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Review article

Childhood trauma in mood disorders: Neurobiological mechanisms and implications for treatment

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ABSTRACT

A contemporary model for the pathogenesis of mood disorders (bipolar and depressive disorders) involves gene-environmental interaction, with genetic predisposition, epigenetic regulation, and environmental effects. Among multiple environmental factors, the experience of childhood trauma can be connected with the pathogenesis, course and the treatment of mood disorders. Patients with mood disorders have the greater frequency of childhood trauma compared with the general population, and adverse childhood experiences can exert a negative impact on their clinical course. In this article, the neurobiological mechanisms of childhood trauma are presented. The influence of negative childhood experiences on the central nervous system can result in many structural and functional changes of the brain, including such structures as hippocampus and amygdala, associated with the development of bipolar and depressive illnesses. Interaction of several genes with childhood trauma to produce pathological, clinical phenomena in adulthood has been demonstrated, the most important in this respect being the serotonin transporter gene and the *FKBP5* gene playing an important role in the pathogenesis of mood disorders. Neurobiological effects can also involve epigenetic mechanisms such as DNA methylation which can exert an effect on brain function over long-term periods. Somatic effects of childhood trauma include disturbances of stress axis and immune-inflammatory mechanisms as well as metabolic dysregulation. Negative childhood experiences may also bear implications for the treatment of mood disorders. In the article, the impact of such experiences on the treatment of mood disorders will be discussed, especially in the context of treatment -resistance to antidepressants and mood-stabilizing drugs.

Contents

Abbreviations: 5-HT3AR, Serotonin 3A receptor; 5-HTTLPR, Serotonin transporter gene promotor polymorphism; BDNF, Brain-derived neurotrophic factor; BMI, Body mass index; CAR, Cortisol awakening response; COMT, Catechol-O-methyltransferase; CRHR1, Corticotropin-releasing factor receptor 1; CRP, C-reactive protein; CTQ, Childhood trauma questionnaire; DSM-5, Diagnostic and Statistical Manual, Fifth Edition; DTI, Diffusion tensor imaging; FKBP5, FK506 binding protein 5; GWAS, Genome-wide association study; HPA, Hypothalamic-pituitary-adrenal; IL, Interleukin; KITLG, Kit ligand; MR, Mineralocorticoid receptor; PTSD, Post-traumatic stress disorder; TLR-2, Toll-like receptor 2; TNF-α, Tumor necrosis factor-alpha; VBM, Voxel-based morphometry.

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Childhood trauma in mood disorders

Genetic-environmental interaction in the pathogenesis of mood disorders

According to the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), mood disorders fall into two categories, i.e., bipolar disorders and depressive disorders. Bipolar disorder is characterized by recurrent episodes of hypomania, mania or depression. A severe type of the illness is the rapid-cycling bipolar disorder with the presence of at least four mood episodes per year. The main form of the depressive disorder is the major depressive disorder characterized by recurrent depressive episodes [1]. A current paradigm for the pathogenesis of mood disorders proposes a model of gene-environmental interaction, with genetic predisposition, epigenetic regulation and environmental effects [2,3]. Both mood disorders have a substantial heritability which is higher in bipolar (85%) [4] than in depressive disorders (37%) [5]. In recent decades, the heritability of mood disorders has been supported by linkage and genetic association research using the candidate gene approach and the genome-wide association studies (GWAS). Current genetics of bipolar disorder was reviewed in 2013 by Craddock and Sklar [6]. A paper summarizing the role of molecular-genetic factors in depressive disorders appeared recently [7]. Epigenetic regulation, especially DNA methylation, can modulate gene expression interacting with the environment, thus influencing the pathophysiology and clinical evolution of mood disorders. Such epigenetic effect in bipolar disorder was recently reviewed by Fries et al. [8], and in depressive disorders by Nagy et al. [9].

Among multiple environmental factors, it has been demonstrated in recent decades that childhood trauma can be one of the most important and can be associated with the pathogenesis, course, and treatment of mood disorders, both bipolar [10] and depressive ones [11]. Such an effect of childhood trauma can be mediated by a genetic predisposition, in which a role of several genes has been demonstrated. The neurobiological effect of childhood trauma can also involve epigenetic mechanisms in which an aberrant DNA methylation can be an important factor. In this article, both genetic and epigenetic interactions with childhood trauma which produce pathological, clinical phenomena in adulthood will be presented and discussed.

