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REVIEW ARTICLE

Impact of childhood stress on psychopathology

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DESCRIPTORS:
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Post-Traumatic Stress Disorder;
Cognition;
Bipolar Disorder.

Abstract

Objective: Advances in our knowledge of mental disorder (MD) genetics have contributed to a better understanding of their pathophysiology. Nonetheless, several questions and doubts persist. Recent studies have focused on environmental influences in the development of MDs, and the advent of neuroscientific methodologies has provided new perspectives. Early life events, such as childhood stress, may affect neurodevelopment through mechanisms such as gene-environment interactions and epigenetic regulation, thus leading to diseases in adulthood. The aim of this paper is to review the evidence regarding the role of the environment, particularly childhood stress, in the pathophysiology of MD. *Methodology*: We reviewed articles that evaluated environmental influences, with a particular focus on childhood trauma, brain morphology, cognitive functions, and the development of psychopathology and MD. *Results and Conclusion*: MRI studies have shown that exposure to trauma at an early age can result in several neurostructural changes, such as the reduction of the hippocampus and corpus callosum. Cognitive performance and functioning are also altered in this population. Finally, childhood stress is related to an increased risk of developing MD such as depression, bipolar disorder, schizophrenia and substance abuse. We conclude that there is robust evidence of the role of the environment, specifically adverse childhood experiences, in various aspects of MD.

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DESCRITORES:
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Transtorno bipolar.

Impacto de estresse na infância na psicopatologia

Resumo
Objetivo: Avanços no conhecimento da genética dos transtornos mentais (TM) contribuíram para um melhor entendimento de suas bases fisiopatológicas. No entanto, dúvidas e questões ainda persistem. Estudos recentes têm se concentrado nas influências do ambiente no desenvolvimento de TM, e o advento de metodologias neurocientíficas oferece novas perspectivas. Eventos precoces de vida, como estresse na infância, podem ser capazes de alterar o neurodesenvolvimento através de mecanismos como interação gene-ambiente e regulação epigenética, resultando em patologias na idade adulta. O objetivo deste artigo é revisar as evidências referentes ao papel do ambiente, em especial o estresse na infância, na fisiopatologia de TM. *Metodologia*: Revisamos artigos que avaliam as influências ambientais, com um foco especial no trauma na infância, na morfologia cerebral, nas funções cognitivas e no desenvolvimento de psicopatologias e TM. *Resultados e Conclusão*: Estudos com ressonância magnética demonstram que a exposição a traumas em uma idade precoce pode levar a diversas alterações neuroestruturais, como a diminuição do hipocampo e do corpo caloso. O desempenho e o funcionamento cognitivo também são alterados nessa população. Por fim, o estresse na infância está ligado a um maior risco de desenvolver TM como depressão, transtorno bipolar, esquizofrenia e abuso de substâncias. Concluímos que existem evidências sólidas quanto à importância do ambiente, especificamente das experiências adversas na infância, em diversos aspectos dos TM.

Introduction

During the last decades, scientific views about causality in Mental Disorders (MD) underwent several changes. Although genetics has progressed quickly with the complete mapping of the entire human genome, this tremendous effort failed to clarify why brain illnesses exist. In fact, genome mapping added even more complexity our understanding of why we are the way we are. Important questions remain unanswered. For example, the reasons and mechanisms behind twin discordance for highly heritable conditions such as schizophrenia are unknown. For this reason, several authors have focused their attention on the role of the environment in determining the occurrence of MD, exploring theoretical frameworks as diverse as psychoanalysis and behaviorism.[1] The aggregation of neuroscientific approaches to previous mind-focused theories has created new perspectives for understanding the effect of the environment on the brain, including the concept of *envirome*, i.e., the set of *environmental* events that influence brain development.[2]

Regarding the old nature versus nurture dichotomy, advances in brain research produced some relatively well-accepted concepts. First, the idea of a single cause of MD was abandoned, and the notion that different causal factors interact in a probabilistic combination to produce vulnerability was accepted.[1] New insights, such as the exploration of gene-environment interaction and epigenetic regulation of gene transcription, renewed researchers' interest in the role of the environment in MD causality. Early life events (e.g., pregnancy complications, childhood trauma, or substance abuse) putatively interact with genomic traits and may lead to altered neurodevelopment and MD in early adulthood. In fact, childhood stress has been shown to exert deleterious effects on the development of children and adolescents, with long-term consequences that often persist in adulthood. The most severe environmental stresses include emotional and physical parental abuse, multiple violent episodes, and sexual abuse.[3] Those individuals exposed to severe sexual abuse are at a greater risk for all types of psychopathologies.[4] The experience of severe traumatic events during childhood is associated with poor functioning, cognitive deficits, and a number of psychiatric conditions in adulthood.[5,6]

