Journal of Depression and Anxiety
ISSN: 2167-1044

Neumeister et al., J Depress Anxiety 2013, S4
DOI: 10.4172/2167-1044.S4-006

Review Article Open Access

The Role of BDNF-TrkB Signaling in the Pathogenesis of PTSD

Alexander Neumeister[1]*, Stefani Corsi-Travali[2] and Christopher R. Green[2]

[1]Molecular Imaging Program, Department of Psychiatry and Radiology, New York University School of Medicine, New York, USA
[2]Steven and Alexandra Cohen Veterans Center for the Study of Posttraumatic Stress and Traumatic Brain Injury, Department of Psychiatry, New York University Langone Medical Center, New York, USA

Abstract

Posttraumatic Stress Disorder (PTSD) is a prevalent, chronic, and disabling anxiety disorder that may develop following exposure to a traumatic event. The majority of individuals with PTSD often have comorbid psychiatric conditions such as major depression, generalized anxiety disorder, and substance use disorders, and are at increased risk for suicide. Despite the public health significance of PTSD, relatively little is known about the etiology or pathophysiology of this disorder, and pharmacotherapy development to date has been largely opportunistic instead of mechanism-based. One promising target for modulation is Tropomyosin Receptor Kinase B (TrkB), the receptor for Brain-Derived Neurotrophic Factor (BDNF), a signaling pathway important for neuronal plasticity, survival, and growth. The following discusses how genetic and environmental alterations to this signaling pathway may contribute to anatomical and functional changes in the hippocampus, amygdala, anterior cingulate cortex, ventromedial prefrontal cortex, and the nucleus accumbens. Changes in these brain regions may in turn contribute to the predisposition to or maintenance of some of the clinical manifestations of PTSD, including intrusive memories, hyperarousal, increased fear, and emotional numbing.

Keywords: Posttraumatic stress disorder; Pathogenesis; Neurotrophic processes; Bdnf-TrkB Signaling

Introduction

Post-Traumatic Stress Disorder (PTSD) is a disease which affects millions of people a year, yet no strong, universal prevention or treatment strategy is available. One promising target for the development of trsategies of treatment and secondary prevention is tropomyosin receptor kinase B (TrkB), the receptor for brain-derived neurotrophic factor (BDNF). This signaling pathway has been implicated in a wide variety of psychiatric diseases, with significant changes in levels of BDNF and TrkB mRNA and protein levels in the hippocampal and pre-frontal cortical regions in the post-mortem brains of individuals with various psychiatric diseases [1-4]. More specific to PTSD, changes in this pathway have been shown to affect contextual fear learning, extinction, and expression and reward responsiveness [5-7]. These alterations may be partially responsible for the development of clinical hallmarks of PTSD such as intrusive memories, hyperarousal, fear, and restricted range of affect (Figure 1). This paper reviews our current understanding of the pathophysiology underlying PTSD with evidence suggesting functional etiologies in the TrkB-BDNF system. By revealing the neurobiological substrates and systems that play a role in the etiology of PTSD, we aim to identify novel targets that offer potential therapeutic value in developing future evidence-based PTSD pharmacologic interventions.

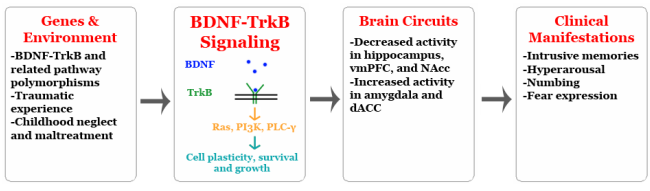

Figure 1: Genetic differences, such as the BDNF Val66Met allele, in combination with environmental exposure, such as childhood neglect, alter the level of BDNF-TrkB signaling, which is important for neuronal plasticity and growth. This contributes to changes in the hippocampus and poorly contextualized fear memories, in the vmPFC and deficient fear extinction, in the NAcc and reduced reward responsiveness, and in the amygdala and dACC, leading to heightened fear response.

Search Methodology

Searches were carried out using primarily Google Scholar and NCBI's PubMed databases. Key search terms used, some in combination, include: "PTSD," "BDNF," "TrkB" "neurogenesis," "stress," "corticosterone," "post-mortem," "depression," "hippocampus," "nucleus accumbens," "prefrontal cortex," "anterior cingulate cortex," "amygdala," "fMRI," "volume," "heterozygous," "child," "Val66Met," "5-HTTLPR," "fear," "contextual fear," and "reward responsiveness." Additional literature was found using review papers to fill in any gaps generated from the above search criteria. The paper itself attempts to describe the strength and quality of evidence found in any given paper, for example, whether it is cross-sectional, genetic, meta-analytic, prospective, or experimental, and whether it was done in humans or animal models. An effort is made to include all literature directly relevant to the arguments made herein, with a special focus on the highest-quality evidence.