The frequency of childhood trauma in mood disorders: comparison with the general population

Childhood trauma can be defined as an important, stressful negative experience during early life such as sexual abuse, physical abuse, emotional abuse, emotional neglect, loss of a parent or parents or separation with them [12].

In recent decades it has been demonstrated that adverse life events, especially in the childhood period, can significantly contribute to the occurrence of mood disorders, both bipolar and depressive ones. It has repeatedly been shown that patients with mood disorder experience negative events in childhood more often than healthy subjects.

Etain et al. [13] compared 206 bipolar patients and 94 control persons. They found that the first group had more complex childhood trauma than controls (63% vs. 33%). Garno et al. [14] demonstrated that the percentage of any childhood trauma in bipolar patients was 51%, that of emotional abuse −37%, physical abuse −24%, emotional neglect −24%, sexual abuse −21%, and physical neglect −12%.

Wise et al. [15] undertook a case-control study to assess the association between childhood trauma and major depressive disorders in women. The study included 236 depressive women and 496 age- matched control women. They found that the risk of depression was 2.5-fold higher in women who reported any abuse during child or adolescent period, 2.4-fold increased with physical abuse only, 1.8-fold increased with sexual abuse only, and 3.3-fold increased with both physical and sexual abuse than in those reporting no abuse.

The incidence of mood disorders can also be connected with an early loss of a mother or father as well as a prolonged separation from them. In 1999, Agid et al. [16] performed a case-control study in which the early parental loss, due to the death of a parent or prolonged separation with parents before 17 years of age was assessed in patients with major depression and bipolar disorder. The individually matched, healthy persons served as the control group. There were 79 illness-control pairs of depression and 79 of bipolar disorder. The likelihood of adult depression was 3.8-fold higher in those reporting such a loss. Furthermore, the permanent separation was more important than the loss due to death, and loss before the age of 9 years was more significant than that occurring in the later period. The likelihood of adult bipolar disorder was 3.6 -fold higher in those reporting a parental loss; however, any connection was found with its kinds.

Slavich et al. [17] found that in subjects experiencing early parental loss or permanent separation as well as in persons with more depressive episodes, an occurrence of the episode was preceded by lower levels of life stress in three months before the episode. A significant connection between childhood separation and a higher risk of bipolar disorder was also reported recently [18].

In our own study, when comparing age- and sex-matched groups of 52 bipolar patients and 52 healthy control persons it was demonstrated that bipolar patients experienced more physical, emotional and sexual abuse, more emotional and physical neglect and also had more frequent such adverse childhood experiences as parental death, abandonment, divorce and prolonged separation, compared to control subjects [19].

The influence of childhood trauma on the course of mood disorders

Negative childhood experiences can exert a significant impact on the clinical course of mood disorders. This is true for both total amount of childhood negative experiences and a variety of associations which have also been reported between the types of negative childhood experiences and the different aspects of the illness.

In bipolar disorder, experiencing physical abuse in childhood was connected with an earlier illness onset and a postponement in proper diagnosis and treatment, as well as with rapid -cycling, the

occurrence of psychotic symptoms, suicide attempts, severe episodes of mania and a higher number of hospitalizations. Patients experiencing physical abuse also more frequently suffered from post-traumatic stress disorder (PTSD) and had problems with psychoactive substances. Sexual abuse in childhood has been connected with early onset of the illness, delayed treatment, rapid-cycling, more suicide attempts and psychotic symptoms as well as more severe episodes of mania. Similar to physical abuse, sexual abuse has been related to co-morbidity of PTSD and abuse of psychoactive substances [20,21]. In a study by Etain et al. [22] emotional abuse was connected with an earlier illness onset, suicide attempts, rapid-cycling, more depressive, manic and hypomanic episodes, and cannabis abuse. Garno et al. [14] observed that emotional abuse was connected with drug abuse and rapid-cycling. Furthermore, neglect in childhood was associated with early -onset bipolar disorder [23].

Mandelli et al. [11] performed a meta-analysis about the association between the occurrence of depression with specific kinds of childhood trauma. They indicated that emotional abuse and neglect exerted a higher impact on the occurrence of depression than the other types of childhood trauma. Furthermore, Angst et al. [24] found that family problems in childhood significantly increased risk for the chronic course of mood disorders, both bipolar and depressive ones.

