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ASSOCIATION BETWEEN CHILDHOOD TRAUMA AND MOOD DISORDERS IN ADULTHOOD

(Review Article)

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Abstract

It is commonly believed that childhood trauma can manifest into mood disorders in adulthood; the aim of our study is to thoroughly review the array of mood disorders that can be caused by childhood trauma and underline the predisposing risk factors and mechanisms of developing negative symptoms. We are trying to investigate the relationship between specific trauma types and mood disorders. For this purpose, we reviewed more than 20 articles on various childhood traumas, mood disorders, their mechanisms, and relationship.

In our research, we specifically focus on the risk of developing mood disorders in the victims of physical abuse, sexual abuse, and neglect, briefly review the statistical data, as well as try to explain the pathophysiologic mechanism by analyzing: genetic factors, neuroplasticity, HPA axis, hippocampal volume and the effect of oxytocin.

Introduction

Many children around the world are exposed to a traumatic event at some point in their lives. These events not only affect children at present time but can also take part in developing mood disorders in adulthood. Nearly 3 in 4 children-or 300 million children- aged 2-4 years regularly suffer physical punishment and/or psychological violence at the hands of parents and caregivers [1]. The numbers are higher for the mood disorders, most common being depression and bipolar disorder which combined affect more than 310 million people worldwide [2]. In 2004, Charles. B Nemeroff conducted the first study which aimed to investigate neurobiological consequences of childhood trauma. His study showed that repeated early-life stressor leads to alterations in central neurobiological systems, particularly in the corticotropin-releasing factors system, leading to increased responsiveness to stress [3].

After this study, several new ones have been conducted but the information about association of childhood trauma and adulthood mood disorders is still rare. Given the destructive potential of mood disorders, it is important to find how early life stressors affect the psychological condition of the child and if those stressors can really cause adulthood mood disorders.

Types of Childhood Trauma

The World Health Organization (WHO) defines child maltreatment as "all forms of physical and emotional ill-treatment, sexual abuse, neglect, and exploitation that results in actual or potential harm to child's health, development or dignity to children under 18 years of age". There are four main types of abuse: neglect, physical abuse, psychological abuse, and sexual abuse. Abuse is defined as an act of commission and neglect is defined as an act of omission in the care leading to potential or actual harm [2]. In the following paragraphs, different forms of childhood emotional trauma will be discussed.

Sexual Abuse

Child sexual abuse (CSA) is defined by WHO as "the involvement of a child in sexual activity that he or she does not fully comprehend and is unable to give informed consent to, or for which the child is not developmentally prepared, or else that violate the laws of social taboos of society. CSA can include exhibitionism, fondling, oral-genital contact, and rectal or vaginal penetration [4].

The exact measurement of the prevalence of childhood sexual abuse is not easy because the definition of CSA varies among studies. For example, the age used to define childhood might vary from study to study, also the types of acts of sexual abuse might be different (e.g., both contact and non-contact). Survey methods used to evaluate CSA, number, and details of screening questions also influence the resulting prevalence estimates [5]. Even if the surveys are anonymous and the screening questions are as delicate as possible, only an incomplete portion of CSA incidents are reported, even smaller numbers are

reported to authorities and the biggest portion of cases remain unreported because of shame, fear, or other factors [6].

The 2006 world report on violence against children provided data, which shows that in 2002 approximately 150 million girls and 73 million boys were subject to contact CSA worldwide [7]. In the US, more than 34,000 adults aged 18 years or older residing in households were face-to-face interviewed in a survey conducted during 2004-2005[8]. Child sexual abuse was defined by the four questions that the Adverse Childhood Events Study used to assess unwanted sexual experience before age 18.: "Before you were 18 years old: 1) How often did an adult or other person touch or fondle you in a sexual way when you didn't want them to or you were too young to know what was happening?; 2) how often did an adult or the other person have you touch their body in a sexual way when you didn't want them to or you were too young to know what was happening?; 3) How often did an adult or other person attempt to have sexual intercourse with you when you didn't want them to or you were too young to know what was happening? And 4) how often did an adult or other person actually have sexual intercourse with you when you didn't want them to or you were too young to know what was happening?" [9] responses to all four questions ranged from 1= "never" to 5= "very often". Individuals who responded never to all these questions were classified as not having a history of CSA. All other individuals were classified as having a history of CSA, resulting in 10.14% (24.8% in men, 75.2% in women) of participants being the victims of CSA [8].

