The Devastating Clinical Consequences of Child Abuse and Neglect: Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders

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A large body of evidence has demonstrated that exposure to childhood maltreatment at any stage of development can have long-lasting consequences. It is associated with a marked increase in risk for psychiatric and medical disorders. This review summarizes the literature investigating the effects of childhood maltreatment on disease vulnerability for mood disorders, specifically summarizing cross-sectional and more recent longitudinal studies demonstrating that childhood maltreatment is more prevalent and is associated with increased risk for first mood episode, episode recurrence, greater comorbidities, and increased risk for suicidal ideation and attempts in individuals with mood disorders. It summarizes the persistent alterations associated with childhood maltreatment, including alterations in the hypothalamic-pituitary-adrenal axis and inflammatory cytokines, which may contribute to disease vulnerability and a more pernicious disease course. The authors discuss several candidate genes and environmental factors (for example, substance use) that may alter disease vulnerability and illness course and neurobiological associations that may mediate these relationships following childhood maltreatment. Studies provide insight into modifiable mechanisms and provide direction to improve both treatment and prevention strategies.

"It is not the bruises on the body that hurt. It is the wounds of the heart and the scars on the mind."

—Aisha Mirza

"We can deny our experience but our body remembers."
—Jeanne McElvaney, *Spirit Unbroken: Abby's Story*

It is now well established that childhood maltreatment, or exposure to abuse and neglect in children under the age of 18, has devastating consequences. Over the past two decades, research has begun not only to define the consequences in the context of health and disease but also to elucidate mechanisms underlying the link between childhood maltreatment and medical, including psychiatric, outcomes. Research has begun to shed light on how childhood maltreatment mediates disease risk and course. Childhood maltreatment increases risk for developing psychiatric disorders (e.g., mood and anxiety disorders, posttraumatic stress disorder [PTSD], antisocial and borderline personality disorders, and substance use disorders). It is associated with an earlier age at onset and a more severe clinical course (i.e., greater symptom severity) and poorer treatment response to pharmacotherapy or psychotherapy. Early-life adversity is also associated with increased vulnerability to several major medical disorders, including coronary artery disease and myocardial infarction,

cerebrovascular disease and stroke, type 2 diabetes, asthma, and certain forms of cancer. The net effect is a significant reduction in life expectancy in victims of child abuse and neglect. The focus of this review is to expand on previous reviews by synthesizing the literature and integrating much recent data, with a focus on investigating childhood maltreatment interactions with risk for mood disorders, disease onset, and early disease heterogeneity, as well as emerging data suggesting modifiable mechanisms that could be targeted for early intervention and prevention strategies. A major emphasis of this review is to provide a clinically relevant update to practicing mental health practitioners.

PREVALENCE AND CONSEQUENCES OF CHILDHOOD MALTREATMENT

It is estimated that one in four children will experience child abuse or neglect at some point in their lifetime, and one in seven children have experienced abuse over the past year. In 2016, 676,000 children were reported to child protective services in the United States and identified as victims of child abuse or neglect (1). However, it is widely accepted that statistics on such reports represent a significant underestimate of the prevalence of childhood maltreatment,

FIGURE 1. National estimates of childhood maltreatment in the United States[a]

