutian A, Reichardt LF. Trk receptors: mediators of neurotrophin action. *Curr Opin Neurobiol.* 2001; 11:272–280. [PubMed: 11399424]

- Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron*. 1996; 16:1137–1145. [PubMed: 8663990]
- Patterson SL, Grover LM, Schwartzkroin PA, Bothwell M. Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. *Neuron*. 1992; 9:1081–1088. [PubMed: 1463608]
- Pattwell SS, Bath KG, Perez-Castro R, Lee FS, Chao MV, Ninan I. The BDNF Val66Met polymorphism impairs synaptic transmission and plasticity in the infralimbic medial prefrontal cortex. *J Neurosci*. 2012a; 32:2410–2421. [PubMed: 22396415]
- Pattwell SS, Duhoux S, Hartley CA, Johnson DC, Jing D, Elliott MD, Ruberry EJ, Powers A, Mehta N, Yang RR, Soliman F, Glatt CE, Casey BJ, Ninan I, Lee FS. Altered Fear Learning Across Development in Both Mouse and Human. *Proc Natl Acad Sci U S A*. 2012b; 109:16318–16323. [PubMed: 22988092]
- Peters J, Dieppa-Perea LM, Melendez LM, Quirk GJ. Induction of fear extinction with hippocampal-infralimbic BDNF. *Science*. 2010; 328:1288–1290. [PubMed: 20522777]
- Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci*. 2004; 24:10099–10102. [PubMed: 15537879]
- Pollak DD, Monje FJ, Zuckerman L, Denny CA, Drew MR, Kandel ER. An animal model of a behavioral intervention for depression. *Neuron*. 2008; 60:149–161. [PubMed: 18940595]
- Qi H, Mailliet F, Spedding M, Rocher C, Zhang X, Delagrangé P, McEwen B, Jay TM, Svenningsson P. Antidepressants reverse the attenuation of the neurotrophic MEK/MAPK cascade in frontal cortex by elevated platform stress; reversal of effects on LTP is associated with GluA1 phosphorylation. *Neuropharmacology*. 2009; 56:37–46. [PubMed: 18657555]
- Radley JJ, Rocher AB, Rodriguez A, Ehlenberger DB, Dammann M, McEwen BS, Morrison JH, Wearne SL, Hof PR. Repeated stress alters dendritic spine morphology in the rat medial prefrontal cortex. *J Comp Neurol*. 2008; 507:1141–1150. [PubMed: 18157834]
- Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry*. 2000; 48:766–777. [PubMed: 11063973]
- Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dille G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol Psychiatry*. 1999; 45:1085–1098. [PubMed: 10331101]
- Rajkowska G, O'Dwyer G, Teleki Z, Stockmeier CA, Miguel-Hidalgo JJ. GABAergic neurons immunoreactive for calcium binding proteins are reduced in the prefrontal cortex in major depression. *Neuropsychopharmacology*. 2007; 32:471–482. [PubMed: 17063153]
- Rattiner LM, Davis M, French CT, Ressler KJ. Brain-derived neurotrophic factor and tyrosine kinase receptor B involvement in amygdala-dependent fear conditioning. *J Neurosci*. 2004; 24:4796–4806. [PubMed: 15152040]
- Rex CS, Lin CY, Kramar EA, Chen LY, Gall CM, Lynch G. Brain-derived neurotrophic factor promotes long-term potentiation-related cytoskeletal changes in adult hippocampus. *J Neurosci*. 2007; 27:3017–3029. [PubMed: 17360925]
- Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, Babbini F, Fabbri ME, Tessarollo L, Maffei L, Berardi N, Caleo M. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. *Eur J Neurosci*. 2006; 24:1850–1856. [PubMed: 17040481]
- Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience*. 2000; 101:305–312. [PubMed: 11074154]
- Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*. 2011; 472:466–470. [PubMed: 21460835]

