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Early Childhood Environment and Genetic Interactions: the Diathesis for Suicidal Behavior

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Abstract Adverse childhood experiences are associated with higher risk for suicide and suicidal behavior later in life. There are known associations between childhood trauma, particularly sexual abuse, and higher rates of suicide, non-lethal suicide attempts, and non-suicidal self-injurious behaviors in adolescence and adulthood. Emotional abuse/neglect, disrupted parental attachment, and cumulative effect of multiple forms of maltreatment, also increase risk. Yet, the causal relationship remains unclear. The diathesis-stress model provides a framework for understanding how early life adverse experiences contribute to suicide vulnerability. Current findings from the fields of biology, neurology, and genetics shed new light on mediating variables and possible causal links between early childhood trauma and suicide. In this paper, we review recent advances, particularly regarding the interaction of early life environmental adverse events with genetics factors, that increase the diathesis for psychological traits are associated with subsequent deliberate self-harm behaviors.

Keywords Trauma · Childhood adverse events · Suicide · Suicide attempts · Genetics · Diathesis-stress

Introduction

Adverse experiences in early childhood are associated with a higher risk for suicide and suicidal behavior later in life. In the past two decades, a substantial literature has developed, documenting a consistent association between childhood trauma, sexual abuse in particular, and higher rates of death by suicide, non-lethal suicide attempts, and non-suicidal self-injurious behaviors (NSSI) in adolescence and adulthood. Emotional abuse and neglect, disrupted parental attachment, and the cumulative effect of multiple forms of maltreatment also increase the risk. These associations have been documented across adolescent, adult, inpatient, and outpatient populations, as well as in epidemiological studies of community and more general populations [1–15].

It makes intuitive sense that physical, sexual, emotional abuse, physical and emotional neglect, parental loss, and maternal separation constitute environmental factors that impede healthy development and reduce the resilience that can be protective against suicide. Yet, the causal relationship between adverse childhood experiences and suicidal behavior remains unclear. Much of the empirical evidence consists of correlational associations gleaned from retrospective and cross-sectional studies. In addition, the science has lacked consistency regarding the definition and measurement of adverse childhood experiences, and of suicidal behaviors, lending variability to the findings across studies.

More recently, a number of prospective studies have been undertaken to overcome the limitations of retrospective reporting [6, 14, 16–18]. And, classification systems put forth by the Center for Disease Control (CDC) [19] and the Columbia-Classification Algorithm for Suicide Assessment (C-CASA) [20] have informed movement toward a more uniform nomenclature for classifying suicidal behaviors, leading to the development of valid and reliable research instruments to codify suicide outcomes.

In addition, longitudinal and prospective studies have been providing more robust support for previous findings regarding both the specific role of early sexual abuse and suicidal

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behavior, as well as the cumulative effects of multiple adverse experiences [2, 13]. And, recent research is expanding what we know about the relationship between childhood abuse and other adverse early life experiences and suicidal behavior within specialized high-risk international populations, as well as in the military [16, 21–24].

Most significantly, current findings from the fields of biology, neurology, and genetics have shed new light on the mediating variables and therefore possible causal link between early childhood trauma and suicide. The diathesis-stress model provides a framework for understanding how early life adverse experiences contribute to a vulnerability to act on suicidal ideation [25, 26, 27•]. The model suggests that suicidal behavior results from the interaction of a behavioral and biological predisposition to act on self-destructive urges, paired with a stressor or trigger such as a recent life event [25, 26]. In a 2013 review article [28], we proposed a modified diathesis-stress model to illustrate how the most recent biological genetic, neurobiological, psychiatric, psychological, and epidemiological findings could explain a putative causal relationship between early life events, mediating biological and psychological factors, and suicidal behavior. In particular, early life events interact with neurobiological and genetic factors to contribute to the diathesis for developing psychological and personality traits that are associated with increased propensity for suicidal ideation and actions. Early life adversities can also contribute to specific life events or stressors related to the original trauma that might trigger the propensity to act, although there is less research examining the contribution of childhood adversity to the stressor end of the model.