In this article, we review the literature on the role of childhood stress and maltreatment in the development of the pathophysiology and clinical expression of MD. To identify related studies, a search was conducted on the Medline database using the keywords "early life stress", "childhood maltreatment", "childhood trauma" and "mental disorders". The search was conducted during July 2011 and was limited to studies of humans that were published in English.

Influence of childhood stress on brain structures: neuroimaging studies

Neuroimaging techniques have been improving and becoming more accessible. Such techniques are valuable tools for unraveling the neurobiological underpinnings of psychiatric disorders. Magnetic Resonance Imaging (MRI) studies suggest that in addition to its functional impact, exposure to severe emotional trauma during childhood may cause alterations in the brain structure.[7,8] In addition, early life stress has been related to changes in specific brain systems that have been implicated in adult psychopathology.[9-11]

Preclinical studies have shown that childhood abuse and neglect promote long-term changes in stress reactivity and brain development.[12,13] Approximately a decade ago, Sanchez and colleagues were the first to demonstrate that early stress, in the form of maternal separation, is associated with a reduced corpus callosum area in non-human primates.[14] Reduced corpus callosum, hippocampus and

temporal lobe regions were also observed in male bonnet macaques that were subjected to variable foraging demand (VFD) rearing.[15] VFD is an early life stress paradigm in which infant bonnet macaques are reared by mothers undergoing an experimentally-induced "perception" of food uncertainty.[16] VFD and non-VFD mothers and infants differ on a number of behavioral and biological indices that persist throughout development, including disrupted maternal-infant attachment,[17] increased stress reactivity,[18] synchronized maternal-infant elevation of corticotrophin-releasing factor (CRF) concentrations in cerebrospinal fluid (CSF),[19] and reduced neuronal integrity.[20,21]

Preclinical research has examined the long-term impact of early life stress in adult animals. These studies aid in the understanding of the pathophysiology of post-traumatic stress disorder (PTSD) in adults, as many of the biological alterations associated with early life stress are also reported in adults with PTSD and other stress-related disorders. The one MRI study that was conducted on pre-pubescent nonhuman primates that were subjected to early life stress demonstrated a reduction in the corpus callosum. However, the lack of studies makes the application of preclinical research findings to pediatric PTSD somewhat limited. Multiple independent MRI studies of maltreated children with PTSD have shown a reduction in the corpus callosum.[22,23] A reduction in callosal fractional anisotropy, a measure of axonal integrity, has also recently been reported in maltreated children with PTSD.[24] Unlike studies that evaluated children and adolescents with PTSD secondary to maltreatment and reported structural callosal abnormalities, studies involving adults with PTSD have consistently reported reductions in hippocampal volume. Only two studies evaluated the structure of the corpus callosum in adults with PTSD who were exposed to early life adversity, and they presented conflicting results. One study reported a reduced posterior callosum area.[25] The second study, which was performed on a smaller scale, failed to replicate these findings.[26]

Emerging evidence suggests that the neurobiological effects of stress vary at different developmental stages. Differences in brain image findings in studies with adults and children may also be attributed to differences in brain maturation. It has been proposed that callosal abnormalities in children with PTSD are due to atrophy or neurodevelopmental deficits that result from traumatic experiences.[22] There is preclinical evidence that very early life experiences can dramatically impact the morphometry of the corpus callosum.[27] The myelination of the corpus callosum begins between the ages of 6 months and 3 years and continues into the third decade of life.[28-30] In addition to the effects of stress and glucocorticoids on cell proliferation in the hippocampus,[31] glucocorticoids have been shown to inhibit the proliferation of the oligodendrocyte precursor throughout the brain.[7] Consistent with the role of oligodendrocyte precursors in myelination, prenatal glucocorticoid exposure has been associated with reduced myelination of the corpus callosum and reduced myelin sheath thickness.[32] The rostral-to-caudal myelination sequence suggests that different regions of the corpus callosum might have different windows of vulnerability to early experiences.[28] Another possibility, however, is that abnormalities in corpus callosum morphology are due to developmental/genetic factors and predispose individuals to develop PTSD after exposure to trauma.[25]