Molecular Biology of BDNF-TrkB Signaling

The effects of BDNF-TrkB signaling are wide ranging and include increased cell plasticity, survival, and growth. TrkB signals through Ras, PI3K, and PLC-gamma and is important for long-term potentiation in the hippocampus [8,9], hippocampal memory consolidation [10], pre-synaptic vesicle docking and release [11,12], increased arborization and synapse number [13], survival of neurons [14], neurogenesis [15], and morphology of neurons [16]. Given its widespread distribution

***Corresponding author:** Alexander Neumeister, Director, Molecular Imaging Program, Department of Psychiatry and Radiology, New York University School of Medicine, One Park Avenue, 8th Floor, Room 225, New York-10016, USA, Tel: (646) 754-4827; E-mail: alexander.neumeister@nyumc.org

Received September 09, 2013; **Accepted** September 30, 2013; **Published** October 04, 2013

Citation: Neumeister A, Corsi-Travali S, Green CR (2013) The Role of BDNF-TrkB Signaling in the Pathogenesis of PTSD. J Depress Anxiety S4: 006. doi: 10.4172/2167-1044.S4-006

throughout the brain and its broad functional role, the BDNF-TrkB pathway interacts with many other signaling systems relevant to psychopathology, including the serotonin, endocannabinoids, and glutamatergic pathways [6]. Regulation of BDNF-TrkB signaling is multivariate and has not been fully elucidated. However, neuronal activity, positive and negative autocrine and paracrine feedback, gluccocorticoids, and complex endosomal signaling are implicated [17].

BDNF-TrkB Signaling Affects Brain Circuits Important in PTSD

To understand how PTSD develops, it must be explained how genetic and environmental variables lead to predisposing neurocircuitry abnormalities, which when confronted with a traumatic stimulus, induce or uncover other abnormalities, resulting in sustained PTSD symptoms. Using various prospective, twin, and genetic studies, there has been some recent work that attempts to differentiate which abnormalities present in individuals with PTSD pre-date the traumatic experience from those acquired during and after the trauma [18]. Building on this work, the following explains the importance of BDNF-TrkB signaling in the hippocampus, amygdala, anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), and nucleus accumbens (NAcc) in the pre-disposition to and maintenance of PTSD symptoms. These structures are highly interconnected and together help determine behaviors important in PTSD [19].

Hippocampus

Cross-sectional studies have associated decreased hippocampal volume, especially in the cornu ammonis region 3 and the dentate gyrus of the hippocampus, with PTSD [20,21]. Stronger evidence for decreased hippocampal volume as a true predisposing factor for PTSD comes from monozygotic twin studies [22,23], although decreases in hippocampal volume may also be acquired post-trauma [24,25]. Functionally, declarative memory deficits have been identified in humans with PTSD [26,27] and animal lesion studies have found the hippocampus to be vital for developing contextual fear memory [28]. In addition, blocking neurogenesis in the hippocampus has been shown to reduce contextual fear learning [29]. Thus, impaired contextual encoding offers one possible explanation for re-experiencing of aversive memories in inappropriate contexts.

While childhood neglect and maltreatment clearly pre-dispose individuals towards increased amygdala reactivity, it is more uncertain whether these factors contribute to decreased hippocampal volume. Some have found decreased hippocampal volume among those maltreated as children [30], while others have found no effect among people who were institutionalized or had depressed mothers as children [31,32]. Although the effect of childhood environment is uncertain, animal models have found that stress and exogenous corticosterone alter BDNF and TrkB mRNA and protein levels in the hippocampus [33-36], pre-natal and adult stress decrease neurogenesis in the hippocampus [37-41], and stress and exogenous corticosterone decrease hippocampal volume [42,43].