- Sairanen M, Lucas G, Ernfors P, Castren M, Castren E. Brain-derived neurotrophic factor and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation, and survival in the adult dentate gyrus. *J Neurosci.* 2005; 25:1089–1094. [PubMed: 15689544]
- Sakata K, Woo NH, Martinowich K, Greene JS, Schloesser RJ, Shen L, Lu B. Critical role of promoter IV-driven BDNF transcription in GABAergic transmission and synaptic plasticity in the prefrontal cortex. *Proc Natl Acad Sci U S A.* 2009; 106:5942–5947. [PubMed: 19293383]
- Sale A, Maya Vetencourt JF, Medini P, Cenni MC, Baroncelli L, De Pasquale R, Maffei L. Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nat Neurosci.* 2007; 10:679–681. [PubMed: 17468749]
- Sandi C, Richter-Levin G. From high anxiety trait to depression: a neurocognitive hypothesis. *Trends Neurosci.* 2009; 32:312–320. [PubMed: 19409624]
- Scharfman HE, Macluskus NJ. Similarities between actions of estrogen and BDNF in the hippocampus: coincidence or clue? *Trends Neurosci.* 2005; 28:79–85. [PubMed: 15667930]
- Schitine C, Xapelli S, Agasse F, Sarda-Arroyo L, Silva AP, De Melo Reis RA, de Mello FG, Malva JO. Ampakine CX546 increases proliferation and neuronal differentiation in subventricular zone stem/progenitor cell cultures. *Eur J Neurosci.* 2012; 35:1672–1683. [PubMed: 22506985]
- Schmidt HD, Duman RS. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. *Neuropsychopharmacology.* 2010; 35:2378–2391. [PubMed: 20686454]
- Schmidt PJ, Rubinow DR. Sex hormones and mood in the perimenopause. *Ann N Y Acad Sci.* 2009; 1179:70–85. [PubMed: 19906233]
- Schnatz PF, Whitehurst SK, O'Sullivan DM. Sexual dysfunction, depression, and anxiety among patients of an inner-city menopause clinic. *J Womens Health (Larchmt).* 2010; 19:1843–1849. [PubMed: 20677995]
- Seedat S, Stein DJ, Carey PD. Post-traumatic stress disorder in women: epidemiological and treatment issues. *CNS Drugs.* 2005; 19:411–427. [PubMed: 15907152]
- Seil FJ, Drake-Baumann R. Neurotrophins and activity-dependent inhibitory synaptogenesis. *Prog Brain Res.* 2000; 128:219–229. [PubMed: 11105681]
- Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N, Okada S, Iyo M. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry.* 2003; 54:70–75. [PubMed: 12842310]
- Shughrue PJ, Lane MV, Merchenthaler I. Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. *J Comp Neurol.* 1997; 388:507–525. [PubMed: 9388012]
- Silveira H, Moraes H, Oliveira N, Coutinho ES, Laks J, Deslandes A. Physical Exercise and Clinically Depressed Patients: A Systematic Review and Meta-Analysis. *Neuropsychobiology.* 2013; 67:61–68. [PubMed: 23295766]
- Simmons DA, Rex CS, Palmer L, Pandeyarajan V, Fedulov V, Gall CM, Lynch G. Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. *Proc Natl Acad Sci U S A.* 2009; 106:4906–4911. [PubMed: 19264961]
- Simpkins JW, Green PS, Gridley KE, Singh M, de Fiebre NC, Rajakumar G. Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer's disease. *Am J Med.* 1997; 103:19S–25S. [PubMed: 9344403]
- Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol Biochem Behav.* 1997; 56:131–137. [PubMed: 8981620]
- Slipczuk L, Bekinschtein P, Katze C, Cammarota M, Izquierdo I, Medina JH. BDNF activates mTOR to regulate GluR1 expression required for memory formation. *PLoS One.* 2009; 4:e6007. [PubMed: 19547753]
- 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.* 1995; 15:1768–1777. [PubMed: 7891134]
- Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature.* 2011; 476:458–461. [PubMed: 21814201]

- Soetanto A, Wilson RS, Talbot K, Un A, Schneider JA, Sobiesk M, Kelly J, Leurgans S, Bennett DA, Arnold SE. Association of anxiety and depression with microtubule-associated protein 2- and synaptopodin-immunolabeled dendrite and spine densities in hippocampal CA3 of older humans. *Arch Gen Psychiatry*. 2010; 67:448–457. [PubMed: 20439826]
- Sohrabji F, Miranda RC, Toran-Allerand CD. Identification of a putative estrogen response element in the gene encoding brain-derived neurotrophic factor. *Proc Natl Acad Sci U S A*. 1995; 92:11110–11114. [PubMed: 7479947]
- Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, Jing D, Tottenham N, Amso D, Somerville LH, Voss HU, Glover G, Ballon DJ, Liston C, Teslovich T, Van Kempen T, Lee FS, Casey BJ. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science*. 2010; 327:863–866. [PubMed: 20075215]
- Solomon MB, Herman JP. Sex differences in psychopathology: of gonads, adrenals and mental illness. *Physiol Behav*. 2009; 97:250–258. [PubMed: 19275906]
- Sotres-Bayon F, Sierra-Mercado D, Pardilla-Delgado E, Quirk GJ. Gating of fear in prelimbic cortex by hippocampal and amygdala inputs. *Neuron*. 2012; 76:804–812. [PubMed: 23177964]
- Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*. 2000; 24:417–463. [PubMed: 10817843]
- Spires TL, Grote HE, Varshney NK, Cordery PM, van Dellen A, Blakemore C, Hannan AJ. Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *J Neurosci*. 2004; 24:2270–2276. [PubMed: 14999077]
- Studer L, Spenger C, Seiler RW, Altar CA, Lindsay RM, Hyman C. Comparison of the effects of the neurotrophins on the morphological structure of dopaminergic neurons in cultures of rat substantia nigra. *Eur J Neurosci*. 1995; 7:223–233. [PubMed: 7757259]
- Suen PC, Wu K, Levine ES, Mount HT, Xu JL, Lin SY, Black IB. Brain-derived neurotrophic factor rapidly enhances phosphorylation of the postsynaptic N-methyl-D-aspartate receptor subunit 1. *Proc Natl Acad Sci U S A*. 1997; 94:8191–8195. [PubMed: 9223337]
- Sunanda, Rao MS, Raju TR. Effect of chronic restraint stress on dendritic spines and excrescences of hippocampal CA3 pyramidal neurons--a quantitative study. *Brain Res*. 1995; 694:312–317. [PubMed: 8974660]
- Surget A, Tanti A, Leonardo ED, Laugeray A, Rainer Q, Touma C, Palme R, Griebel G, Ibarguen-Vargas Y, Hen R, Belzung C. Antidepressants recruit new neurons to improve stress response regulation. *Mol Psychiatry*. 2011; 16:1177–1188. [PubMed: 21537331]
- Sutachan JJ, Chao MV, Ninan I. Regulation of inhibitory neurotransmission by the scaffolding protein ankyrin repeat-rich membrane spanning/kinase D-interacting substrate of 220 kDa. *J Neurosci Res*. 2010; 88:3447–3456. [PubMed: 20936698]
- Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. *Mol Psychiatry*. 2010; 15:80–92. [PubMed: 19621014]
- Tanaka J, Horiike Y, Matsuzaki M, Miyazaki T, Ellis-Davies GC, Kasai H. Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. *Science*. 2008; 319:1683–1687. [PubMed: 18309046]
- Tardito D, Perez J, Tiraboschi E, Musazzi L, Racagni G, Popoli M. Signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms in the action of antidepressants: a critical overview. *Pharmacol Rev*. 2006; 58:115–134. [PubMed: 16507885]