PTSD is characterized by an abnormal hypothalamic-pituitary-adrenal (HPA) axis, and the sensitization of this axis is consistent with the clinical picture of hyperreactivity and hyperresponsiveness observed in PTSD patients. Most biological findings in adults with PTSD are compatible with those of chronic stress response, such as reduced hippocampal volume.[32-37] Preclinical studies have shown that chronic stress may affect the hippocampus through the excessive release of glucocorticoids,[38] corticotrophin-releasing hormone,[39] glutamate,[40] inhibition of neurogenesis,[41] impaired long-term potentiation induction,[42] inhibition of brain-derived neurotrophic factor (BDNF),[43] and alteration in the serotonergic receptor function.[44] Early life stress may alter synaptogenesis, dendritic proliferation, and pruning, but these effects may not manifest until adolescence or early adulthood. For example, preclinical studies have shown that differences in hippocampal synaptic density, as a consequence of attenuated synaptogenesis, arise only postpubertally in rats exposed to early stress.[45]

Influence of childhood stress on cognitive performance

At birth, the brain is one of the most immature organs. Therefore, its development, which is influenced by both genetic and environmental factors, is critical for its functioning, including cognitive performance.[46] The circuits that are responsible for most refined cognitive functions also depend on the factors that operate in specific periods of development, modulating the function of frontal areas that are responsible for abstract thinking, the limbic area that is responsible for regulating emotions and attachment, and other systems in the brain stem that regulate heart rate, blood pressure, and arousal states.[47]

Brain maturation and cognitive function are sensitive to the timing of the environmental experience.[48] Timing is the key to understanding the impact of environmental factors on neurocognitive development because it affects the development of the underlying brain structures and functions.[49]

To understand the impact of abuse, especially neglect, one strategy is to observe the development of children who grew up in institutions. An important finding of such studies is that children who were deprived of parental care and raised in institutions displayed a globally suppressed growth.[50] In addition, there is some evidence that children who are removed from an adverse environment after undergoing neglect and/or abuse demonstrate developmental improvement.[51] A randomized controlled trial of infants, with follow-ups at 30, 42, and 54 months of age, showed that the interaction between caregivers and children is an important predictor of the catch-up growth in height and weight of institutionalized children after adoption.[52] Despite these findings, this study found an impaired growth at baseline and cognitive compromise and smaller head size at 42 months.

In general, there is a sensitive period for growth recovery (1 year old), which is shorter than the sensitive period for developmental impairment (approximately 2 years old).[52,53] There is evidence that a history of institutional deprivation

is related to lower cognitive and academic performance. Deprived children tend to have long-lasting global cognitive impairment, especially in terms of their IQ.[54] Other studies found no significant associations between the duration of the institutional deprivation from 6 to 42 months of age and cognitive outcomes; however, at age 11, children who experienced less than 6 months of deprivation presented lower verbal IQ and reading comprehension scores.[55]

In line with these results, some studies found deficits in the intellectual and cognitive functioning of maltreated children as compared to children who had not been abused.[36,56] Research has consistently found that maltreatment increases the risk of lower academic achievement and problematic school performance.[57]

Impact of early traumatic experiences on the vulnerability to psychiatric disorders

Epidemiological studies and clinical trials on childhood trauma associate this experience with a number of psychiatric disorders at every stage of development, including bipolar disorder, major depression, post-traumatic stress disorder, substance abuse, affective problems, anxiety, personality disorders, and suicide.[4,58,60] Childhood adversity has been shown to increase the risk and severity of psychotic symptoms in adult life.[61,62] Thus, many psychiatric patients with a history of childhood trauma present worse outcomes and higher rates of clinical disorders than those without such history.[4,63-65] Individuals who have experienced negative life events take three times longer to show improvements in mood disorder symptoms.[66] In addition, patients with early trauma often present a higher risk of suicide attempt and may require more health services in adulthood.[60,65] In general, earlier age of exposure to a traumatic experience is associated with worse outcomes. For example, severe depressive symptoms are higher among those abused before the age of 12 years than among those abused after that age.[67] However, children with a psychiatric disorder are more susceptible to experience a traumatic episode.[3] Furthermore, individuals with genetic risks and a history of trauma seem to show an earlier development of MD compared to those without genetic risks.[68] These individuals commonly present difficulties with interpersonal relationships and tend to be more isolated, more refractory to treatment, and at greater risk of recurrent mood episodes.[60] In addition, the cycle of violence is often difficult to interrupt, as individuals with a history of childhood trauma present a higher risk of becoming sexual abusers in adulthood.[69]