A. National Estimate, Rounded Number of Victims (thousands)
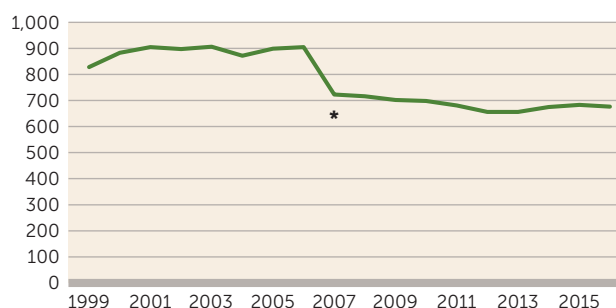
B. Rates of Victimization per 1,000 Children
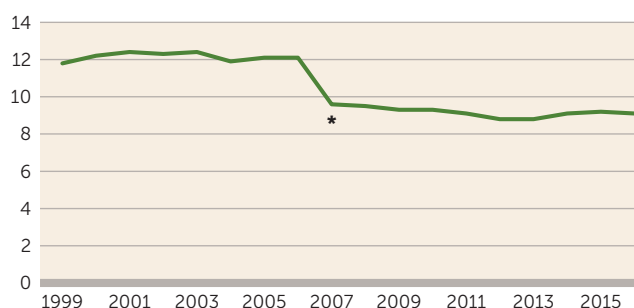
[a] Panel A graphs the prevalence of maltreatment (calculated national estimate/rounded number of victims by year, and panel B graphs rates of victimization per 1,000 children, between 1999 and 2016, as reported by the Children's Bureau, which produces an annual Child Maltreatment report including data provided by the United States to the National Child Abuse and Neglect Data Systems. Estimated rates of maltreatment have remained high over the past two decades. The asterisk calls attention to the fact that before 2007, the national estimates were based on counting a child each time he or she was the subject of a child protective services investigation. In 2007, unique counts started to be reported. The unique estimates are based on counting a child only once regardless of the number of times he or she is found to be a victim during a reporting year. (Information obtained from https://www.acf.hhs.gov/cb/research-data-technology/statistics-research/child-maltreatment.)

because the majority of abuse and neglect goes unreported. This is especially true for certain types of childhood maltreatment (notably emotional abuse and neglect), which may never come to clinical attention but have devastating consequences on health independently of physical abuse and neglect or sexual abuse. Although rates of children being reported to child protective services have remained relatively consistent over recent decades (Figure 1), our understanding of the devastating medical and clinical consequences of childhood maltreatment has grown, and childhood maltreatment is now well established as a major risk factor for adult psychopathology. In this review, we seek to summarize the burgeoning literature on childhood maltreatment, specifically focusing on the link between childhood maltreatment and mood disorders (depression and bipolar disorder). The data converge to point toward future directions for education, prevention, and treatment to decrease the consequences of childhood maltreatment, especially in regard to mood disorders.

CHILDHOOD MALTREATMENT INCREASES RISK FOR ILLNESS SEVERITY AND POOR TREATMENT RESPONSE IN MOOD DISORDERS

The link between childhood maltreatment and risk for mood disorders and differences in disease course following illness onset has been well documented (2–8). Multiple studies have demonstrated greater rates of childhood maltreatment in patients with major depression and bipolar disorder (9–11). Indeed, a recent meta-analysis revealed that 46% of individuals with depression report childhood maltreatment (12). Patients with bipolar disorder also report high levels of childhood maltreatment (13, 14), with estimates as high as 57% (15). Childhood maltreatment is associated with an increased risk and earlier onset of unipolar depression, with syndromal depression occurring on average 4 years earlier in individuals with a history of childhood maltreatment compared with those without such a history (12). Childhood

maltreatment is also associated with a more pernicious disease course, including a greater number of lifetime depressive episodes and greater depression severity, with the majority of studies showing more recurrence and greater persistence of depressive episodes (16–18). For example, Wiersma et al. (19), in an analysis of 1,230 adults with major depressive disorder drawn from the Netherlands Study of Depression and Anxiety, found that childhood maltreatment (measured with the Childhood Trauma Interview) was associated with chronicity of depression, defined as being depressed for ≥24 months over the past 4 years, independent of comorbid anxiety disorders, severity of depressive symptoms, or age at onset. Increased risk for suicide attempts and comorbidities, including increased rates of anxiety disorders, PTSD, and substance use disorders, are reported in individuals with depression who experience childhood maltreatment. Individuals with major depressive disorder and atypical features report significantly more traumatic life events (including physical abuse, sexual abuse, and other forms of trauma) both before and after their first depressive episode, independently of sex, age at onset, or duration of depression (20). Additionally, childhood maltreatment has consistently been shown to be associated with poor treatment outcome (after psychotherapy, pharmacotherapy, and combined treatment) in depression, as assessed by lack of remission or response or longer time to remission (12, 18, 21, 22).