Post et al. [25], examining 900 bipolar patients demonstrated that childhood trauma, particularly physical, emotional and sexual abuse were connected with co-morbid somatic diseases. In patients experiencing physical abuse there were more frequent allergies, chronic fatigue syndrome, hypertension, and hypotension and also head injuries. Sexual abuse was connected with irritable bowel syndrome and emotional abuse – with arthritis and migraine. There was a relationship between the overall childhood trauma and the total number of somatic diseases such as allergy, arthritis, asthma, chronic fatigue syndrome, menstrual disturbances, fibromyalgia, head injury, hypertension, hypotension, and migraine.

Recent meta-analysis on the association between negative childhood experiences and clinical outcome in bipolar disorder shows that bipolar patients with a history of childhood trauma had earlier age of onset, greater number and severity of manic and depressive episodes, greater psychosis severity, higher risk of co -morbidity with post-traumatic stress disorder, anxiety disorders, substance and alcohol abuse disorder, higher risk of rapid cycling and of suicide attempts, than bipolar patients not experiencing childhood trauma [26].

Our study included 52 patients with bipolar disorder, aged 47±12 years. A questionnaire for the family history and the course of bipolar disorder, the Polish version of the Childhood Trauma Questionnaire (CTQ) and own questionnaire for childhood negative experiences were used and given to the patients during a remission period. Emotional abuse and neglect were associated with the highest number of unfavorable clinical features, predicting such aspects of the illness as psychotic symptoms, suicidal attempts, rapid cycling and anxiety disorders. Also, emotional abuse was connected with the lower risk of hypertension. The total result of the CTQ was correlated with psychotic symptoms and rapid cycling, sexual abuse was linked to earlier onset of illness, and long-term separation from parents -to anxiety disorders and obesity. Some of these associations were sex-dependent. Some connections were also found between unfavorable clinical features of bipolar disorder and a family history of psychiatric disorders. The results obtained confirm the relationship between childhood trauma and the disadvantageous features of the illness course. They also suggest an effect of these events on some somatic conditions in adulthood in bipolar patients [27].

Neurobiological mechanisms of childhood trauma

The effect of childhood trauma on the central nervous system

Recent research has been trying to identify the mechanisms by which early stress exerts an effect on brain development. Negative events during early life result in the release of various mediators and neurotransmitters of stress in specific areas of the brain. These mediators interact with developing neurons and neuronal networks causing structural and functional abnormalities which may result in cognitive and emotional alterations. Therefore, early stress can adversely change cognitive and emotional processes in adolescence by disturbing the maturation of the brain networks connected with these processes [28].

Molet et al. [29] proposed a naturalistic rodent model of chronic early life stress. In this model, mice and rats undergoing such stress develop structural and functional deficits in the limbic-cortical circuits of the brain. Cognitive consequences of early life stress are connected with hippocampus-dependent deficits in learning and memory, and emotional sequelae are associated with alterations in amygdala circuitry. In a subsequent study, high-resolution magnetic resonance imaging (MRI) and intra-hippocampal diffusion tensor imaging (DTI) were employed to examine for structural signatures of cognitive adolescent vulnerabilities in this model. In adversity-experiencing rats, a loss of dorsal hippocampal volume and disruption of the dendritic structure, already occurring during late adolescence was observed [30].

In clinical studies, it has been demonstrated that childhood trauma exerts prolonged effects on prefrontal-limbic gray matter. Paquola et al. [31] performed a meta-analysis of studies measuring hippocampal and amygdala volumes as well as studies using whole brain voxel-based morphometry (VBM) in subjects with and without childhood trauma. Adult subjects experiencing childhood maltreatment had lesser volumes of the hippocampus and amygdala. The most conspicuous results of the whole brain VBM meta-analysis in this group were decreased gray matter in the right dorsolateral prefrontal cortex and right hippocampus. Aas et al. [32] showed that persons experiencing physical and sexual abuse in childhood, especially carriers of the met allele of val66met BDNF gene polymorphism, had significantly reduced hippocampal subfield volumes in the dentate gyrus. Carballedo et al. [33] examined the volume of the hippocampus and the frontal brain regions in healthy subjects at genetic risk of depression. They found that subjects with a family history of depression and emotional abuse in childhood had significantly smaller left and right hippocampal heads than matched control subjects. Using the VBM method, the authors demonstrated smaller dorsolateral prefrontal cortices, medial prefrontal cortices and anterior cortex cinguli in patients with depression risk who experienced emotional abuse in childhood.