In the current paper, we update the model we proposed in 2013 to incorporate the most recent findings of the past 3 years. We highlight the methodological upgrades that are leading to less variability in the measurement of key variables and review the studies that investigate and document the relationship between early life adversity and suicide in new populations. In particular, we review the most recent advances in the area of genetic studies, regarding genomic plasticity and how the early life environment can affect DNA methylation. The newest findings provide further documentation and more specific knowledge regarding the effect of adverse childhood experiences on genetic changes that affect the neurobiological systems, leading to psychological traits that predispose to suicidal behavior.

Methodological Advances

Definitions and Measures of Suicidal Behavior

The variability in findings throughout the vast literature regarding the relationship between adverse childhood experiences and suicidal behavior later in life has been due in part to a lack of consistency regarding the definition and measurement of the outcome variables. The past few years have seen advances in the field of suicidology regarding standardization in the classification and definition of a wide spectrum of suicidal and self-harm behaviors [29]. Recently developed measures of suicidal behavior have widely adopted the following definition of suicide attempt: "a non-fatal self-directed potentially injurious behavior with at least some intent to die as a result of the behavior." Non-suicidal self-injury (NSSI) is defined as: "behavior that is self-directed and deliberately results in injury or the potential for injury to oneself, with no evidence, whether implicit or explicit, of suicidal intent (CDC, 2011) [19]."

While many survey studies continue to rely on self-reported (and therefore self-defined) suicidal behavior, several semi-structured interview measures that incorporate the new definitions have emerged as valid and reliable measures, increasing standardization as well as the ability to more systematically distinguish between suicide attempts and NSSI behaviors. The Columbia Suicide Severity Rating Scale (C-SSRS) [30], the Suicide Attempt Self-injury Interview (SASII) [31], and the Self-Injurious Thoughts and Behaviors Interview (SITBI) [32] quantify the severity of suicidal ideation, suicide attempts, and NSSI, in clinical and research settings. The Deliberate Self-Harm Inventory (DSHI) [33] is a behavior-based 17-item self-report that measures the frequency, severity, duration, and type of NSSI. The C-SSRS in particular has become widely disseminated in recent years and demonstrates reliability and validity in numerous clinical and community populations [34–36].

Retrospective Vs. Prospective Measures of Adverse Childhood Experiences

Despite its limitations, retrospective report remains one of the most common methods for the measurement of childhood adversity. Nevertheless, the field is moving toward increased consistency in the retrospective measurement of childhood abuse/neglect across studies with the widespread use of The Childhood Trauma Questionnaire (CTQ), a valid and reliable measure that obtains retrospective self-report of the presence or absence of physical and sexual abuse and/or emotional or physical neglect, or emotional abuse [37]. Internationally, the World Health Organization is developing and validating The ACE International Questionnaire (ACE-IQ) [38], intended to measure Adverse Childhood Experiences such as family dysfunction; physical, sexual and emotional abuse, and neglect by parents or caregivers; peer violence; witnessing community violence; and exposure to collective violence.

Types of Environmental Risk Factors

Although past studies have highlighted the specific risk that childhood sexual abuse plays in suicide, newer studies examine additional adverse childhood risk factors [17, 18]. A recent

systematic review and critical examination of various forms of childhood maltreatment suggests that sexual and emotional abuse may contribute to adolescent suicidality more than physical abuse or neglect [39]. Insecure maternal attachment is another early environmental risk factor that contributes to both suicidal and non-suicidal self-injurious behaviors [40, 41]. Two longitudinal studies in adolescents found evidence of poor maternal attachment related to NSSI behaviors. In one, adolescents referred for mental health treatment and who had recent NSSI behaviors were followed over a course of 6 months. Those with insecure maternal attachments were more likely than those with secure attachments to have repeated NSSI behaviors and to exhibit less capacity for problem solving [40]. In another, maternal withdrawal in infancy was predictive of borderline symptoms and NSSI behaviors in later adolescence [41]. Relatedly, one study found that low parental care had a greater impact on suicide attempt and NSSI than did physical, sexual, or psychological abuse in a sample of depressed adults. Low maternal care was significantly associated with suicide attempt, and low paternal care was linked to NSSI [18].