Although the studies cited above describe a link between childhood maltreatment and a more pernicious depression course, most studies have been cross-sectional, and the possibility of recall bias and mood effects (owing to the retrospective investigation of childhood maltreatment in individuals who are currently depressed) cannot be ruled out. However, studies over the past few years comparing retrospective and prospective measurement of childhood maltreatment suggest consistency between retrospective reports and prospective designs (23, 24), although a recent meta-analysis (25) suggested poor agreement between these

measures, with better agreement observed when retrospective measures were based on interviews and in studies with smaller samples. Longitudinal and prospective studies are emerging that have further confirmed and extended our understanding of the devastating consequences of childhood maltreatment on illness course (5, 7). Ellis et al. (26) recently reported that childhood maltreatment increased risk for more severe trajectories of depressive symptoms during a 7-year longitudinal study in 243 adolescents in the Orygen Adolescent Development Study. Gilman et al. (27) reported that childhood maltreatment increased the risk for recurrent depressive episodes and suicidal ideation by 20%−30% during a 3-year follow-up of 2,497 participants diagnosed with major depressive disorder in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Additionally, Widom et al. (7), in a study that followed a cohort of 676 children with documented childhood maltreatment and compared risk for major depression in adulthood between them and a cohort of 520 children matched on age, race, sex, and family social class who were not exposed to childhood maltreatment, found a clear association between childhood maltreatment and both increased risk for depression and earlier onset of the disorder.

Although more research has been reported investigating the link between childhood maltreatment and disease onset and course in unipolar depression, more recent evidence supports the link between childhood maltreatment and disease onset and course in bipolar disorder (28). Childhood maltreatment is associated with increased disease vulnerability and earlier age at onset of bipolar disorder (29). Jansen et al. (30) sought to determine whether childhood maltreatment mediated the effect of family history on diagnosis of a mood disorder. The findings indicated that one-third of the effect of family history on risk for mood disorders was mediated by childhood maltreatment. As with depression, studies on bipolar disorder with a prospective or longitudinal approach are few, but they are informative. Using data from the NESARC (N=33,375), Gilman et al. (31) found that childhood physical and sexual abuse were associated with increased risk for first-onset and recurrent mania independently of recent life stress. An association between childhood maltreatment and prodromal symptoms has also been reported in bipolar disorder (32), suggesting that childhood maltreatment may contribute to disease vulnerability before onset of the first manic episode. Childhood maltreatment in the context of bipolar disorder is also associated with a more pernicious disease course, including greater frequency and severity of mood episodes (both depressive and manic), greater severity of psychosis symptoms, and greater risk for comorbidities (i.e., anxiety disorders, PTSD, substance use disorders), rapid cycling, inpatient hospitalizations, and suicide attempts (28, 33–41). Studies are beginning to emerge investigating treatment response in bipolar disorder following childhood maltreatment. Such studies remain few, but they suggest that childhood maltreatment is associated with a poor response to benzodiazepines

(42) and anticonvulsants (41) in bipolar disorder. The concatenation of findings in depression and bipolar disorder are concordant in that childhood maltreatment increases risk for, and early onset of, first mood episode and episode recurrence. Childhood maltreatment affects disease trajectories, including in its association with more insidious mood episodes, poor treatment response, a greater risk for comorbidities, and a greater risk for suicide ideation, attempts, and completion. The link between childhood maltreatment and increased prevalence of suicide-related behaviors is of particular importance given the high rate of suicide ideation, attempts, and completion in depression and bipolar disorder. Despite many prevention strategies (e.g., education and outreach and clinical studies to identify risk factors for impending suicide attempts in individuals with mood disorders), suicide rates have not decreased but in fact have increased in the United States. The link between childhood maltreatment and suicide-related behavior has been reviewed by several groups (21, 33, 43–47). Dube et al. (48) reported that adverse childhood experiences, including childhood maltreatment, increased the risk for suicide attempts twofold to fivefold in 17,337 adults in the now classic Adverse Childhood Experiences Study. Gomez et al. (49) reported that physical or sexual abuse increased the odds of suicide ideation, planning, and attempts among the 9,272 adolescents in the U.S. National Comorbidity Survey Adolescent Supplement. Miller et al. (50) examined the relationship between childhood maltreatment and prospective suicidal ideation in a cohort of 682 youths followed over a 3-year period. Emotional maltreatment predicted suicidal ideation, independently of previous suicidal ideation and depressive symptom severity. Childhood maltreatment is also associated with earlier age at first suicide attempt (51). Additionally, an association between childhood maltreatment and suicide risk in 449 individuals age 60 or older was recently reported from the Multidimensional Study of the Elderly, in the Family Health Strategy in Porto Alegre, Brazil (52). The effect was independent of depressive symptom severity. These findings suggest that childhood maltreatment increases risk for suicide-related behavior across the lifespan. More work is warranted in investigating the biological mechanisms that may mediate the association between childhood maltreatment and suicide-related behaviors.