- Taylor SM. Electroconvulsive therapy, brain-derived neurotrophic factor, and possible neurorestorative benefit of the clinical application of electroconvulsive therapy. *J ECT*. 2008; 24:160–165. [PubMed: 18580563]
- Tyler WJ, Pozzo-Miller LD. BDNF enhances quantal neurotransmitter release and increases the number of docked vesicles at the active zones of hippocampal excitatory synapses. *J Neurosci*. 2001; 21:4249–4258. [PubMed: 11404410]
- 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*. 1997; 28:103–110. [PubMed: 9220467]

- Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci.* 2004; 20:2580–2590. [PubMed: 15548201]
- Verhagen M, van der Meij A, van Deurzen PA, Janzing JG, Arias-Vásquez A, Buitelaar JK, Franke B. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. *Mol Psychiatry.* 2010; 15:260–271. [PubMed: 18852698]
- Vicario-Abejon C, Collin C, McKay RD, Segal M. Neurotrophins induce formation of functional excitatory and inhibitory synapses between cultured hippocampal neurons. *J Neurosci.* 1998; 18:7256–7271. [PubMed: 9736647]
- Vicario-Abejon C, Owens D, McKay R, Segal M. Role of neurotrophins in central synapse formation and stabilization. *Nat Rev Neurosci.* 2002; 3:965–974. [PubMed: 12461553]
- Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci.* 2002; 22:6810–6818. [PubMed: 12151561]
- Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. *J Neurosci.* 2008; 28:1374–1384. [PubMed: 18256257]
- Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS. Tianeptine attenuates stress-induced morphological changes in the hippocampus. *Eur J Pharmacol.* 1992a; 222:157–162. [PubMed: 1468492]
- Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res.* 1992b; 588:341–345. [PubMed: 1393587]
- Wei SM, Eisenberg DP, Kohn PD, Kippenhan JS, Kolachana BS, Weinberger DR, Berman KF. Brain-derived neurotrophic factor Val(6)(6)Met polymorphism affects resting regional cerebral blood flow and functional connectivity differentially in women versus men. *J Neurosci.* 2012; 32:7074–7081. [PubMed: 22593075]
- West AE, Chen WG, Dalva MB, Dolmetsch RE, Kornhauser JM, Shaywitz AJ, Takasu MA, Tao X, Greenberg ME. Calcium regulation of neuronal gene expression. *Proc Natl Acad Sci U S A.* 2001; 98:11024–11031. [PubMed: 11572963]
- Wezenberg E, Verkes RJ, Ruigt GS, Hulstijn W, Sabbe BG. Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers. *Neuropsychopharmacology.* 2007; 32:1272–1283. [PubMed: 17119538]
- Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA, Hempstead BL, Lu B. Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. *Nat Neurosci.* 2005; 8:1069–1077. [PubMed: 16025106]
- Woon FL, Sood S, Hedges DW. Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010; 34:1181–1188. [PubMed: 20600466]
- Xia YF, Arai AC. AMPA receptor modulators have different impact on hippocampal pyramidal cells and interneurons. *Neuroscience.* 2005; 135:555–567. [PubMed: 16125852]
- Xia YF, Kessler M, Arai AC. Positive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulators have different impact on synaptic transmission in the thalamus and hippocampus. *J Pharmacol Exp Ther.* 2005; 313:277–285. [PubMed: 15626725]
- Xie Y, Hayden MR, Xu B. BDNF overexpression in the forebrain rescues Huntington's disease phenotypes in YAC128 mice. *J Neurosci.* 2010; 30:14708–14718. [PubMed: 21048129]