In addition to potential stress induced changes in BDNF-TrkB signaling and hippocampal volume, genetic variation in this pathway probably also contributes to some PTSD vulnerability with respect to hippocampal volume. The BDNF Met allele is associated with declarative memory deficits, decreased hippocampal NAA levels [44], and decreased hippocampal volume [45-49], although others have found no effect on volume [50-52]. In addition, BDNF signaling is vital for neurogenesis in the hippocampus [15,53]. As was discussed earlier, BDNF-TrkB signaling has been found to be important for long-term potentiation in the hippocampus [8], hippocampal memory consolidation [10], increased pre-synaptic vesicle docking and release in hippocampal neurons [11,12], and increased arborization, synapse number [13], survival, [14] and normal morphology of neurons [16]. Most importantly, animal models of BDNF heterozygous knockouts and TrkB heterozygous knockouts show diminished hippocampal-LTP, with corresponding decreases in contextual fear conditioning [5,9,54,55]. Furthermore, overexpression of TrkB in mice led to improved memory, contextual fear conditioning, and overall reduced anxiety [56]. Finally, BDNF expression in the hippocampus is vital for extinction of fear memories [57]. These findings suggest that a genetic and/or environmentally caused deficiency in the BDNF-TrkB signaling pathway could lead to improper development and maintenance of hippocampal volume, robustness, and plasticity. This could predispose individuals to poorly contextualized memories and weakened fear extinction, ultimately contributing to intrusive memories and difficulty forming new memories.

Amygdala and anterior cingulate cortex (ACC)

Given the importance of both of these structures in bringing about the fear response, and in the case of the dACC inhibiting fear extinction, increased responsivity to emotional stimuli in these areas may account for some of the increased fear expression, hyperarousal and to a lesser extent intrusive memories seen in PTSD [18,58-60]. In two prospective studies of military personnel, increased activity in the amygdala in response to emotional stimuli was associated with a greater vulnerability to developing PTSD symptoms [24,61]. Increased resting metabolic activity and activation to an interference task in the dorsal anterior cingulate cortex (dACC) also predicts an increased likelihood of developing PTSD [62,63]. In addition to changes in dACC activity, overall decreases in ACC volume are associated with a predisposition to develop PTSD among adolescents and adults [64,65]. Furthermore, the BDNF Val66Met polymorhism, which results in decreased activity dependent secretion of BDNF [44], has been associated with decreased ACC grey matter volume (GMV) among adolescents [66]. This suggests a potential role for BDNF-TrkB signaling in this area. Deficient BDNF secretion could lead to inadequate growth signaling in the ACC, diminished volume in this region, and ultimately a predisposition to developing PTSD. Whether and how overall changes in ACC GMV are related to dACC activity specifically is unclear.

Changes in the function of the amygdala have been associated with childhood maltreatment, deprivation, and institutionalization [31,67-70] and genetic polymorphisms, such as the serotonin transporter (5-HTT) gene [71]. BDNF may influence the serotonin system as it relates to amygdala activity. The serotonin transporter linked polymorphic region (5-HTTLPR) short allele is associated with increased amygdala activation in response to emotional stimuli [72] and with PTSD among individuals with childhood adversity [73]. Furthermore, in the setting of depression, evidence indicates that, among maltreated children, Val66Met alleles in combination with 5-HTTLPR short alleles produces the greatest risk for depression [74,75]. This suggests that BDNF signaling could also play a role in modulating the effect of the serotonin system on amygdala dysfunction in PTSD.

Nonetheless, it should be noted that increased BDNF signaling could theoretically increase the risk of PTSD, if present in certain brain areas such as the amygdala. During fear acquisition BDNF expression and TrkB phosphorylation are increased in the basolateral amygdala, while inhibition of TrkB in the BLA resulted in disrupted

fear acquisition [76]. All together, the above suggests that dysregulated BDNF signaling may interfere with normal functioning of the ACC and amygdala, leading to heightened fear responses, ultimately contributing to the potential development of PTSD.

Ventromedial prefrontal cortex (vmPFC)

Another major brain area important in PTSD is the ventromedial prefrontal cortex, an area involved in fear extinction [6]. In the lab, humans who have acquired PTSD have increased fear acquisition, yet decreased fear extinction [77-79]. Some evidence does suggest that the fear extinction deficit in PTSD is an acquired trait rather than a pre-existing one [80]. Nonetheless, even if impaired fear extinction is more of an acquired deficit, it may contribute to the maintenance of many clinically relevant features of PTSD, such as re-experiencing, avoidance, and anxious arousal. Functionally, changes in fear extinction among those with PTSD have been associated with under-activation of the vmPFC and over-activation of the dACC during extinction training [81]. The vmPFC is thought to generally exert inhibitory control over the amygdala and is important for acquiring and recalling fear extinction [58,82-84]. Moreover, BDNF signaling likely plays an important role in this brain region. BDNF met alleles have been associated with deficient fear extinction and activation in the vmPFC, [85,86] the process of fear extinction increases BDNF in the vmPFC, [87] and systemic BDNF agonist increases fear extinction [88].