TIMING OF CHILDHOOD MALTREATMENT: ARE THERE PERIODS OF HEIGHTENED SENSITIVITY?

Although childhood maltreatment at any age can result in long-lasting consequences (53), there is evidence that the timing, duration, and severity of maltreatment mediate the risk for later psychopathology (54). Childhood maltreatment that occurs earlier in life and continues for a longer duration is associated with the worst outcomes (55). This is supported by preclinical models (rodent and nonhuman primate) that investigated maternal separation (56, 57), a paradigm more similar to neglect in humans. One study in rodents found that maternal separation during the early postnatal period (days 2–15) but not the later postnatal period (days 7–20) is

associated with anxious and depressive-like behaviors in adulthood (57). Although this postnatal period coincides with in utero development in humans, there is evidence that in utero insults in the form of stress can have consequences similar to early-life trauma (58, 59), supporting the translational validity of these models. Clinical studies also support the importance of timing of childhood maltreatment in moderating risk for psychopathology. Cowell et al. (60) investigated the timing and duration of childhood maltreatment in 223 maltreated children between the ages of 3 and 9 and found that children who were maltreated during infancy and those who experienced chronic maltreatment had poorer inhibitory control and working memory. Dunn et al. (61) investigated the relationship between timing of childhood maltreatment and depression and suicidal ideation in early adulthood among 15,701 participants in the National Longitudinal Study of Adolescent Health, and found that exposure to early maltreatment, especially during the preschool years (between ages 3 and 5), was most strongly associated with depression. Additionally, sexual abuse occurring during early childhood, compared with adolescence, was reported to be more strongly associated with suicidal ideation (61). While these studies suggest that childhood maltreatment that occurs earlier in development may further increase risk for developing mood disorders and associated behaviors in adulthood, it is important to emphasize that evidence suggests that exposure to maltreatment during later childhood and adolescence also independently increases risk for mood disorders. Emotional abuse and neglect, especially if it occurs between ages 8 and 9, increases depressive symptoms (62). Emotional abuse during adolescence also increases risk for depression (63).

More work is emerging investigating the negative consequences of bullying. A study of 1,420 participants (ages 9–16) revealed that victims of bullying showed an increased prevalence of generalized anxiety disorder, depression, and suicide-related behavior (64). A recent study of more than 5,000 children that comprised a longitudinal data set (the Avon Longitudinal Study of Parents and Children in England and the Great Smoky Mountains Study in the United States) (65) found an increased risk for mental health problems, including anxiety, depression, and self-harm, in individuals who experienced bullying, but not other maltreatment. Additionally, an association between childhood bullying by peers and risk for suicide-related behaviors (ideation, planning, attempting, and onset of plan among ideators), independent of childhood maltreatment by adults, was reported in a sample of U.S. Army soldiers (66).

Some studies suggest that differential periods of sensitivity to different subtypes of maltreatment are distinctly associated with an increased risk for mood disorders. Recently, a stronger relationship was reported between adult depression and early childhood sexual abuse (occurring at age 5 or earlier) and later childhood physical abuse (occurring at age 13 or later), compared with maltreatment that occurred during other developmental periods (67). Harpur et al. (68)

reported that early childhood maltreatment (between birth and age 4) predicted more anxiety symptoms, and maltreatment that occurred in late childhood or early adolescence (between ages 10 and 12) predicted more depressive symptoms in adolescence. Taken together, these studies suggest that maltreatment at any age and across different contexts (physical and emotional, familial- and peer-induced) often result in long-lasting and severe consequences and that there may be specific sensitive periods in development when exposure to distinct types of maltreatment may differentially increase risk for affective disorders in adulthood. To date, the majority of research investigating the impact of childhood maltreatment timing on illness risk and course in mood disorders has focused on depression. One study (69) reported that early sexual or physical abuse (before age 11) in 225 early psychosis patients (6.7% with a bipolar disorder diagnosis) coincided with lower scores on the Global Assessment of Functioning Scale and the Social and Occupational Functioning Assessment Scale during a 3-year follow-up period, whereas late sexual or physical abuse (between ages 12 and 15) did not. More work investigating timing of maltreatment and associated clinical outcomes is warranted.