Sexual abuse in childhood often occurs alongside other forms of abuse or neglect and are more common in families with low socioeconomic status. There are several factors that are thought to increase the risk of child sexual abuse and are divided into 4 big categories. These categories include individual, family, environmental and social factors. The psychological health of the child also plays the role in the occurrence of CSA, meaning that children who are impulsive, emotionally needy, and who have learning or physical disabilities and substance use disorder are more prone to be the victim of sexual abuse [10].

Child Neglect

Child neglect includes both isolated incidents, as well as a pattern of failure over time on the part of a parent of other family members to provide for the development and well-being of the child- where the parent is in a position to do so in one or more of the following areas: health, education, emotional development, nutrition, shelter, and safe living conditions. The parents of neglected children are not necessarily poor [11]. There are 7 types of neglect: 1) physical – inadequate food, clothing, shelter, hygiene; 2) medical- failure to provide prescribed medical care or treatment of failure to seek appropriate medical care in a timely manner; 3) dental- failure to provide adequate dental care or treatment; 4) supervisional- failure to provide age-appropriate supervision; 5) emotional- failure to provide adequate nurturance of affection, failing to provide necessary psychological support, or allowing children to use drugs and/or alcohol; 6) educational- failure to enroll a child in school or failure to provide adequate homeschooling, failure to comply with recommended special education, allowing chronic truancy; 7) other- includes exposing a child to domestic violence, or engaging or encouraging children to participate in illegal activities such as shoplifting or drug dealing [11].

The main contributor to the neglect is the parental problem, including mental health issues, intellectual deficits, and substance abuse. However, often several factors interact and play a role in the occurrence of neglect- for example, a single parent with substance abuse and mental health problems in a community with low socioeconomic status [12]. Children with complex medical problems and children with developmental disabilities are at the risk of neglect, one of the reasons being the increased requirement of care, financial aid, complicated parent-child relationships, and increased family stress. The community and society in which the child lives is one more contributor to the occurrence of neglect. If the community does not have community centers, mental health support organizations and are impoverished often have a higher prevalence of neglect [13].

The number of research papers about childhood emotional and physical neglect is small. The number of studies reporting about physical neglect is 16, and only 13 for emotional abuse.

The participants for those studies were 59,406 and 59,655 respectively. The results showed the prevalence of physical neglect to be 163/1000 and prevalence of emotional neglect - 184/1000 with no

apparent gender differences [14]. These numbers were extremely low in comparison to a meta-analysis published in the same year about child sexual abuse yielding over 200 publications using self-report measures of sexual abuse over 40,000 participants [15].

Physical Abuse

Child physical abuse (CPA) committed by parents or other caregivers is a major public health problem and social welfare problem all around the world (Gilbert et al., 2009; Pinheiro, 2006). To examine the prevalence rates of child abuse committed by parent/caretaker a population-based survey was carried out in 2008 in Sodenmarland Country, Sweden among all pupils in three different grades (n=8494). Children were asked about their exposure to violence. Contact persons in the school as nurses and teachers were responsible for the distribution of the questionnaires. To maintain total confidentiality, the questionnaires were sealed in the envelopes. A total of 15.2% of children reported that they had been hit [16].

Mechanisms

Stress response is created in humans by a complex interplay between several endocrine, autonomic, inflammatory and behavioral components, all stemming from a large neuronal circuit that includes the prefrontal cortex, hippocampus, amygdala, and brainstem regions. Hypothalamus-Pituitary-Adrenal (HPA) axis is a network of central nervous system (CNS) and peripheral nervous system (PNS), combining numerous nuclei, ganglia, and neurotransmitters. Oxytocin is a hormone neuropeptide which assumes an opposite role and can be thought of as a stress-protective. Inflammation, expression of various receptors and growth factors affect CNS neuroplasticity in various ways, often illustrated by hippocampal volume as well as microscopic studies. Finally, genetic and epigenetic factors offer a lot of leads but not too many answers as of yet; only few of them are discussed here. Although each of the above elements is discussed in separate paragraphs, it is of utmost importance to see all these parts as exactly that - “parts” of something whole, even if that “whole” is not perfectly coherent from our current data.