Altogether, these studies suggest that childhood trauma is associated with an increased severity of mental disorders and that the impact of negative experiences shows enduring and persistent effects.[3,60,65] For instance, Alvarez et al. examined 102 patients with schizophrenia, bipolar disorder and schizoaffective disorder and showed that nearly half (47.5%) of these patients had suffered childhood abuse. Hospital admissions were twice as high among victims of psychological abuse, and patients with a history of sexual abuse were more than twice as likely to attempt suicide.

Those with bipolar disorder (BD) seem to be particularly vulnerable to traumatic experiences. Approximately 30% to 50% of these patients report traumatic childhood events, the most common of which is emotional abuse.[3,60,68,70] The rates of emotional abuse are higher in these patients compared to those with other psychiatric diseases, such as major depressive disorder.[71] Childhood trauma in BD patients is associated with recurrent depressive symptoms in adulthood, along with lower premorbid functional levels and poorer adherence to treatment.[72] Patients who suffered sexual and physical abuse show more severe mania symptoms.[73] Childhood trauma can occur before the development of bipolar disorder and trigger the first episode, which is often associated with psychosocial stressors.[74] Leverich et al. examined the impact of childhood trauma on the course of bipolar illness and found that a history of physical or sexual abuse was associated with an earlier onset of BD, increased comorbidity and higher rates of suicide attempts.[75]

In comparison with patients without trauma, BD patients with trauma present higher rates of substance abuse, anxiety comorbidity, post-traumatic stress disorder (PTSD), and depressive symptoms of higher intensity, particularly women.[3,65] Men with BD, despite reporting lower rates of trauma than women, are more often exposed to sexual and physical abuse than men with major depressive disorder.[71] Children with BD are likely to have a greater number of family members that experience alcohol abuse, which is related to parental disorganization and a greater risk of childhood trauma.[3] More severe and frequent abuse is associated with higher stress in adulthood and a greater chance of developing PTSD symptoms in the future.[76] Children with early trauma are more likely to present conduct disorder and violent behavior, such as substance abuse, suicides attempts and psychiatric comorbidity, particularly during adolescence.[60,64,77-84] Patients with anxiety disorder and childhood trauma have a higher risk factor of developing comorbidities such as substance abuse and mood disorder.[82]

There has been particular interest in understanding how childhood abuse may increase the risk of developing personality disorders in adulthood.[85] A history of sexual abuse during childhood increases the risk of suicidal behavior and the lifetime number of suicide attempts in adults with borderline personality disorder.[86] These patients report more childhood trauma, such as emotional abuse, compared to patients with other psychiatric disorders, such as schizophrenia.[87] The rates of early traumatic events in alcohol and drug users are higher than in patients with major depression without comorbidity.[81] The prevalence and severity of trauma in this population are also higher than those of the general population, and males who experienced childhood maltreatment have an increased risk of developing alcohol abuse.[88,89] Evidence suggests that PTSD may be one pathway that links childhood abuse and later psychopathology. One explanation that has been offered to account for the relationship between childhood abuse and the wide range of associated mental health problems is the occurrence of PTSD among adults with a history of childhood abuse.[85] Approximately 25% of people who experience a traumatic event develop PTSD, and the presence of mental illness may increase the risk of PTSD and trauma exposure.[90] Perkonigg et al. evaluated PTSD and obesity in a community sample and found that obesity was associated with a history of trauma.[91]