Teicher et al. [34] in their review indicate that parental verbal abuse, witnessing domestic violence and sexual abuse exert their effect on brain regions (auditory, visual and somatosensory cortex) and pathways that process and convey the aversive experience. The authors conclude that childhood trauma can be connected with morphological changes in the anterior cingulate, dorsal lateral prefrontal and orbitofrontal cortex, corpus callosum and adult hippocampus. Another consequence of the trauma could be an increased response of amygdala to emotion-expressing faces as well as a decreased response of the striatum to the anticipation of the reward. Frodl et al. [35] recently pointed at another brain structure connected with the impact of childhood adversity. They analyzed 3036 participants for subcortical brain volumes and demonstrated that higher experience of childhood trauma in women, in particular, emotional neglect and physical neglect, was connected with the lesser volume of the caudate.

The effect of childhood trauma on brain structure and function can also be reflected in cognitive dysfunctions. It was found that childhood trauma was connected with working memory impairment for positive emotion in female university students [36]. Aas et al. [37], studying patients with psychotic disorders (schizophrenia and affective spectrums) and using the CTQ observed a significant interaction between *5-HTTLPR* genotypes and negative childhood experiences. Patients with s/s genotype experiencing physical neglect and abuse in childhood had significantly impaired cognitive functions compared to remaining genotypes. Green et al. [38], in schizophrenic patients, showed that *COMT* val158met polymorphism could play a role in the effects of childhood trauma on cognitive functions. In their study, poorer cognitive performance connected with childhood trauma was demonstrated in met allele carriers. Recently Aas et al. [39] in patients with schizophrenia or bipolar disorder examined a relationship between childhood maltreatment and brain activation, measured with functional magnetic resonance imaging, in reaction to emotion-expressing faces. They found that higher intensity of negative childhood experiences was associated with the bigger difference in brain responses between faces expressing negative and positive emotions in the right angular gyrus, supramarginal gyrus, middle temporal gyrus and the lateral occipital cortex.

In conclusion, many structural and functional abnormalities of the brain connected with early life trauma has been demonstrated. Both animal and human data agree on the involvement of the hippocampus and amygdala in depressive behavior connected to early life stress. However, in humans, some differences between bipolar and depressive disorders in this respect have been observed [40–43].

Genetic factors in childhood trauma

Genetic factors can give a predisposition to the effect of childhood trauma in a given subject. They can interact with the occurrence of childhood trauma to produce various negative clinical phenomena in adulthood. Interaction of several genes has been demonstrated. The very first reported interaction of this kind was that between the *MAO-A* gene and childhood maltreatment in the development of antisocial behavior. This was first described by Caspi et al. [44] in 2002 and confirmed in two subsequent studies [45,46]. For mood disorders, the most important could be the interactions between childhood trauma with the serotonin transporter (5-HTT) gene, and the FK506 binding protein gene 5 (FKBP5) because a role of these genes has been demonstrated in their pathogenesis [47–49].

Promotor polymorphism of the serotonin transporter gene *(5HTTLPR*) is functional, and its alleles determine either higher (allele "l", long) or lower (allele "s", short) activity of the transporter. The pivotal study by Caspi et al. [50] in 2003 demonstrated an interaction between this gene and developing depression following negative life events which was more pronounced with the s allele. In healthy carriers of s allele, an increased cortisol secretion under stress was also observed what may have implications for the pathogenesis of depression [51]. A meta-analysis performed in 2011 by Karg et al. [52], including 54 studies, demonstrated the evidence that the *5-HTTLPR* s allele is connected with a higher risk of developing depression under stress. In the analysis of the kind of stressor, the strongest evidence was found for an association between the s allele and increased stress sensitivity following the childhood trauma. A study by Taylor et al. [53] examined the relationship between early and recent stress, the *5-HTTLPR,* and depressive symptoms in 118 subjects. They found that a stressful early family environment was meaningfully connected with depressive symptoms. Also, interactions between the *5-HTTLPR* and both early and current stress were demonstrated. Individuals with the s/s genotype had more depressive symptoms if they had encountered early or current stress but fewer depressive symptoms if they declared a supportive early environment or recent positive experiences than the subjects with the s/l or l/l genotype. It has been hypothesized that in the carriers of the s allele of the *5-HTTLPR* polymorphism, abnormalities of serotonergic neurotransmission connected with stress reaction can cause disturbances in emotional processing and increased susceptibility for the development of mood disorders following negative childhood experiences [54].

Recently, Culverhouse et al. [55] performed a new meta-analysis on 31 datasets containing 38 802 European-ancestry subjects genotyped for *5-HTTLPR* and assessed for depression, childhood trauma, and other stressful events. They did not find a strong interaction between stress and *5-HTTLPR* genotype in the development of depression. They concluded that if an interaction exists in which the S allele of the *5-HTTLPR* increases risk of depression it must be of modest effect size and observable only in limited situations.