HPA axis

HPA axis is a cornerstone of neuroendocrine stress response in mammals. It was first described in 1956 that plasma cortisol concentrations are elevated in those patients who fit the criteria for a diagnosis of MDD [17]; further, HPA axis is more resistant to negative feedback inhibition (i.e. dexamethasone suppression test) in depressed patients than in non-depressed individuals. Both of the above-described effects – of hypercortisolism and resistance to negative feedback inhibition – are reversible upon resolution of MDD [18]. Hence the association between stress and depression has been defined for the better part of a century. But not everyone under stress develops depression, and pre-existing factor(s) that determine an individual's ability to process the emotional challenge must be at fault. Age at which a person experiences stress seems to be exactly that kind of factor, as demonstrated in a pioneering study in 1994 by Brown and Moran [19]. Several other studies [20,21] in the years that followed further quantified the association between childhood trauma and MDD, including the fact that childhood, but not adolescent, physical or sexual abuse is associated with an increased rate of depression or anxiety symptoms. Experience of childhood trauma sensitizes individuals to stress in such a way that these people are at higher risk for developing depression, especially in response to further stress [22]. In a study conducted in 2008 by Heim et al., subjects subdivided into 4 categories according to presence or absence of childhood stress and current psychiatric disorder were compared by their response to a mild stress stimulus in adulthood. In response to standardized psychosocial protocols (e.g. public speaking, mental arithmetic) that have reliably been shown to induce sympathetic activation in humans [23], the difference was striking – subjects with a history of childhood stress with or without current MDD exhibited higher ACTH, Cortisol, and heart rate than control groups.

The results solidified that childhood stress is the single strongest predictor of ACTH hyperactivity. The number of abuse events, adulthood traumas, and depression were the other, relatively weaker predictors.

Whereas psychosocial stress engages HPA axis starting from the cognitive-emotional processing, pharmacological stress tests (i.e., CRF stimulation) only exerts effect at the level of pituitary. Abused women without depression showed similarly elevated ACTH response to the pharmacological stress test as they did in the psychosocial stress test; depressed women both with or without childhood abuse showed a blunted ACTH response, which is expected in MDD. This result signifies the CRF receptor changes on pituitary corticotropes due to overactivity of the hypothalamic Paraventricular Nucleus (PVN)-median eminence in the HPA axis. As for the glucocorticoid-mediated feedback regulation, a low-dose dexamethasone test in abused women with depression showed increased suppression of cortisol. This finding is believed to be a major mechanism of stress sensitization and is also a prominent finding in PTSD. As an advancement of the simple glucocorticoid suppression test, the combination of dexamethasone/CRF test was performed in study subjects composed of men subdivided into all 4 groups; this combination of negative feedback (by dexamethasone) and escape from suppression (by CRF) is considered to be the most sensitive indicator of HPA axis hyperactivity. Men with a history of childhood abuse responded with higher cortisol levels to the dexamethasone/CRF test than did men without a history of abuse. Similar results had already been previously demonstrated in women with borderline personality disorder [24], signifying that the dexamethasone/CRF test is sensitive in elucidating HPA hypersensitivity regardless of sex.

Apart from assuming the primary role in the HPA axis through the PVN, CRF also acts as a kick-starter for autonomic and behavioral changes of stress. CRF levels in the CSF have been thus found to positively correlate with symptoms of depression [25,26] and levels of escalating perceived stress [27]. Heim et al., 2008, found that CSF CRF concentrations were progressively more elevated in subjects who had undergone childhood abuse, with higher concentrations found in those who had experienced both physical and sexual abuse (rather than sexual alone) and correlated with severity ($r=0.43$, $p=0.004$ for physical; $r=0.33$, $p=0.026$ for sexual) and duration ($r=0.34$, $p=0.023$ for physical; $r=0.29$, $p=0.05$ for sexual) abuse. Elevated CSF CRF levels were also stratified according to the age of the women at the time of abuse; women who had experienced abuse in later childhood had a higher concentration of the neurotransmitter than those abused at or below the age of 6.

Oxytocin

Neurotransmitter Oxytocin has drawn attention in this field of research due to its known role in bonding, trust, social support, and anti-stress properties. During a highly plastic period of the development of the brain, Oxytocin decreases amygdala reactivity [28]. Childhood abuse and disruption of the caretaker-child relationship were shown by Francis et al. in 2000 to affect persistent negative effects in CNS Oxytocin receptor expression in rats. In 2008, Heim et al. provided the first such evidence in humans – markedly decreased CSF Oxytocin concentrations were found in women with a history of childhood abuse. This offers insight into the interplay between stress-inducing (HPA axis) and stress-protective (Oxytocin) in adults, and how disbalance in them may put an adult at particularly high risk when exposed to stress later in life.

Hippocampal volume

As one of the most neuroplastic regions of the brain, the hippocampus also controls aspects of the HPA axis, contributes to memory and specifically contextual memory regarding fear.