Some recent prospective studies [16, 17] have improved upon retrospective and cross-sectional studies to provide greater accuracy in the measurement of childhood adversity and its impact on suicidal behavior later in life. One of these [17] followed the 1958 British Birth Cohort from birth up until adulthood (12,399 participants, 44 suicides), examining prenatal and childhood antecedents of suicide and utilizing data collected at birth and at age 7 from various informants. Findings were that low birth weight, younger maternal age, higher birth order, high number of emotional adversities (mainly parental death and bullying), and externalizing problems in males were related to eventual death by suicide.

Thus, childhood sexual abuse, although the most consistently documented, is only one of many types of adverse experiences recognized as risk factors for self-harm and suicidal behaviors. There is increasing evidence for the role of emotional neglect and disrupted parental attachment that warrants further study.

Special Populations

Most of what we know about adverse childhood experiences and suicidal behavior is from clinical and community populations in the USA and other first world countries. More recently, studies have explored this relationship in more specialized populations, especially in those with high adolescent suicide rates. Cluver et al. [16] conducted the first known prospective study of children and adolescent suicidal behavior in sub-Saharan Africa, an area known for high rates of childhood exposure to parental death, violence, and abuse. In this study in which 3515 children and adolescents were interviewed, there was a strong, graded relationship between cumulative number of adverse childhood events and suicidal behaviors. Additionally, this study looked at the severity of childhood adversities, reporting that the more severe experiences were correlated with an increase in mental health disorders, suicide attempts threefold and suicide planning fivefold.

A cross-sectional special population study in Latvia [21] examined the prevalence of self-reported suicide attempts in young adults and their exposure to violence and neglect in childhood. Data was collected from 1259 students aged 18–25 during a 6-month period using a questionnaire based on the ACE questionnaire. Results supported previous findings that both physical and emotional adverse experiences increase the risk of attempted suicide, and therefore the recommendation that special attention be paid to emotional factors and neglect, since they are less recognized forms of violence against children.

In addition to military-related stressors such as multiple deployments, studies are examining the role of pre-existing mental health characteristics that might contribute to the high prevalence of suicide and suicide risk in military populations. Perales et al. [22] report that the prevalence of childhood trauma, mostly family problems and abuse, was 43 % among those in the US military who died by suicide, and almost 65 % among those who attempted suicide between the years of 2005 and 2009. A 10-year longitudinal study [23] examined pre- and post-recruit training predictors of subsequent suicide in the US Marines using a proximal-distal risk factor model and found that about 50 % reported at least one significant life stressor (childhood sexual, physical or emotional abuse, emotional neglect, physical neglect) prior to recruit training. Similarly, in a survey study comparing samples of the Canadian general population and of the Canadian Armed Forces (CAF) found associations between childhood abuse (sexual, physical, and exposure to intimate partner violence) in both [24]. However, the prevalence of exposure to childhood abuse was significantly higher in the CAF population, leading to the conclusion that individuals with childhood abuse history may be more likely to enter the military.

Neurobiological Mediators Between Environment and Behavior

Diathesis-Stress Model

As reviewed in 2013 [28], the most significant advances in understanding the mechanisms by which adverse childhood experiences contribute to suicide risk in adolescent and adulthood have been in the fields of genetics and neurobiology. Exciting findings from the field of epigenetics [42–46] have demonstrated that DNA methylation can serve as mechanism that adapts genome function to changing environmental contexts. A critical time point for this process is in early childhood

when the social and physical environment defines lifelong trajectories of physical and mental health. Thus, environmental trauma early in life can increase the diathesis for suicidal and NSSI behaviors, not only via psychological processes but through biological impact on neurotransmitter systems and genetic endotypes and phenotypes.