Nucleus accumbens (NAcc)

Another brain region implicated in the pathogenesis of PTSD is the nucleus accumbens area. Evidence indicates that in PTSD the nucleus accumbens may be less active, corresponding to a decrease in reward responsiveness [89,90]. However, one prospective study suggests that decreased NAcc responsivity may be an acquired, post-traumatic deficit [61]. Nonetheless, individuals with decreased BDNF-TrkB signaling may be less able to cope with diminished activity in the NAcc due to a combination of genetic vulnerability and traumatic experience. Indeed, both BDNF and TrkB expression are vital for reward responsiveness in BDNF knockout and replacement models in mice [91,92]. In humans, there is some evidence that the BDNF met allele diminishes reward seeking and aversive stimuli avoidance behavior [7]. In conclusion, diminished BDNF signaling in the NAcc may contribute to decreased reward responsiveness, leading to the restricted range of affect, or emotional numbing, commonly seen in individuals with PTSD.

Peripheral BDNF and PTSD

Changes in peripheral concentrations of BDNF have been found in a diverse set of psychiatric diseases, including schizophrenia, depression, bipolar disorder [93-95]. Peripheral measurements of BDNF, in addition to more central ones such as measurements from CSF, provide a potential way to both study the pathogenesis of PTSD as well as act as a biomarker of disease. Evidence for the relevance of peripheral BDNF comes from an experiment that administered exogenous BDNF peripherally in an animal model. BDNF was found to improve anxiety and depression characteristics across different tasks. On a cellular level, exogenous peripheral BDNF increased neurogenesis in the hippocampus, with elevated hippocampal BDNF, pCREB, and Perk [96]. This suggests that BDNF has the ability to cross the blood brain barrier and that peripheral BDNF may potentially be relevant for studying psychiatric diseases.

Overall, there is moderately strong evidence to suggest that increased peripheral BDNF is associated with a current diagnosis of PTSD. One study found increased BDNF serum concentrations among those with PTSD, but only in the PTSD group whose traumatic experienced occurred in the past year [97]. Another paper found increased serum BDNF among those with un-medicated PTSD, with a corresponding positive correlation between Clinician-Administered PTSD Scale (CAPS) score and serum BDNF level [98]. Among those with the BDNF Val66Met allele, those with a probable diagnosis of PTSD had higher average BDNF plasma concentrations [99]. Nonetheless, one study did find a conflicting result, in that those with PTSD had lower plasma BDNF levels compared to controls [100].

Although there is evidence that suggests an elevation in peripheral BDNF after developing PTSD, it is unclear how this is related to the pathogenesis of the disease. For instance, it may be a compensatory response, rather than a predisposing one. More prospective studies need to be carried out to determine how peripheral BDNF levels are related to the neurocircuitry models discussed in the other sections of this paper.

Conclusion

Overall, it appears that alterations in BDNF-TrkB signaling may play an important role in PTSD. In the hippocampus, vmPFC, ACC, and NAcc deficient BDNF-TrkB signaling likely aids in the pre-disposition to maintenance of impaired contextual fear learning, fear extinction, and restricted range of affect. In turn, these may be associated with some of the clinical manifestations of PTSD, such as intrusive and incomplete memories, hyperarousal, fear expression, and restricted range of affect.

Although a decrease in signaling in the BDNF-TrkB pathway is likely a contributing factor in PTSD, as a neurotrophin and regulator of plasticity, changes in either direction in BDNF signaling, depending on its location, intensity, and time course may moderate the risk of developing stress related psychopathology. In animal models, systemic administration of TrkB receptor modulators have resulted in changes in phenotypes related to human PTSD, such as fear acquisition and extinction [88] and anxiety related phenotypes [101]. These experiments suggest a potential therapeutic role for altering BDNF-TrkB signaling. More translational research in humans in now needed to verify and refine animal models. For example, PET imaging studies using radioligands specific for TrkB may be used to help identify in vivo changes in BDNF-TrkB signaling in various brain regions. Although a drug targeting this system for treatment of PTSD in humans is currently unavailable, research into this area may someday provide a means of preventing or treating patients with PTSD.

Conflict of Interest/Financial Disclosures

The authors report no conflicts of interest relevant to this article.