Decreased hippocampal volume has been described both in patients with current MDD and in remitted patients [29,30]. Notably, after controlling for childhood abuse, it was revealed that only those subjects who had experienced childhood abuse had left hippocampal volume decreased by 18% from normal, while depressed patients without a history of abuse had a normal volume of hippocampus. Childhood trauma seems to be associated with smaller hippocampal volume, regardless of current or past psychiatric status. CRF and Cortisol hyperactivity acutely in childhood, and/or chronically thereafter (due to HPA axis hyperactivity) is suspected to contribute to this finding. On a molecular level, abnormally high glucocorticoid effects on the hippocampus include a reduction in dendritic branching, loss of dendritic spines, and reduced neurogenesis, particularly in the CA3 region.

Inflammation and neuroplasticity

Described first in 1983 by Kronfol et al. [31], depression has since then many times been demonstrated to have a definitive association with innate immunity inflammation. In 2008, Danese et al. [32] were the first to demonstrate that childhood abuse is also associated with increased inflammation (specifically measured inflammatory marker CRP) – and this association was especially strong in those subjects who proceeded to develop MDD in adult life. Other inflammatory markers, such as IL-6, have also been demonstrated to rise in abused individuals. The inflammatory reaction is most likely attributed to epigenetic changes induced by childhood stress; the most prevalent epigenetic modification is considered to be selective DNA methylation [33]. According to a model proposed by Miller and Chen [34], stress that occurs during early ages permanently influences the inflammatory system. This includes brain inflammatory cells, such as Macrophages, Microglia, and Dendritic cells, which will be over-expressed chronically once the expression of a few key regulator genes have been altered. Some of the better studied of these regulator genes are NF-kB and BDNF, both of which determine levels of pro-inflammatory cytokines, synthesis of neurotrophin (and other neuromodulators), and expression of glucocorticoid receptors. While most of the epigenetic variables concerning early life stress has only been examined in mice and monkey models, human data is starting to catch up; in post-mortem brain studies, early life abuse was associated with increased methylation of the GR exon 1f promoter in the hippocampus, one of the first such findings in humans [35].

Genetic factors

It is also necessary to note that genetic factors predispose each individual to susceptibility to childhood stress-related neuroendocrine changes. For example, the dexamethasone/CRF test is known to vary not only with childhood abuse but also with FKBP5 gene (which codes for

GR-regulating cochaperone hsp-90). Promoter polymorphisms of the Serotonin receptor gene (5HTTLPR) [36], MAO-A gene, Corticotropin-releasing hormone type 1 receptor gene (CRHR1) are only a few examples of the several known genes that moderate the link between childhood stress and dysfunctional emotional regulation.

Psychological supportive data

The above-described combination of endocrine, autonomic, and behavioral components of the stress response encompasses the brainstem, hippocampus, amygdala, and prefrontal cortex. In concert with the physiologic findings already described, psychological research data proves immensely valuable in illuminating some of the earlier, subtler effects of childhood abuse. Children with a history of abuse have a deeply skewed perception of social and emotional relations; such children tend to interpret ambiguous facial expressions as angry and show increased amygdala activity when reacting to what was perceived as "angry" [37].

EEG findings of abused children further support the evidence of impaired cortical-limbic connectivity [38].

Array of Mood Disorders Caused by Childhood Trauma

Different forms of childhood trauma can have strong associations with a wide variety of mood disorders in adulthood like Major Depressive Disorder, Persistent Depressive Disorder, Bipolar Disorder and even Postpartum Depression. In this review we will try to summarize the different outcomes of childhood trauma based on multiple research articles.

Childhood Trauma and Its Relation to Chronic Depression in Adulthood

All the studies reviewed aimed to examine the prevalence of retrospectively recalled childhood trauma in the group of chronically depressed patients. Reported studies were based on distinct samples and relied on a variety of measures and diagnostic procedures. Therefore, several studies used the Childhood Trauma Questionnaire (CTQ), some used childhood trauma questions and childhood trauma interviews, in some of the articles even criminal court records were used. Some studies relied on diagnostic interviews conducted with DSM-III/IV diagnoses, while others relied on medical diagnoses [39].