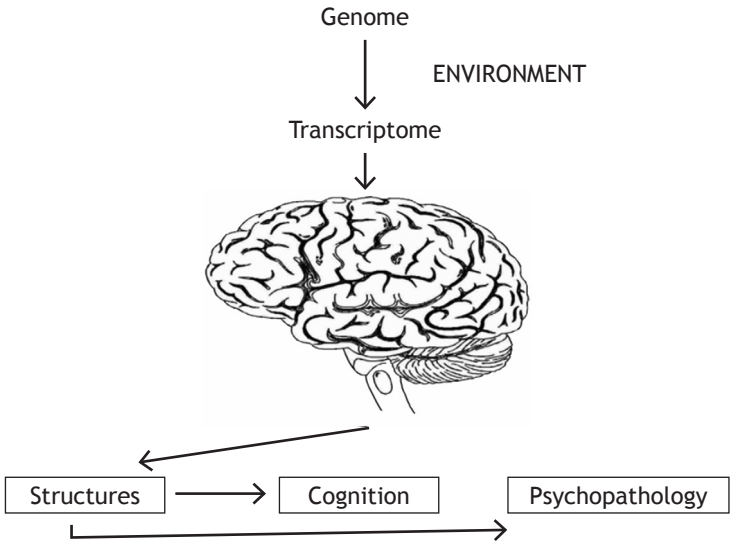

Figure 1 The environment interacts with the genome in the regulation of gene transcription. When these processes occur during development, the structure and function of the brain are changed, predisposing individuals to psychopathology.

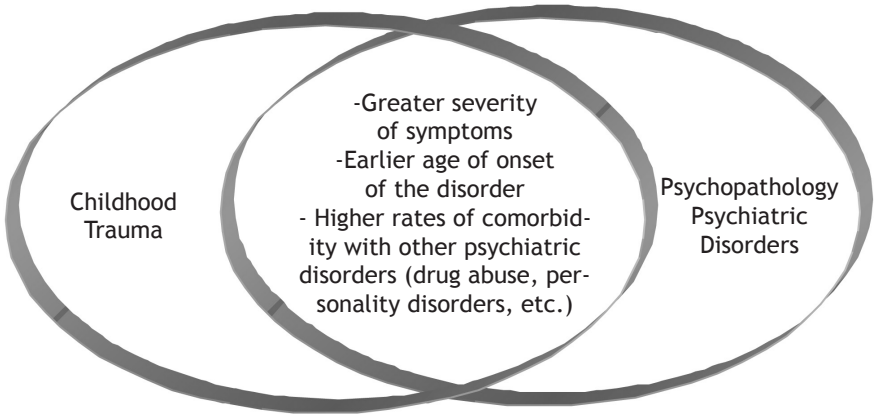

Figure 2 Impact of the association between trauma and psychopathology.

Studies have also shown a possible association between exposure to trauma and the development of psychosis; 94% of patients with schizophrenia reported a childhood trauma.[92] A history of trauma is also associated with persecutory ideation and hallucinations.[93] This diagnosis is determined earlier in victims of childhood abuse and is associated with a larger number of previous hospitalizations, first hospitalization at an earlier age, anxiety symptoms, depression and suicide.[62,94] Dissociative symptoms and functional and social impairment in patients with schizophrenia spectrum disorders are related to childhood trauma.[61,95] In a study by Goff et al., patients with psychotic disorders and a history of childhood trauma reported significantly more dissociative symptoms than patients without abuse experiences.[96] Psychotic symptoms were more common in subjects exposed to a larger number of traumas and were associated with higher rates of childhood adversity, emotional and behavioral disturbance, and dysfunctional parenting.[97] Exposure to multiple traumas, rather than a single major trauma, increases the risk of later psychosis.[97]

Recently, the role of trauma in obesity has been investigated.[98] In populations of patients who were candidates for bariatric surgery, a high prevalence of traumatic experiences was found.[98,99] Men who suffered emotional abuse during childhood are more likely to be obese in adulthood.[100] Lifetime trauma exposure has also been associated with eating disorders such as bulimia and anorexia, particularly in the presence of depressive symptoms and PTSD.[101,102] Anorexia and PTSD co-occur, and traumatic events tend to occur before the onset of anorexia. These results underscore the importance of assessing the trauma history of these patients.[103]

Conclusions

Although it is neither a sufficient nor a necessary condition, there is strong evidence supporting the role of childhood stress as a risk factor in the pathway leading to MD, including brain structures, cognition, and expression of symptoms. The impact of this evidence in clinical settings remains largely unknown, and few studies have used more integrative approaches. In addition, differences in treatment response and prognosis when comparing patients with and without a history of psychological trauma remains a relatively underexplored topic.

Future studies should adopt longitudinal designs to assess the exact contribution of environmental factors to the pathophysiology of MD. Exploring the developmental trajectory using a multimodal methodology could also offer new insights on the reversibility of the damage caused by childhood stress. In addition, such studies would identify possible compensatory mechanisms that could enhance individuals' resilience. Understanding the neurobiological impact of childhood stress can aid in developing efficient strategies for the primary prevention of MD.

Disclosures

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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