EXPERIENCING SINGLE SUBTYPES OF ABUSE AND NEGLECT VERSUS EXPERIENCING MULTIPLE TYPES

Several groups have sought to determine the impact of single types of childhood maltreatment on mood disorders. Although all types of childhood maltreatment (physical, emotional, and sexual) increase disease vulnerability and risk for more severe illness course in mood disorders, including increased risk for suicide (52), there may be some distinctions between individual subtypes and associated outcomes (70). An association between sexual abuse and lifetime risk for anxiety disorders, depression, and suicide attempts independent of other types of maltreatment has been reported (2, 71, 72). In bipolar disorder, physical abuse and sexual abuse independently increase risk for illness vulnerability and more severe course (13). One study of 446 youths (ages 7 to 17) found that physical abuse was independently associated with a longer duration of illness in bipolar disorder, a greater prevalence of comorbid PTSD and psychosis, and a greater prevalence of family history of a mood disorder when compared with sexual abuse, which was only associated with a greater prevalence of PTSD (13). Recent life stress in adulthood was found to increase risk for first-onset mania in individuals with a history of childhood physical maltreatment, but not individuals with a history of sexual maltreatment (31). However, it should be noted that early-life sexual abuse in the study was a strong risk factor for mania even in the absence of recent life stress.

Neglect is the least studied form of early-life adversity, and emerging data suggest differential consequences following neglect as compared with abuse (73). Similarly, long-lasting consequences following emotional maltreatment, independently

of other forms of maltreatment, have also been reported (47, 74, 75). In a 2015 meta-analysis, emotional abuse showed the strongest association with depression, followed by neglect and sexual abuse (76), a finding supported by another recent meta-analysis (77). Spertus et al. (78) reported that emotional abuse and neglect predicted depressive symptoms even after controlling for physical and sexual abuse, further suggesting emotional abuse and neglect to be independently related to illness severity in depression. Parental "verbal aggression" was found to increase risk for depression and anxiety in adolescents, with risk suggested to be greater following verbal aggression compared with physical abuse (79). Khan et al. (63) recently reported that nonverbal emotional abuse in males and peer emotional abuse in females are important predictors of lifetime history of major depression and are more predictive than number of types of maltreatment experienced. Another recent meta-analysis (12) reported that in individuals with depression, emotional neglect was the most common reported form of childhood maltreatment, and emotional abuse was most closely related to symptom severity. High prevalence of emotional maltreatment is also reported in bipolar disorder (approximately 40%), with emotional maltreatment associated with disease vulnerability and more severe illness course, including rapid cycling, comorbid anxiety or stress disorders, suicide attempts or ideation, and cannabis use (80).

Although studies on subtypes of maltreatment are only now burgeoning, they are concordant in implicating emotional maltreatment, in addition to physical and sexual maltreatment, in increasing risk for, and differences in disease course of, mood disorders. Emotional maltreatment and neglect are clearly the least studied of all forms of childhood adversity. This is in part because they are often overlooked and least likely to come to clinical attention, as compared with physical and sexual abuse, which can, of course, result in physical injury. Because emotional maltreatment and neglect are likely the most prevalent forms of childhood maltreatment in psychiatric populations (81), and given findings suggesting that independent of other forms of maltreatment, emotional maltreatment has long-lasting consequences that increase risk for mood disorders and illness outcome (74, 75), more research on the role of emotional maltreatment and neglect are urgently needed.