Funding Information

The project described was supported by the National Institutes of Health through the following awards: R21MH096105, R21MH085627, and R01MH096876, and the Department of Defense (DoD): 11173006. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH or the DoD.

References

1. Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, et al. (2003) Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 60: 804-815.

2. Pandey GN, Ren X, Rizavi HS, Conley RR, Roberts RC, et al. (2008) Brain-derived neurotrophic factor and tyrosine kinase B receptor signalling in post-mortem brain of teenage suicide victims. Int J Neuropsychopharmacol 11: 1047-1061.

3. Thompson Ray M, Weickert CS, Wyatt E, Webster MJ (2011) Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders. J Psychiatry Neurosci 36: 195-203.
4. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001) Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 50: 260-265.
5. Liu IY, Lyons WE, Mamounas LA, Thompson RF (2004) Brain-derived neurotrophic factor plays a critical role in contextual fear conditioning. J Neurosci 24: 7958-7963.
6. Andero R, Ressler KJ (2012) Fear extinction and BDNF: translating animal models of PTSD to the clinic. Genes Brain Behav 11: 503-512.
7. Gasic GP, Smoller JW, Perlis RH, Sun M, Lee S, et al. (2009) BDNF, relative preference, and reward circuitry responses to emotional communication. Am J Med Genet B Neuropsychiatr Genet 150B: 762-781.
8. Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B (1996) Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381: 706-709.
9. Minichiello L, Korte M, Wolfer D, Kühn R, Unsicker K, et al. (1999) Essential role for TrkB receptors in hippocampus-mediated learning. Neuron 24: 401-414.
10. Lee JL, Everitt BJ, Thomas KL (2004) Independent cellular processes for hippocampal memory consolidation and reconsolidation. Science 304: 839-843.
11. Li YX, Zhang Y, Lester HA, Schuman EM, Davidson N (1998) Enhancement of neurotransmitter release induced by brain-derived neurotrophic factor in cultured hippocampal neurons. J Neurosci 18: 10231-10240.
12. Collin C, Vicario-Abejon C, Rubio ME, Wenthold RJ, McKay RD, et al. (2001) Neurotrophins act at presynaptic terminals to activate synapses among cultured hippocampal neurons. Eur J Neurosci 13: 1273-1282.
13. Alsina B, Vu T, Cohen-Cory S (2001) Visualizing synapse formation in arborizing optic axons in vivo: dynamics and modulation by BDNF. Nat Neurosci 4: 1093-1101.
14. Gorski JA, Zeiler SR, Tamowski S, Jones KR (2003) Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. J Neurosci 23: 6856-6865.
15. Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, et al. (2005) Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 192: 348-356.
16. Baquet ZC, Gorski JA, Jones KR (2004) Early striatal dendrite deficits followed by neuron loss with advanced age in the absence of anterograde cortical brain-derived neurotrophic factor. J Neurosci 24: 4250-4258.
17. Nagappan G, Lu B (2005) Activity-dependent modulation of the BDNF receptor TrkB: mechanisms and implications. Trends Neurosci 28: 464-471.
18. Admon R, Milad MR, Hendler T (2013) A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. Trends Cogn Sci 17: 337-347.
19. Kaplan GB, Vasterling JJ, Vedak PC (2010) Brain-derived neurotrophic factor in traumatic brain injury, post-traumatic stress disorder, and their comorbid conditions: role in pathogenesis and treatment. Behav Pharmacol 21: 427-437.
20. Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD (2005) Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. J Affect Disord 88: 79-86.
21. Wang Z, Neylan TC, Mueller SG, Lenoci M, Truran D, et al. (2010) Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. Arch Gen Psychiatry 67: 296-303.
22. Pitman RK, Gilbertson MW, Gurvits TV, May FS, Lasko NB, et al. (2006) Clarifying the origin of biological abnormalities in PTSD through the study of identical twins discordant for combat exposure. Ann N Y Acad Sci 1071: 242-254.
23. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, et al. (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5: 1242-1247.
24. Admon R, Lubin G, Stern O, Rosenberg K, Sela L, et al. (2009) Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. Proc Natl Acad Sci U S A 106: 14120-14125.
25. Admon R, Leykin D, Lubin G, Engert V, Andrews J, et al. (2012) Stress-induced reduction in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. Hum Brain Mapp.
26. Jelinek L, Jacobsen D, Kellner M, Larbig F, Biesold KH, et al. (2006) Verbal and nonverbal memory functioning in posttraumatic stress disorder (PTSD). J Clin Exp Neuropsychol 28: 940-948.
27. Bremner JD, Vermetten E, Afzal N, Vythilingam M (2004) Deficits in verbal declarative memory function in women with childhood sexual abuse-related posttraumatic stress disorder. J Nerv Ment Dis 192: 643-649.
28. Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106: 274-285.
29. Drew MR, Denny CA, Hen R (2010) Arrest of adult hippocampal neurogenesis in mice impairs single- but not multiple-trial contextual fear conditioning. Behav Neurosci 124: 446-454.
30. Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, et al. (2012) Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biol Psychiatry 71: 286-293.
31. Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, et al. (2009) Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. J Child Psychol Psychiatry 50: 943-951.
32. Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, et al. (2011) Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. Proc Natl Acad Sci U S A 108: 14324-14329.
33. Kozlovsky N, Matar MA, Kaplan Z, Kotler M, Zohar J, et al. (2007) Long-term down-regulation of BDNF mRNA in rat hippocampal CA1 subregion correlates with PTSD-like behavioural stress response. Int J Neuropsychopharmacol 10: 741-758.
34. Jacobson JP, Mork A (2006) Chronic corticosterone decreases brain-derived neurotrophic factor (BDNF) mRNA and protein in the hippocampus, but not in the frontal cortex, of the rat. Brain Res 1110: 221-225.
35. Bazak N, Kozlovsky N, Kaplan Z, Matar M, Golan H, et al. (2009) Pre-pubertal stress exposure affects adult behavioral response in association with changes in circulating corticosterone and brain-derived neurotrophic factor. Psychoneuroendocrinology 34: 844-858.
36. Nibuya M, Takahashi M, Russell DS, Duman RS (1999) Repeated stress increases catalytic TrkB mRNA in rat hippocampus. Neurosci Lett 267: 81-84.
37. Coe CL, Kramer M, Czéh B, Gould E, Reeves AJ, et al. (2003) Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. Biol Psychiatry 54: 1025-1034.
38. Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E (1997) Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 17: 2492-2498.
39. Gould E, Tanapat P, McEwen BS, Flügge G, Fuchs E (1998) Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A 95: 3168-3171.
40. Tanapat P, Galea LA, Gould E (1998) Stress inhibits the proliferation of granule cell precursors in the developing dentate gyrus. Int J Dev Neurosci 16: 235-239.
41. Lemaire V, Koehl M, Le Moal M, Abrous DN (2000) Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc Natl Acad Sci U S A 97: 11032-11037.
42. Murray F, Smith DW, Hutson PH (2008) Chronic low dose corticosterone exposure decreased hippocampal cell proliferation, volume and induced anxiety and depression like behaviours in mice. Eur J Pharmacol 583: 115-127.
43. Czéh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, et al. (2001) Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci U S A 98: 12796-12801.
44. Wiener M, Lohoff FW, Coslett HB (2011) Double dissociation of dopamine genes and timing in humans. J Cogn Neurosci 23: 2811-2821.
45. Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, et al. (2004)