FK506 binding protein 5 (FKBP5) plays an important role in the hypothalamic-pituitary adrenal (HPA) axis activity through its regulatory action on glucocorticoid receptor (GR) sensitivity. Polymorphisms in the *FKBP5* gene associate with differential upregulation of FKBP5 following GR activation. Higher expression of the *FKBP5* results in an increased negative feedback of the HPA axis, leading to higher stress hormone system activation following exposure to stress. This may make a risk factor for stress-related psychiatric disorders [56]. In was found that minor allele carriers of a haplotype derived of four variants, referred to as CATT carriers, are at greater risk of developing psychiatric disorders, including mood disorders, in adulthood following childhood trauma than major allele carriers [57]. Previously, it was shown that polymorphisms in *FKBP5* are associated with a greater number of depressive episodes [58]. Recently, it was observed that, in adolescents, the *FKBP5* gene moderates the relationship between negative childhood experiences and dysfunctional emotional regulation [59].

Another gene connected with the HPA axis is the corticotropin-releasing hormone type 1 receptor *(CRHR1)* gene. Heim et al. [60] investigated sex differences in the effects of the *CRHR1* gene and its rs110402 polymorphism on the relationship between negative childhood experiences and the occurrence of depression during adulthood. The most frequent type of trauma in men was physical abuse, while such a type in women was sexual abuse. In men, a protective effect of the rs110402 A-allele against developing depression after childhood trauma was found, and the rs110402 A-allele was connected with lower cortisol response in the dexamethasone/CRH test. No such findings were obtained in women. Among the A-allele carriers, women with negative childhood experiences had higher cortisol response than men. Their results show that sex differences could be reflected in the interaction between *CRHR1* gene and childhood trauma. Krazler et al. [61] reported that a haplotype of this gene moderated the effect of childhood trauma on the lifetime risk of depression in African-American women. Other sex-dependent moderation of depression susceptibility following childhood maltreatment were investigated for haplotypes of the mineralocorticoid receptor (MR), the regulator of the HPA axis. The CA haplotype of the *MR* gene exerted a different effect on the relationship between childhood trauma and depression; female subjects were protected, whereas males were at increased risk. On the other hand, female GA haplotype carriers displayed increased vulnerability, and male CG-carriers showed increased resilience. The authors concluded that gender is significant in determining whether functional genetic variation in *MR* is favorable or unfavorable. The CA haplotype can

be advantageous for women, while the GA and CG haplotype – for men [62].

Dysfunction of the immune system can also cause a genetic link between childhood trauma and mood disorders. Oliveira et al. [63] showed that the effect of sexual abuse on the early onset of bipolar disorder could be connected with polymorphism of the Toll-like receptor gene (*TLR-2,* rs3804099), associated with the activity of immune system. Recently Cohen-Woods et al. [64] observed an interaction between childhood maltreatment and polymorphism of genes for inflammatory markers such as interleukin-6 (*IL-6*) and C-reactive protein (*CRP*) genes. These inflammatory markers show an association with the pathogenesis of depression [65].

In two papers published in 2013, a relationship was found between val166met catechol-O-methyltransferase (*COMT*) gene polymorphism, childhood trauma and the occurrence of psychotic symptoms in adolescent and adult population [66,67]. In 2014, Aas et al. [32] investigated a relationship between childhood trauma and the val66met polymorphism of the brain-derived neurotrophic factor (*BDNF*) gene, and the BDNF mRNA level. They found that a history of childhood trauma or being a met carrier of the *BDNF* val66met polymorphism was associated with significantly reduced BDNF mRNA level and met carriers with high levels of childhood trauma had the lowest BDNF mRNA levels.

Another aspect of genetics and childhood trauma may be connected with telomere shortening and alterations of mitochondrial biogenesis which are involved in cellular aging and psychiatric disorders. A recent study by Tyrka et al. [68] showed that childhood trauma was connected with shorter telomeres and higher mtDNA copy numbers. Significantly shorter telomeres and higher mtDNA copy numbers were seen in depressive disorders, as well as in subjects reporting a parental loss and other childhood adversities.