Also in our previous article, we presented a diathesis-stress model to illustrate the genetic and neurological changes that can be attributed to early life stress and the neurobiological correlates which are associated with certain character traits that increase risk for suicidal behavior. These include serotonin, opioid, oxytocin, and HPA axis activity. The character traits that are known to increase risk for suicide include impulsive aggression [47–49], emotional dysregulation [50], poor attachment [33], chronic hopelessness/pessimism [51], and impaired cognition [52, 53].

We also proposed a more specific framework for future research to investigate whether certain types of adverse experiences might result in specific genetic and/or neurobiological changes which lead to particular types of traits correlated with suicidal or NSSI behaviors. For example, physical or sexual abuse might reduce serotonergic functioning, leading to increased impulsive aggression and subsequent suicidal behavior [54, 55]. Or, childhood neglect/disruptions in maternal/paternal attachment might decrease oxytocin, disrupt the propensity for attachment, and lead to increased emotional dysregulation and suicidal behavior [56–59]. Sexual abuse might adversely affect the HPA axis and cortisol levels (and blunt the stress response), which might contribute to emotional dysregulation that leads to suicidal behavior [60, 61]. Physical or sexual abuse might decrease opioid functioning, thereby increasing propensity for engaging in NSSI [62].

The latest findings summarized here provide some evidence for our 2013 speculations, particularly regarding the contributing role of childhood adversity to epigenetic changes affecting the HPA axis and stress response system.

HPA Axis

Recent studies have further examined the relationship between the hypothalamic-pituitary-adrenal (HPA) axis (which regulates the stress response) and risk of suicide. Building on the work of McGirr et al. [63] who found that relatives of suicide completers exhibited a blunted cortisol response, Melhem et al. [64] found lower cortisol output on the Trier Social Stress Test, indicating blunted HPA axis activity, in offspring of depressed parents with suicide attempts and suicide-related behavior, as compared to offspring with no suicide-related behavior. While these studies provide support for the association of blunted cortisol and HPA axis responsiveness in suicidal behavior, they do not address the role of adverse childhood experiences.

Environment/Gene Interactions Related to HPA Axis

There is evidence that early life adversity can lead to epigenetic regulation of genes involved in HPA axis (stress response) system. In a comprehensive review, Turecki et al. [65•] describe how early life adversity increases the risk of suicide by influencing the development of stable emotional, behavioral, and cognitive phenotypes that are likely to result from the epigenetic regulation of HPA axis. Such phenotypes include high anxiety, impulsive/aggressive traits, and impaired decision-making and problem-solving, all of which contribute to the diathesis for suicide. In a related empirical study, Kaminsky et al. [66] found that SKA2 methylation interacted with childhood abuse, as measured by the CTQ, to predict lifetime suicide attempt in saliva and blood and to mediate suppression of cortisol following a Dexamethasone Suppression Test. Thus, epigenetic variation at SKA2 seems to mediate vulnerability to suicide behaviors (and post-traumatic stress disorder) through the dysregulation of the HPA axis in response to stress. Roy [67] found a similar relationship between HPA axis gene cRHBP and CTQ scores to predict suicide attempt in African Americans, with an additive effect with the FKBP5 gene. These results suggest that genetic and environmental factors interact to impair the stress response both on a genetic as well as neurobiological level, and thereby increase an individual's vulnerability for attempting suicide.

Serotonin

Low serotonergic functioning, as measured by lower CSF 5HIAA levels, has been consistently associated with increased impulsivity and self-destructive as well as aggressive behavior in adults [47, 68]. Genetic studies provide some evidence that certain gene polymorphisms related to serotonergic functioning moderate the relationship between childhood trauma, depression, and suicidal behavior. [48, 54, 69–72] A number of studies show that childhood trauma is related to low-expressing 5-HTTLPR genotypes and increased risk for suicide attempts in patients with bipolar disorder [73] and substance dependence [54] and adult inpatients [55].