Although the findings described above suggest the hypothesis that different subtypes of early-life adversity may independently increase risk for mood disorders and that some subtypes may be more closely related to specific differences in illness course and severity, it is clear that subtypes of abuse and neglect, as a rule, do not occur in isolation but instead occur together in the same individuals. For example, individuals experiencing physical or sexual abuse likely also experience emotional maltreatment. Some studies have investigated the impact of multiple types of childhood maltreatment. A recent meta-analysis reported that 19% of individuals with major depression report more than one form of childhood maltreatment and, while all childhood maltreatment subtypes have been shown to increase the risk

of depression, experiencing multiple forms of childhood maltreatment further elevates this risk (12). The Adverse Childhood Experiences study provided evidence of an additive effect of eight early-life stress events (including abuse but also other early-life stressors, such as divorce, domestic violence, household substance abuse, and parental loss) on adult psychopathology. Specifically, individuals with four or more early-life stress events had significantly increased risk for depression, anxiety, suicide attempts, substance use disorders, and other detrimental outcomes (82, 83). An additive or cumulative effect of early-life stress on increased risk for mood, anxiety, and substance use disorders has also been reported by others (5, 6). Multiple adverse childhood experiences (maltreatment plus other forms of stressful events) also result in higher rates of comorbidities (7, 82). Likewise, a dose-response relationship between number of types of childhood maltreatment and illness severity in bipolar disorder has been suggested, including increased risk for comorbid anxiety disorders and substance use disorders (84).

UNDERLYING MECHANISMS BY WHICH CHILDHOOD MALTREATMENT INCREASES RISK FOR MOOD DISORDERS AND CONTRIBUTES TO DISEASE COURSE

As depicted in Figure 2, several putative biological mechanisms by which childhood maltreatment may increase the risk for mood disorders and disease progression have been described (21, 85). These include, but are not limited to, inflammation and other immune system perturbations, alterations in the hypothalamic-pituitary-adrenal (HPA) axis, and genetic and epigenetic processes as well as structural and functional brain imaging changes. These studies provide insight into modifiable targets and provide direction to improve both treatment and prevention strategies.

Biological Abnormalities Associated With Childhood Maltreatment

Several persistent biological alterations associated with childhood maltreatment may mediate the increased risk for development of mood and other disorders. Childhood maltreatment is associated with systemic inflammation (86, 87) as assessed by measurements of C-reactive protein (CRP) and inflammatory cytokines including tumor necrosis factor-alpha and interleukin-6. Childhood maltreatment was found to be associated with increased plasma CRP levels and increased body mass index in 483 participants identified as being on the psychosis spectrum (88). Patients with depression and bipolar disorder have also been reported to exhibit increased levels of inflammatory markers (89–92). It is unclear whether childhood maltreatment–associated inflammation is responsible for the observations in patients with mood disorders. Anti-inflammatory drugs are a promising novel therapeutic strategy in the subgroup of depressed patients with elevated inflammation (93), although the findings thus

FIGURE 2. Child maltreatment, its consequences, and windows for intervention across development[a]
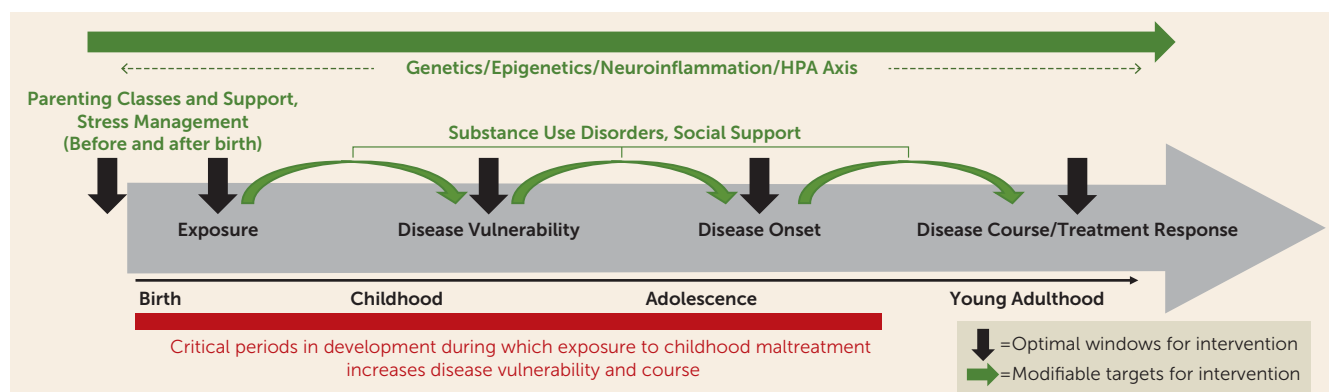
[a] The gray arrow represents the development of disease vulnerability, disease onset, and variations in disease course and treatment. Exposure to childhood maltreatment at any point during development (red bar) can result in long-lasting consequences, including increasing disease vulnerability and illness severity in mood disorders. There may be optimal windows (black arrows) across development when interventions could decrease disease burden by decreasing disease vulnerability and improving illness course; these include before and after birth (parenting classes and parenting support groups), at the time of maltreatment, when prodromal symptoms begin to emerge, immediately following disease onset, and during disease course (e.g., improving treatment response). Modifiable targets are beginning to emerge (green arrows and text) and point to behavioral and environmental factors, as well as genetic and other molecular factors, that could be focused on for interventions.