Roberts et al. [69] even suggest that genetic trauma for the effects of negative childhood experiences may have multigenerational character. They examined whether the maternal experience of childhood trauma can be connected with depressive symptoms occurring in their offspring during adolescence and early adulthood period. It was found that the offspring of women who had severe childhood trauma displayed more frequently depressive symptoms. Maternal mental health and offspring's exposure to trauma accounted for more than 50% of the risk of depression. Depressive symptoms in offspring due to maternal childhood trauma were apparent at age 12 and continued through age 31.

In conclusion, several genes have been implicated which can interact with childhood trauma to produce clinical disturbances in the adulthood. Among them, the most significant for this review is the serotonin transporter *(5-HTT*) gene, and the FK506 binding protein gene 5 (*FKBP5*) which play an important role in the pathogenesis of mood disorders,

Epigenetic factors in childhood trauma

Epigenetic mechanisms modify gene expression not producing changes in DNA sequence. The majority of studies in this respect has focused on a possibility of abnormal DNA methylation. The early development represents a particularly sensitive period to epigenetic modification of the genome [70]. It has been shown that the intensity of DNA methylation of the *FKBP5* gene is most pronounced in early life period and that childhood trauma can induce persistent epigenetic changes [71]. Recently, Perroud et al [72] studied the impact of childhood maltreatment on the methylation status of the serotonin 3 A receptor - (*5-HT3 A-R*) gene in relation with a functional genetic polymorphism of the gene in patients with bipolar, borderline personality and attention deficit hyperactivity disorders. They showed that in bipolar disorder childhood trauma was associated with greater severity of the disease reflected in a higher number of mood episodes, history of suicide attempts, more hospitalization, and younger age at onset This effect was mediated by two *5-HT3 A-R* CpGs sites. Compared to T allele carriers, CC carriers had higher methylation status at one CpG located one bp upstream of this variant.

The genome-wide studies of the epigenetic effect of childhood trauma can confirm a synergistic effect between exposure to early stress and epigenetic changes. Suderman et al. [73] showed that childhood trauma resulted in increased DNA methylation of multiple loci in adult subjects. Yang et al. [74] examined whole-genome DNA methylation differences between 96 children experiencing trauma and 96 control children, matched for sex and age. They found that children experiencing trauma had significantly increased methylation compared to control children which could result in more health problems during adulthood. Houtepen et al. [75] performed a genome-wide analysis of blood DNA methylation in 85 healthy subjects, assessing childhood maltreatment and cortisol reactivity under stress. They showed that a locus in the Kit ligand *(KITLG)* gene showed the strongest association with cortisol stress reactivity, thus mediating its relationship with childhood trauma and associated with programming such reactivity in the human brain. Although the results of the GWAS studies seem interesting, some problems connected with such research such as, e.g., multiple testing, should be taken into account.

Lutz et al. [76] reviewed the human studies suggesting that DNA methylation is important for mediating neurobiological consequences of childhood trauma throughout life. The DNA methylation can augment dysfunctional behavioral patterns and increase the risk of psychopathology. They put forward a hypothesis that epigenetic mechanisms, in particular, DNA methylation, make a form of molecular memory that may exert an effect on brain function over long-term periods. They may also constitute a biomarker of behavioral phenotypes connected with childhood trauma.

Somatic effects of childhood trauma

Somatic effects of childhood trauma include disturbances of stress axis and immune-inflammatory mechanisms as well as metabolic dysregulation. Lu et al. [77] examined the effect of childhood maltreatment on HPA axis activity both in patients with depression and healthy control subjects to determine the differences in HPA axis functioning that may be connected with a predisposition to depression following a childhood trauma. Regardless of depression, subjects with a history of childhood trauma exhibited an enhanced cortisol awakening response (CAR), associated with CTQ physical neglect scores and CTQ total scores. They also exhibited the highest cortisol concentration after the dexamethasone suppression test and a decreased glucocorticoid feedback inhibition. Thus, childhood trauma resulted in hyperactivity of the HPA axis as measured by CAR and dysfunction of the GR-mediated negative feedback, which could make a person more vulnerable for developing depression. These results were confirmed by Wielaard et al. [78] who investigated the effect of childhood trauma on cortisol levels and the cortisol awakening response in depressed and non-depressed older adults. They found a significant negative relationship between childhood trauma and morning cortisol levels. In subjects without depression, both emotional and sexual abuse were connected with more intense changes of the HPA axis in response to awakening. Recently, Bernard et al. [79] performed a meta-analysis of 27 studies examining the association between childhood trauma and indicators of diurnal cortisol regulation such as wake-up cortisol levels, the CAR, and the diurnal cortisol slope. They found a

significant association between such trauma and blunted wake-up cortisol levels, suggesting a pattern of hypocortisolism.