Most recently, early life experiences of interpersonal conflict have surfaced as an environmental factor that contributes to alterations of genes related to CSF 5-HIAA (a serotonin metabolite), cortisol and DHEAS in suicide attempters [74]. Gorodetsky et al. [75] found that childhood physical abuse, as measured by the CTQ, and depression, were predictors of self-directed aggression (suicide attempts and NSSI) in a population of 702 male Italian prisoners, but that there was no interactive effect between trauma and measures of the serotonin transporter gene polymorphism 5-HTTLPR. These inconsistent findings indicate the need for further study regarding the relationship between trauma and serotonin-related genetic changes that can lead to suicidal behavior.

Oxytocin

The hormone oxytocin is thought to support affiliation and attachment through its role in stress reduction [56], and there is some evidence that early childhood adverse experiences can alter brain development through its effects on the oxytocin-vasopressin stress response system [57]. Low CSF oxytocin levels have been found in suicide attempters with high suicide intent [58]. Neuropeptides, including the opioids, oxytocin, and vasopressin, serve a crucial role in the regulation of affiliative behaviors and are disrupted in individuals with borderline personality disorder (BPD), who are at high risk for engaging in suicidal and NSSI behaviors [59]. Most recently, Chatzittofis et al. [76] found that although exposure to violence as a child did not have significant impact on CSF and plasma oxytocin levels, significantly lower plasma oxytocin levels and a more negative childhood emotional climate were found in re-victimized suicide attempters compared to non-re-victimized suicide attempters, indicating a complex relationship between early trauma and the oxytocin system. Further research is necessary to investigate the pathway from adversity in childhood, specifically disruptions in parental attachment, genetic and neurobiological changes related to oxytocin, and suicidal behaviors.

Personality Traits

Childhood adversity impacts directly on neurological systems related to suicide-related traits of impulsivity, aggression, and hopelessness [77]. Childhood abuse also seems to contribute to emotional dysregulation and poor attachment patterns that are related to suicidal and self-harm behaviors [32, 49]. More recently, research has focused on cognitive traits related to impaired decision-making. Guillaume et al. [78] found that suicidal individuals with a history of childhood sexual abuse obtained lower scores on the Iowa Gambling Task (IGT), indicating a poor decision-making. In addition in this study, polymorphisms within HPA axis-related CRHR1 and CRHR2 genes interacted with childhood sexual abuse and emotional neglect to influence the IGT score.