far are preliminary, and further study on inflammation as a modifiable target is warranted.

Another mechanism through which childhood maltreatment may increase risk for mood disorders is through alterations of the HPA axis and corticotropin-releasing factor (CRF) circuits that regulate endocrine, behavioral, immune, and autonomic responses to stress. Research documenting how childhood maltreatment contributes to altered HPA axis and CRF circuit activity in preclinical and clinical studies has been reviewed in detail elsewhere (21). Childhood adversity likely increases sensitivity to the effects of recent life stress on the course of both unipolar and bipolar disorder. Soldiers exposed to childhood maltreatment have a greater risk for depression or anxiety following recent life stressors (94). Likewise, individuals exposed to childhood maltreatment have a greater risk of mania following recent life stressors compared with individuals without childhood maltreatment (31, 34). Individuals with depression or bipolar disorder and early-life stress report lower levels of stress prior to recurrence of a mood episode compared with individuals with depression or bipolar disorder without early-life stress (34, 95); this suggests that less stress is required to induce a mood episode in individuals who were exposed to childhood maltreatment. These findings support theoretical sensitization frameworks on the role of stress in unipolar depression and bipolar disorder (96–99). Alterations in the HPA axis and CRF circuits following childhood maltreatment are mechanisms that likely contribute to increased risk for mood episodes following stressful life events and may be modifiable targets. Indeed, Abercrombie et al. (100) recently reported that therapeutics targeting cortisol signaling may show promise in the treatment of depression in adults with a history of emotional abuse.

In addition to the biological mechanisms noted above, genetic predisposition undoubtedly also plays a role in the

pathogenesis of mood disorders following early-life stress. As previously reviewed (21), studies support the interaction of genetic predisposition and childhood maltreatment in increasing risk for mood disorders and affecting disease course. Indeed, this is now considered a prototype of how gene-by-environment interactions influence disease vulnerability. Polymorphisms in genes comprising components of the HPA axis and CRF circuits increase the risk for adult mood disorders in adults exposed to childhood maltreatment. For example, polymorphisms in the FK506 binding protein 5 (FKBP5) gene interact with childhood maltreatment to increase risk for major depression, suicide attempts, and PTSD (101–105). Caspi et al. (106) found that adults exposed to childhood maltreatment who carried the short arm allele of the serotonin transporter promoter polymorphism (heterozygotes and homozygotes) exhibited an increased risk for a depressed episode, greater depressive symptoms, and greater risk for suicidal ideation and attempts compared with homozygotes with two long arm alleles. A large number of studies now support the interaction between early-life stress, the serotonin transporter promoter, and other serotonergic gene polymorphisms and disease vulnerability and illness course in depression and bipolar disorder (107–111), although conflicting findings have also been reported (112). Childhood maltreatment has also been reported to interact with corticotropin-releasing hormone receptor 1 gene (CRHR1) polymorphisms to predict syndromal depression and increase risk for suicide attempts in adults (113–115). Early-life stress interactions with other genetic polymorphisms to influence risk for mood disorders and illness course include, but are not limited to, brain-derived neurotrophic factor (BDNF) Val66Met polymorphism (116, 117), toll-like receptors (118), the oxytocin receptor (119), inflammation pathway genes (120), and methylenetetrahydrofolate reductase (121), although negative findings have also been reported (122).