Baumeister et al. [80] performed a meta-analysis to find a connection between childhood trauma and pro-inflammatory phenotypes in adult persons. They found that persons experiencing sexual and physical abuse in childhood had significantly elevated baseline peripheral levels of CRP, IL-6, and TNF-α. It was also reported that in bipolar patients, serum CRP levels were significantly higher than in control subjects; more than 50% of the variance in the CRP was explained by the effects of age, body mass index (BMI) and childhood trauma, predominantly sexual abuse [81]. A recent study investigated the relationships between several kinds of negative childhood experiences and a composite measure of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) and CRP in saliva collected when children were 17 months old. It turned out that familial stress, maternal depression, and security of attachment were associated with the indices of salivary inflammation what may suggest that negative experiences very early in life may produce a pro-inflammatory phenotype with possible negative health implications for later periods of life [82].

Childhood adversity may be related to obesity in patients with mood disorder [83]. Aas et al. [84], in adults with schizophrenia and bipolar disorder, showed that childhood maltreatment severity is associated not only with elevated CRP but also higher BMI. In our study of bipolar patients, a connection was found between obesity and long-term separation from parents [26]. Our results were confirmed in Morris et al.'s [85] study who examined several kinds of social adversity from birth to 4 years and subsequent BMI trajectories to age 17 in 7021 children in the Avon Longitudinal Study of Parents and Children. They found that higher BMI throughout ages 12–17 occurred in children whose parents had separated.

Recently, Moraes et al. [86] compared patients with mood disorders (both bipolar and unipolar) with healthy controls, using the CTQ to assess specific negative life experiences and measuring the markers of nitro-oxidative stress, lipid peroxidation, and protein oxidation. They showed that in both bipolar and unipolar mood disorders physical neglect and sexual and emotional abuse were significantly correlated with a number of these markers as well as many clinical factors.

In conclusion, among various somatic disturbances produced by childhood trauma, the most important seems a hyperactivity of the HPA axis and a pro-inflammatory status which can play an important role in the development of mood disorders in the adulthood [87].

Childhood trauma and treatment of mood disorders

Therapeutic implications

Childhood trauma and its neurobiological mechanisms can be important for therapeutic interventions in mood disorders. Such interventions should be preceded by a detailed interview taking into account possible negative childhood experiences. Such an interview should be obligatory in patients showing a severe course of illness which is more likely in patients with a history of childhood trauma.

The pivotal study in this respect was that of Nemeroff et al. in 2005 [88] where 681 patients with chronic forms of major depression were treated with the antidepressant nefazodone, cognitive behavioral psychotherapy or a combination of both. It was found that the effects of the antidepressant alone and psychotherapy alone were equal and significantly less effective than combination treatment. However, among the patients having a history of early childhood trauma, such as loss of parents at an early age, physical or sexual abuse, or neglect, psychotherapy alone was superior to antidepressant monotherapy. In these patients, the combination of psychotherapy and pharmacotherapy was only slightly better than psychotherapy alone. The authors conclude that psychotherapy may be an essential element in the treatment of patients with chronic forms of major depression and a history of childhood trauma.

Presently, cognitive-behavioral psychotherapy is a promising form of treatment for patients experiencing childhood trauma. It should contain an element of psychoeducation but also focuses on the developmental profile of the patient and the effect of experiences on the development of the most important cognitive structures made during the childhood period.

It was also observed that in patients with childhood trauma, psychotherapy could exert a biological effect. Perroud et al. [89] measured the percentage of methylation at BDNF CpG exons I and IV in 115 subjects with the borderline personality disorder before and after four weeks of dialectical behavior therapy. In these patients, the greater the amount of childhood trauma, the higher was the methylation status. Responders to the psychotherapeutic treatment exhibited a reduction in methylation status over time which was not the case in non-responders.

Childhood trauma can also determine a kind of pharmacotherapy. It has already been mentioned that the serotonin transporter status can influence the relationship between negative childhood experiences and depression. Quilty et al. [90], in 52 depressed outpatients receiving up to 26 weeks of pharmacotherapy, stratified antidepressants with a high versus low affinity for the serotonin transporter. They found that higher intensity of childhood trauma was connected with higher severity of depression after treatment only in those patients receiving antidepressant medications with a weak affinity for the serotonin transporter. This may suggest that patients with a history of childhood trauma should be treated with antidepressant with a high affinity for the serotonin transporter.