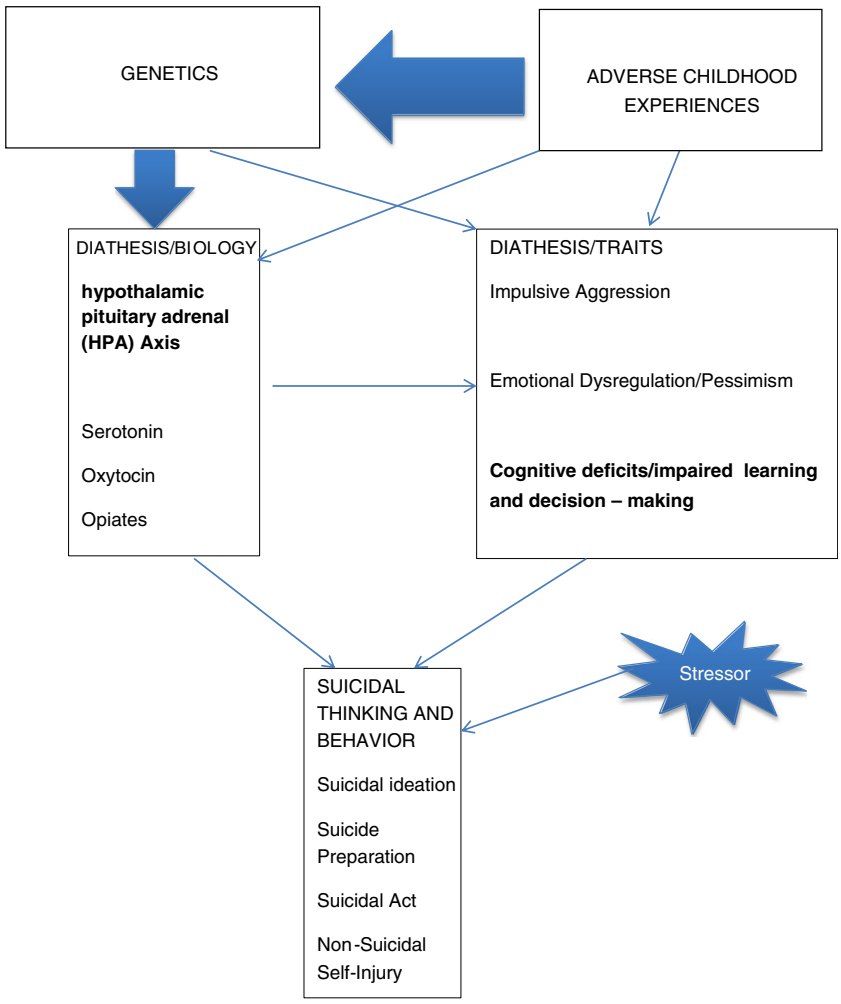

Fig. 1 Gene/environment interaction and the diathesis for suicidal Behavior

Updating the Model: the Diathesis for Suicidal and Self-Harm Behaviors

The findings of the past 3 years shed additional light on the mechanisms by which adverse childhood experiences contribute to the diathesis of suicidal and self-harm behaviors in later adolescence and adulthood. Figure 1 updates the diathesis-stress model for suicide and self-harm to incorporate and highlight the new evidence describing and supporting the impact of environmental factors on genetic mutability that could impact the expression of neurological and psychological traits that predispose to suicide and self-harm. Most particularly (and indicated in bold lettering in Fig. 1), there is increased evidence of the role of childhood abuse on genes that disrupt the HPA axis, blunting the cortisol response and reducing resilience in managing stress. And, in addition to the traits of impulsive aggression and hopelessness/pessimism, we now know more about the effect of these environmental/genetic interactions on the development of impaired cognition and decision-making. In a recent comprehensive review of the literature, Mandelli and Serretti [79•] cautiously advocate for, while acknowledging the limitations and infancy of, the approach of examining gene/environment interaction to gain more specific understanding of the mediating and possible causal mechanisms that increase the diathesis for depression and suicidal behavior.

Conclusions

Recent developments build upon what is known about the association between adverse childhood experiences and suicidal behavior later in life. Improvements in methodology include increased standardization in definitions and measurement of the variables in question, as well as increased use of prospective and longitudinal study design. Secondly, while sexual abuse continues to be a consistent and strong suicide risk factor, there is growing evidence for the role of cumulative and additional types of adverse childhood experiences, namely emotional abuse and neglect, witnessing violence, and disruptions in parental attachment. These results are being replicated in international, developing countries, and military populations.

Most notably, the latest research expands into a more specific understanding of this relationship beyond association and prediction, toward possible mediating and causal factors. Earlier applications of the diathesis-stress model to suicide prediction named psychological traits as mediating factors that contribute to the diathesis for suicidal behavior, and how these traits may be impacted by early adversity. However, advances in the field of epigenetics have revealed a more than previously imagined complex interaction between genes and the environment, which informs and updates the diathesis-stress theory of suicidal behavior. Early childhood adversity appears to lead to genetic polymorphisms that modify the expression of the neurological systems that impact on biological and psychological trait development within an individual's lifetime, thereby increasing the diathesis for the propensity to react to stressors for suicidal behavior. Although the gene/environment interaction approach is in its infancy and has many limitations, it also holds promise for elucidating the causal and mediating factors between early environment and suicidal behavior. Future research is necessary to reach more definitive conclusions regarding whether and which types of early adverse events affect which particular genetic expressions and neurobiological pathways that then lead to specific trait factors and vulnerability to specific stressors for suicide.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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