The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci 24: 10099-10102.

46. Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, et al. (2006) BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. Biol Psychiatry 59: 812-815.

47. Szeszko PR, Lipsky R, Mentschel C, Robinson D, Gunduz-Bruce H, et al. (2005) Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. Mol Psychiatry 10: 631-636.

48. Joffe RT, Gatt JM, Kemp AH, Grieve S, Dobson-Stone C, et al. (2009) Brain derived neurotrophic factor Val66Met polymorphism, the five factor model of personality and hippocampal volume: Implications for depressive illness. Hum Brain Mapp 30: 1246-1256.

49. Frodl T, Schüle C, Schmitt G, Born C, Baghai T, et al. (2007) Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. Arch Gen Psychiatry 64: 410-416.

50. Jessen F, Schuhmacher A, von Widdern O, Guttenthaler V, Hofels S, et al. (2009) No association of the Val66Met polymorphism of the brain-derived neurotrophic factor with hippocampal volume in major depression. Psychiatr Genet 19: 99-101.

51. Benjamin S, McQuoid DR, Potter GG, Payne ME, MacFall JR, et al. (2010) The brain-derived neurotrophic factor Val66Met polymorphism, hippocampal volume, and cognitive function in geriatric depression. Am J Geriatr Psychiatry 18: 323-331.

52. Koolschijn PC, van Haren NE, Bakker SC, Hoogendoorn ML, Hulshoff Pol HE, et al. (2010) Effects of brain-derived neurotrophic factor Val66Met polymorphism on hippocampal volume change in schizophrenia. Hippocampus 20: 1010-1017.

53. Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, et al. (2006) Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. Eur J Neurosci 24: 1850-1856.

54. Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, et al. (1996) Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 16: 1137-1145.

55. Korte M, Carroll P, Wolf E, Brem G, Thoenen H, et al. (1995) Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci U S A 92: 8856-8860.

56. Koponen E, Võikar V, Riekki R, Saarelainen T, Rauramaa T, et al. (2004) Transgenic mice overexpressing the full-length neurotrophin receptor trkB exhibit increased activation of the trkB-PLCgamma pathway, reduced anxiety, and facilitated learning. Mol Cell Neurosci 26: 166-181.

57. Choi DC, Maguschak KA, Ye K, Jang SW, Myers KM, et al. (2010) Prelimbic cortical BDNF is required for memory of learned fear but not extinction or innate fear. PNAS 107: 2675-2680.

58. Sierra-Mercado D, Padilla-Coreano N, Quirk GJ (2011) Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology 36: 529-538.

59. Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ (2009) Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure. J Neurosci 29: 8474-8482.

60. Milad MR, Rauch SL, Pitman RK, Quirk GJ (2006) Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol 73: 61-71.

61. Admon R, Lubin G, Rosenblatt JD, Stern O, Kahn I, et al. (2013) Imbalanced neural responsivity to risk and reward indicates stress vulnerability in humans. Cereb Cortex 23: 28-35.

62. Shin LM, Lasko NB, Macklin ML, Karpf RD, Milad MR, et al. (2009) Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. Arch Gen Psychiatry 66: 1099-1107.

63. Shin LM, Bush G, Milad MR, Lasko NB, Brohawn KH, et al. (2011) Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: a monozygotic twin study of posttraumatic stress disorder. Am J Psychiatry 168: 979-985.

64. Sekiguchi A, Sugiura M, Taki Y, Kotozaki Y, Nouchi R, et al. (2013) Brain structural changes as vulnerability factors and acquired signs of post-earthquake stress. Mol Psychiatry 18: 618-623.

65. Schulz-Heik RJ, Schaer M, Eliez S, Hallmayer JF, Lin X, et al. (2011) Catechol-O-methyltransferase Val158Met polymorphism moderates anterior cingulate volume in posttraumatic stress disorder. Biol Psychiatry 70: 1091-1096.

66. Mueller SC, Aouidad A, Gorodetsky E, Goldman D, Pine DS, et al. (2013) Gray matter volume in adolescent anxiety: an impact of the brain-derived neurotrophic factor Val(66)Met polymorphism? J Am Acad Child Adolesc Psychiatry 52: 184-195.

67. Dannlowski U, Kugel H, Huber F, Stuhrmann A, Redlich R, et al. (2012) Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. Hum Brain Mapp.

68. Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, et al. (2011) Elevated amygdala response to faces following early deprivation. Dev Sci 14: 190-204.

69. Maheu FS, Dozier M, Guyer AE, Mandell D, Peloso E, et al. (2010) A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. Cogn Affect Behav Neurosci 10: 34-49.

70. Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, et al. (2010) Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev Sci 13: 46-61.

71. Morey RA, Hariri AR, Gold AL, Hauser MA, Munger HJ, et al. (2011) Serotonin transporter gene polymorphisms and brain function during emotional distraction from cognitive processing in posttraumatic stress disorder. BMC Psychiatry 11: 76.

72. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, et al. (2002) Serotonin transporter genetic variation and the response of the human amygdala. Science 297: 400-403.

73. Xie P, Kranzler HR, Farrer L, Gelernter J (2012) Serotonin transporter 5-HTTLPR genotype moderates the effects of childhood adversity on posttraumatic stress disorder risk: a replication study. Am J Med Genet B Neuropsychiatr Genet 159B: 644-652.

74. Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, et al. (2006) Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biol Psychiatry 59: 673-680.

75. Wichers M, Kenis G, Jacobs N, Mengelers R, Derom C, et al. (2008) The BDNF Val(66)Met x 5-HTTLPR x child adversity interaction and depressive symptoms: An attempt at replication. Am J Med Genet B Neuropsychiatr Genet 147B: 120-123.

76. Rattiner LM, Davis M, French CT, Ressler KJ (2004) Brain-derived neurotrophic factor and tyrosine kinase receptor B involvement in amygdala-dependent fear conditioning. J Neurosci 24: 4796-4806.