Childhood trauma and treatment resistance for antidepressant and mood-stabilizing drugs

Recent studies have shown that childhood trauma can play an important role in producing treatment refractoriness in psychiatric disorders, including mood disorders. Kim and Lee [91] suggest that in bipolar disorder, this may be due to the association between childhood trauma and early onset of the illness and greater severity of manic and depressive symptoms. In major depressive disorder, this may result from the association between childhood trauma and severity and chronicity of depressive symptoms as well as their frequent recurrence. The authors try to delineate the interactions between genes and childhood trauma on refractoriness in mood disorders pointing on, among other, serotonin transporter and the *BDNF* gene.

Recently Williams et al. [92] investigated the role of childhood adversities in predicting acute response to antidepressants in 1008 patients with the major depressive disorder. Three-hundred and thirty-six matched healthy controls were also studied. Depressed patients significantly more frequently reported childhood trauma than control subjects; 62.5% of depressed patients had a history of more than two negative childhood experiences what was the case in 28.4% of control subjects. The most frequent events of childhood trauma were emotional, sexual and physical abuses. Abuse occurring at $\leqslant$7 years of age was a predictor of poor response to eight-week treatment with such antidepressants as escitalopram, sertraline, and venlafaxine. Furthermore, abuses occurring between ages 4 and 7 years were connected with the poorest response to the treatment with sertraline.

Conus et al. [93] assessed the prevalence of childhood and adolescent trauma such as sexual and physical abuse in 118

patients with bipolar I disorder treated for the first episode of psychotic mania. Patients with such experiences had the poor premorbid functioning, and, most importantly, were more likely to discontinue treatment. The authors recommend specific psychological interventions for the improvement of the treatment of such patients.

There have also been studies examining the relationship between childhood trauma and refractoriness to treatment with mood stabilizers in bipolar disorder. Cakir et al. [94] studied 135 patients with bipolar disorder type I, also using CTQ. They did not find differences in childhood trauma scores between groups with good and poor responses to long-term lithium treatment. However, lifetime diagnosis of post-traumatic stress disorder was associated with poor response to lithium. On the other hand, poor responders to long-term anticonvulsant treatment had higher scores of emotional and physical abuse than the responders to anticonvulsants. Recently, Etain et al. [95] examined the response to lithium and childhood trauma in 148 bipolar patients. They found that a higher level of physical abuse significantly correlated with worse response to lithium. Patients having at least two traumatic experiences such as emotional, physical or sexual abuse were nearly five-fold more at risk to be lithium non-responders than the patients not reporting any abuse. The association with lithium non-response was also shown for the lifetime presence of mixed episodes and alcohol abuse. However, the results of multivariate analyses pointed at physical abuse and mixed episodes as the factors independently connected with a poor response to lithium.

In conclusion, the presence of childhood trauma in patients with depressive disorders can make them more refractory to the treatment with antidepressants and, in patients with bipolar disorder, their treatment with mood-stabilizing drugs can be less efficacious.

Conclusions

Among environmental factors, negative childhood experiences are one of the most important to interact with genetic predisposition in the development of mood disorders. They produce many structural and functional abnormalities of the brain, among them the most important involve hippocampus and amygdala which have been associated with the pathogenesis of mood disorders. A number of genes have been implicated interacting with childhood trauma, and, among them, the most important seems the serotonin transporter *(5-HTT)* gene, and the FK506 binding protein gene 5 (*FKBP5*) which play an important role in the pathogenesis of mood disorders, The role of epigenetic factors, especially and aberrant DNA methylation has also been demonstrated in this process.

The presence of childhood trauma can also be important for planning both pharmacological and psychotherapeutic treatment of mood disorders. Any therapeutic intervention should be preceded by a detailed interview taking into account possible negative childhood experiences. Patients showing a severe course of illness are more likely to have a history of childhood trauma. For planning a pharmacological intervention, it should be remembered that the presence of childhood trauma in patients with depressive disorders can make them more refractory to the treatment with antidepressants and, in patients with bipolar disorder, their treatment with mood-stabilizing drugs can be less efficacious.

The association between childhood trauma and the development of psychiatric disorders, in this case, mood disorders, can make a model of interaction between psychological, genetic and epigenetic factors in psychiatry. Therefore, further studies on the role of negative childhood experiences in the pathogenesis and treatment of mood disorders should integrate both psychological and neurobiological approaches.

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Conflict of interest

The authors declare no conflict of interest that could influence their work.

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