Chronicity was operationalized as a function of time: Major depressive episodes were defined to last for at least 12 months already at the beginning of the study, while diagnosis of dysthymia or double depression indicate depressive symptoms for at least 24 months or even longer. BDI-2 and the QIDS-C were used to assess symptom severity. In the end 75.6% of the chronically depressed patients reported being abused at least once (clinically significant abuse) while 37% of the chronically depressed patients experienced multiple childhood traumas. Experiences of multiple traumas also led to much more severe depressive symptoms. Multiplicity turned out to be the only significant predictor for symptom severity for chronic depression. While emotional neglect, psychological abuse, physical abuse, and sexual abuse were significantly associated with the chronicity of depression [40]. Physically abused (OR = 1.54; 95% CI 1.16–2.04), emotionally abused (OR = 3.06; 95% CI 2.43–3.85), and neglected (OR = 2.11; 95% CI 1.61–2.77) people turned out to have a higher risk of developing chronic depression compared to non-abused individuals [41]. The test for heterogeneity showed high significance, with $p<0.01$ for both abuse types and neglect. The OR estimates were slightly higher in males, but it did not show statistical significance, while women were significantly more often exposed to childhood trauma. Even though primary analyses showed a higher risk of drug use associated with physical abuse, emotional abuse or neglect, the significance was only borderline and a dose–response relationship was not consistently seen [42]. Physically abused (OR = 3.00; 95% CI 2.07–4.33), emotionally abused (OR = 3.08; 95% CI 2.42–3.93), and neglected (OR = 1.85; 95% CI 1.25–2.73) individuals had a significantly increased risk for suicidal behavior compared with non-abused individuals, which manifested in both, suicide attempts and ideation [42].

Multiple childhood trauma can be specifically related to chronic depression and we can integrate this trauma aspect for the treatments.

Childhood trauma in Bipolar Disorder

All the studies reviewed here were as well retrospective in nature, studies were conducted using childhood trauma questionnaires in the group of patients diagnosed with bipolar disorder and control groups.

These papers demonstrate strong association between childhood trauma and bipolar disorder. Higher CTQ scores were found in patients, who were diagnosed with either bipolar I or bipolar II disorder compared to controls. The studies included different types of childhood traumas and their outcomes, there turned out to be a strong association between all types of childhood traumas and bipolar disorder, other than sexual abuse [43].

In bipolar patients, who had the symptoms of melancholia, the scores of emotional and physical neglect in childhood were higher. Unlike some older studies, newer studies found that emotional neglect is the single most important risk factor, instead of physical abuse [44]. However, some of the research done on this topic is small in size, which potentially increases the risk of type II error.

Maternal childhood trauma and Postpartum Depression

Our review is based on the study done on a longitudinal sample of South African women, who were followed throughout the pregnancy and postpartum, it is a prospective study on a woman who experienced childhood trauma based on a childhood trauma questionnaire.

Women with childhood trauma experienced greater depressive symptoms through six months postpartum, which itself predicted negative child outcomes at one year. It even affected maternal-infant bonding and infant growth. This study demonstrated the intergenerational transmission of negative symptoms, it shows that in an environment of high trauma settings perinatal intervention can be of serious importance [45]. This study can have limitations because of the small sample size and potential confounders, but it is one of the rare studies on this topic [46].

Conclusion

We reviewed sociologic, epidemiologic, and neuroendocrine characteristics of childhood trauma and their relation with development of depressive disorders in later life. Although childhood trauma in general is associated with high incidence of depressive symptoms in adulthood, the reviewed literature suggests that there are some tangible differences in incidence when controlling for physical or sexual

abuse and child neglect. WHO data makes it clear that a sizable adult population reports a history of abuse, and even larger groups of population are assumed to be experiencing but not reporting abuse; this population has a lifelong high risk for developing depressive symptoms. Some neuroendocrine and inflammatory effects of childhood trauma are very clear and well-defined, but the existing gaps in research make it hard to paint a clear picture. Genetic factors make some children particularly susceptible to developing epigenetic modifications in response to stress; this results in over- and under- expression of receptors, neuromodulators, inflammatory cytokines, and consequently alters the major neuroendocrine axis and neuroplasticity of the CNS. Children with the typical reactive changes are not adequately equipped to healthily cope with stress in adulthood, and are hence susceptible to develop depressive disorders.

Although most of the reviewed literature focuses on MDD, other affective disorders such as Bipolar and Postpartum depression have also been definitively described. Our results demonstrate that the high prevalence of childhood abuse might be strongly linked with the high prevalence of affective disorders (especially MDD); considering the high disease burden of MDD, it is imperative that additional research addresses the complex mechanisms behind the association. Any new advancements in this area stand to shed much light on ways to improve effectiveness of early detection, prevention, and treatment response, of MDD.

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