- Xu F, Plummer MR, Len GW, Nakazawa T, Yamamoto T, Black IB, Wu K. Brain-derived neurotrophic factor rapidly increases NMDA receptor channel activity through Fyn-mediated phosphorylation. *Brain Res.* 2006; 1121:22–34. [PubMed: 17045972]
- Yamada MK, Nakanishi K, Ohba S, Nakamura T, Ikegaya Y, Nishiyama N, Matsuki N. Brain-derived neurotrophic factor promotes the maturation of GABAergic mechanisms in cultured hippocampal neurons. *J Neurosci.* 2002; 22:7580–7585. [PubMed: 12196581]
- Yan Q, Rosenfeld RD, Matheson CR, Hawkins N, Lopez OT, Bennett L, Welcher AA. Expression of brain-derived neurotrophic factor protein in the adult rat central nervous system. *Neuroscience.* 1997; 78:431–448. [PubMed: 9145800]

- Yano H, Ninan I, Zhang H, Milner TA, Arancio O, Chao MV. BDNF-mediated neurotransmission relies upon a myosin VI motor complex. *Nat Neurosci.* 2006; 9:1009–1018. [PubMed: 16819522]
- Yau SY, Lau BW, Tong JB, Wong R, Ching YP, Qiu G, Tang SW, Lee TM, So KF. Hippocampal neurogenesis and dendritic plasticity support running-improved spatial learning and depression-like behaviour in stressed rats. *PLoS One.* 2011; 6:e24263. [PubMed: 21935393]
- Ying SW, Futter M, Rosenblum K, Webber MJ, Hunt SP, Bliss TV, Bramham CR. Brain-derived neurotrophic factor induces long-term potentiation in intact adult hippocampus: requirement for ERK activation coupled to CREB and upregulation of Arc synthesis. *J Neurosci.* 2002; 22:1532–1540. [PubMed: 11880483]
- Young D, Lawlor PA, Leone P, Dragunow M, During MJ. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nat Med.* 1999; 5:448–453. [PubMed: 10202938]
- Yu H, Wang Y, Pattwell S, Jing D, Liu T, Zhang Y, Bath KG, Lee FS, Chen ZY. Variant BDNF Val66Met polymorphism affects extinction of conditioned aversive memory. *J Neurosci.* 2009; 29:4056–4064. [PubMed: 19339601]
- Zafra F, Castren E, Thoenen H, Lindholm D. Interplay between glutamate and gamma-aminobutyric acid transmitter systems in the physiological regulation of brain-derived neurotrophic factor and nerve growth factor synthesis in hippocampal neurons. *Proc Natl Acad Sci U S A.* 1991; 88:10037–10041. [PubMed: 1658793]
- Zeidan MA, Igoe SA, Linnman C, Vitalo A, Levine JB, Klibanski A, Goldstein JM, Milad MR. Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. *Biol Psychiatry.* 2011; 70:920–927. [PubMed: 21762880]
- Zender R, Olshansky E. Women's mental health: depression and anxiety. *Nurs Clin North Am.* 2009; 44:355–364. [PubMed: 19683096]
- Zeng Y, Lv F, Li L, Yu H, Dong M, Fu Q. 7,8-dihydroxyflavone rescues spatial memory and synaptic plasticity in cognitively impaired aged rats. *J Neurochem.* 2012; 122:800–811. [PubMed: 22694088]
- Zhao J, Bao AM, Qi XR, Kamphuis W, Luchetti S, Lou JS, Swaab DF. Gene expression of GABA and glutamate pathway markers in the prefrontal cortex of non-suicidal elderly depressed patients. *J Affect Disord.* 2012; 138:494–502. [PubMed: 22357337]
- Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. *Nat Rev Neurol.* 2009; 5:311–322. [PubMed: 19498435]

Highlights

- BDNF influences affective behaviors by modifying neurogenesis and synapses.
- Altered synaptic plasticity due to reduced BDNF might cause affective disorders.
- Enhancement of cortical BDNF signaling might improve affective symptoms.

Figure 1.
Decreased BDNF signaling impairs adult neurogenesis, synaptic transmission, synaptic and structural plasticity.