77. Rothbaum BO, Kozak MJ, Foa EB, Whitaker DJ (2001) Posttraumatic stress disorder in rape victims: autonomic habituation to auditory stimuli. J Trauma Stress 14: 283-293.

78. Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, et al. (2000) De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. J Abnorm Psychol 109: 290-298.

79. Peri T, Ben-Shakhar G, Orr SP, Shalev AY (2000) Psychophysiologic assessment of aversive conditioning in posttraumatic stress disorder. Biol Psychiatry 47: 512-519.

80. Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL, et al. (2008) Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. J Psychiatr Res 42: 515-520.

81. Rougemont-Bücking A, Linnman C, Zeffiro TA, Zeidan MA, Lebron-Milad K, et al. (2011) Altered processing of contextual information during fear extinction in PTSD: an fMRI study. CNS Neurosci Ther 17: 227-236.

82. Milad MR, Quirk GJ (2002) Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 420: 70-74.

83. Quirk GJ, Likhtik E, Pelletier JG, Paré D (2003) Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. J Neurosci 23: 8800-8807.

84. Rosenkranz JA, Grace AA (2002) Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons in vivo. J Neurosci 22: 324-337.

85. Yu H, Wang Y, Pattwell S, Jing D, Liu T, et al. (2009) Variant BDNF Val66Met polymorphism affects extinction of conditioned aversive memory. J Neurosci 29: 4056-4064.

86. Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, et al. (2010) A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science 327: 863-866.

87. Bredy TW, Wu H, Crego C, Zellhoefer J, Sun YE, et al. (2007) Histone modifications around individual BDNF gene promoters in prefrontal cortex are associated with extinction of conditioned fear. Learn Mem 14: 268-276.

88. Andero R, Heldt SA, Ye K, Liu X, Armario A, et al. (2011) Effect of 7,8-dihydroxyflavone, a small-molecule TrkB agonist, on emotional learning. Am J Psychiatry 168: 163-172.

89. Elman I, Lowen S, Frederick BB, Chi W, Becerra L, et al. (2009) Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. Biol Psychiatry 66: 1083-1090.

90. Sailer U, Robinson S, Fischmeister FP, König D, Oppenauer C, et al. (2008) Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. Neuropsychologia 46: 2836-2844.

91. Bahi A, Boyer F, Chandrasekar V, Dreyer JL (2008) Role of accumbens BDNF and TrkB in cocaine-induced psychomotor sensitization, conditioned-place preference, and reinstatement in rats. Psychopharmacology (Berl) 199: 169-182.

92. Hall FS, Drgonova J, Goeb M, Uhl GR (2003) Reduced behavioral effects of cocaine in heterozygous brain-derived neurotrophic factor (BDNF) knockout mice. Neuropsychopharmacology 28: 1485-1490.

93. Pillai A, Kale A, Joshi S, Naphade N, Raju MS, et al. (2010) Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. Int J Neuropsychopharmacol 13: 535-539.

94. Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, et al. (2006) Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci Lett 398: 215-219.

95. Sen S, Duman R, Sanacora G (2008) Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiatry 64: 527-532.

96. Schmidt HD, Duman RS (2010) Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacology 35: 2378-2391.

97. Hauck S, Kapczinski F, Roesler R, de Moura Silveira E Jr, Magalhães PV, et al. (2010) Serum brain-derived neurotrophic factor in patients with trauma psychopathology. Prog Neuropsychopharmacol Biol Psychiatry 34: 459-462.

98. Matsuoka Y, Nishi D, Noguchi H, Kim Y, Hashimoto K (2013) Longitudinal changes in serum brain-derived neurotrophic factor in accident survivors with posttraumatic stress disorder. Neuropsychobiology 68: 44-50.

99. Zhang L, Benedek DM, Fullerton CS, Forsten RD, Naifeh JA, et al. (2013) PTSD risk is associated with BDNF Val66Met and BDNF overexpression. Mol Psychiatry .

100. Dell'Osso L, Carmassi C, Del Debbio A, Catena Dell'Osso M, Bianchi C, et al. (2009) Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 33: 899-902.

101. Cazorla M, Jouvenceau A, Rose C, Guilloux JP, Pilon C, et al. (2010) Cyclotraxin-B, the first highly potent and selective TrkB inhibitor, has anxiolytic properties in mice. PLoS One 5: e9777.

This article was originally published in a special issue, **Posttraumatic Stress Disorder** handled by Editor(s). Dr. Gautham Ullah, MC Master University, Canada