

# Childhood abuse, brain-derived neurotrophic factor and psychiatric disorders

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## Brain-derived neurotrophic factor (BDNF)

Neurotrophins comprise a family of secreted proteins that promote growth, survival, and differentiation of neurons in the central and peripheral nervous systems [1]. Brain-derived neurotrophic factor (BDNF) is a principle mediator in neuronal survival, structure, and function [2, 3]. BDNF modulates the efficacy of synaptic transmission [3]. This effect appears to be presynaptic in origin and to be mediated by the Trk family of receptor tyrosine kinases. The functional importance of the pro region of BDNF was demonstrated in a recent study that investigated the consequences of a single nucleotide polymorphism in this region. This polymorphism is defined by replacement of valine<sup>66</sup> with methionine and is associated with memory deficits and abnormal hippocampal function in humans [4]. At the cellular level, the Val/Met substitution affects the intracellular trafficking of BDNF to synapses and reduces the regulated activity-dependent release of BDNF. An association between BDNF dysfunction and different psychiatric pathologies has been shown; however, the mechanism of this process is not well understood. Stressors, specifically childhood abuse, have an effect on BDNF levels, making the link between past abuse, BDNF levels, and psychopathology worth investigating [5, 6]. Different psychiatric conditions such as depression, suicide, bipolar disorder, and psychosis have been studied in an attempt to understand the abuse-BDNF relationship [7-10].

## Childhood abuse

Early stress is associated with long-term alterations in brain circuits and systems that mediate the stress response [11-16]. Early stressors have lasting effects on the hypothalamic-pituitary adrenal (HPA) axis, norepinephrine, benzodiazepine, opiate, dopaminergic, BDNF and other brain systems. These neurochemical systems modulate function in various brain regions, including the hippocampus, amygdala, and prefrontal cortex. Long-term alterations in these brain regions play a role in the pathophysiology of PTSD, depression, and other symptoms and syndromes related to childhood abuse. Early stress could start a chain reaction of neurohormonal and neurotransmitter effects that would damage brain structure and functions. For example, high levels of cortisol could precipitate hippocampal neurotoxic lesions and excessive stress would act as a toxic agent interfering in the usual neurodevelopment process [15].

Early social experiences and experience-related changes in neural correlates of cognition and emotion play a pivotal role in transgenerational transmission of phenotype [1]. Increased susceptibility to cognitive impairments and psychiatric illnesses in adults with a history of childhood maltreatment may reflect a lasting imprint of early maltreatment on epigenetic mechanisms regulating gene expression [16].

## Animal research

A study was performed to investigate the epigenetic effects of childhood maltreatment on the BDNF gene, using infant rats [17]. During their first postnatal week, infant rats were exposed to caretakers with abusive behaviors. Results showed that early-life maltreatment resulted in methylation of BDNF DNA throughout the lifespan, which resulted in reduced BDNF gene expression. The epigenetic effects were, however, reversible with chronic treatment of a DNA methylation inhibitor. Lastly, rats that experienced abuse were more likely to mistreat their own offspring, causing them to have significant DNA methylation, and thus restarting the cycle [16]. It was also found that those rats with early abuse had an increase in methylation of exon IV of the BDNF promoter leading to a decrease in BDNF mRNA in the prefrontal cortex. These differences persisted throughout the lifetime, and analysis showed that the BDNF exon IV methylation was transmitted to the next generation [17].

## Depression

Individuals who were abused and neglected during childhood have a higher risk of major depression when they become adults [18, 19]. Child abuse has been linked to depression in clinical populations and community surveys. Any stressful experiences during the childhood may be associated with depression. For example, a follow-up study of 1,658 members of the Helsinki Birth Cohort, born in 1934-1944 (Finland), 410 of whom were evacuated to foster care during World War II has been conducted [20]. More than six decades later, the adults who were evacuated as children had significantly higher depressive symptom scores than the adults who were not evacuated.

Studies were performed to explore the relationship between the BDNF genotype, maltreatment history, and a serotonin transporter gene [10, 21]. After analyzing saliva samples, results showed a significant three-way interaction between these variables. The severity of depression was predicted by the interaction between a functional polymorphism of the promoter region of the serotonin transporter and the BDNF val66met polymorphism. The vulnerability associated with these genotypes was only seen in those children that were mistreated [10].

Childhood abuse also has an effect on adults with Major Depressive Disorder (MDD) [22, 23]. Those with MDD who reported childhood abuse are more likely to have a current episode of MDD, more chronic MDD, increased symptom severity, and comorbid anxiety and alcohol use disorders, compared to those without histories of child abuse. The impact of childhood abuse on serum BDNF levels is dependent on the variation of BDNF polymorphism in those with MDD. In BDNF met carriers, having a history of childhood abuse is associated with reduced BDNF levels [24].

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## Bipolar disorder

A history of childhood abuse also has an effect on bipolar disorder, mediated through BDNF levels. Bipolar patients with a history of traumatic events have lower BDNF levels and a more severe psychopathology compared to those without a history of traumatic events. Bipolar patients with a traumatic history have higher occurrences of alcohol abuse/dependence, anxiety comorbidity, and lower BDNF serum levels compared to those without a traumatic history [25].

## Psychotic disorder

Preliminary data in a twin study suggests that BDNF genes may interact with psychosocial stress to create psychosis later on in life. There is an interaction between BDNF Val66Met and social stress [26]. BDNF Met carriers show more stress-induced paranoia, than those that are Val/Val carriers [27].

## Suicide

The trauma of childhood physical and sexual abuse has repeatedly been reported as linked with suicidal behavior [28-30]. Adult women with a history of abuse are at an increased risk for developing depression, anxiety, substance abuse and suicidality [28]. In both clinical and community populations of adults who report childhood sexual and/or physical abuse suicidality is higher than in comparison groups who do not have a history of childhood abuse [29]. For example, Briere [31] found that 51% of sexual abuse victims (vs. 34% of non-abused participants) demonstrated a history of suicide attempts, and that 31% of victims (vs. 19% of non-abused individuals) reported self-harm ideation. Gutierrez [32] found that college-

aged women who had been abused as children claimed higher levels of suicidal ideation and felt less repulsion for death and more repulsion for life. Childhood abuse may also increase the likelihood of developing negative beliefs associated with suicide. Hopelessness is a robust predictor of suicide [33] and correlates with a history of childhood abuse [34]. Furthermore, it was found that hopelessness mediated the relation between a childhood abuse history and a history of suicide attempt in a cross-sectional sample [34].

BDNF function and a history of childhood abuse play roles in the frequency and lethality of suicide attempts [35-38]. The frequency of violent suicide attempts is higher in individuals that report severe sexual abuse and that carry the met BDNF allele [39]. The Val66Met allele of BDNF may influence the effects of childhood trauma in relation to the risk of suicide attempts, through its effects on serotonin neurons [40].

## CONCLUSION

Multiple lines of evidence suggest that childhood abuse may affect the BDNF function and is associated with the development of psychiatric disorders in childhood, adolescence and adulthood. It is interesting to speculate that certain interventions, such as early exposure to complex environments (enrichment), handling, or treatment with DNA demethylases or histone deacetylase inhibitors, might be useful as treatment strategies for reversing harmful effects of early-life adversity. Further studies of the neurobiological effects of childhood abuse are needed to develop new therapeutic interventions.

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