Studies employing polygenic risk score (PRS) analyses, an approach assessing the combined impact of multiple genotyped single-nucleotide polymorphisms, have reported that PRS is differentially related to risk for depression in individuals with a history of childhood maltreatment compared with those without maltreatment (123, 124), although negative findings have also been reported (125).

Studies investigating the role of epigenetics (e.g., the modification of gene expression through DNA methylation and acetylation) in mediating detrimental outcomes following early-life stress have recently appeared (126). For example, a recent study reported that hypermethylation of the first exon of a monoamine oxidase A (MAOA) gene region of interest mediated the association between sexual abuse and depression (127). Childhood maltreatment is also associated with epigenetic modifications of the glucocorticoid receptor (128), the FKBP5 gene (101), and the serotonin 3A receptor (129), with these modifications associated with suicide completion, altered stress hormone systems, and illness severity, respectively. Childhood maltreatment–associated epigenetic changes in individuals who died by suicide have been identified in human postmortem studies (130). These studies, and others not cited here, support gene–by–childhood maltreatment interactions, including epigenetic modifications, in risk for mood disorders and in illness course.

Epigenetics may also be one mechanism that contributes to the intergenerational transmission of trauma (131–133), although it is important to note that nongenomic mechanisms are also implicated in the intergenerational transmission of behavior (134). There is a robust literature in rodent models supporting the intergenerational transmission of maternal behavior—maternal traits being passed to offspring—including abuse-related phenotypes (132, 135). Intergenerational transmission of behavior is also implicated in humans. Yehuda et al. (136, 137) investigated risk for psychopathology in offspring of Holocaust survivors. These pivotal studies identified increased risk for PTSD, mood disorders, and substance use disorders in offspring. These offspring also reported having higher levels of emotional abuse and neglect, which correlated with severity of PTSD in the parent (136, 137), implicating early-life stress in transmission of psychopathology. While there is evidence that children with developmental disabilities are at a higher risk for neglect (138–140), there is a paucity of studies investigating whether offspring of individuals with mental illness are more liable to abuse. However, as discussed above, higher rates of maltreatment are reported in individuals with mood disorders, but whether and what familial factors may drive these elevated rates, or whether these interactions contribute to the intergenerational transmission of psychopathology, are not known. In light of the emerging data on intergenerational transmission of trauma, this is an important, complex area in need of further study. There have not been many genetic studies in this area. In a study investigating early-life maltreatment in a rodent model, early-life abuse

(defined as stepping on, dropping, or dragging offspring, and active avoidance) was associated with altered BDNF expression and methylation in the prefrontal cortex in adult offspring, with adult offspring also showing poorer maternal care patterns when rearing their own offspring (135). Altered expression and methylation of BDNF is reported in individuals with mood disorders (141, 142). These studies highlight the importance of understanding the intergenerational transmission of trauma and psychopathology to identify modifiable targets to improve outcomes, for example, the family unit and interpersonal relationships. It is noteworthy that while the majority of research has focused on intergenerational transmission of maternal traits, research is also emerging that supports the important role of paternal care on intergenerational transmission of behavior (131). More study on intergenerational transmission of trauma is needed.

Pathways to Mood Disorder Outcomes

More work on mechanisms and pathways by which childhood maltreatment increases risk for and ultimately results in adult mood disorders is essential for early intervention. Childhood maltreatment is associated with a marked increase in medical morbidities and an array of physical symptoms, and in general it predicts poor health and a shorter lifespan (143, 144). Higher rates of comorbid substance use disorders in individuals with mood disorders who report experiencing childhood maltreatment is of particular interest. Childhood maltreatment has consistently been associated with a number of high-risk health behaviors, including smoking and alcohol and drug use—behaviors thought to contribute to the association between childhood maltreatment and poor health (145–148). These behaviors on their own increase risk for, and alter disease course in, mood disorders (149–153). More study on the relationship between early-life adversity, substance use disorders, and mood disorders is therefore warranted. For example, childhood maltreatment is associated with increased risky alcohol use, alcohol-related problems, and alcohol use disorders (154, 155), and alcohol use disorders are an established risk factor for both depression and bipolar disorder (149–151) in addition to increasing risk for a more severe clinical course, such as further increasing risk for suicide (152, 153). A recent study reported that depression mediates the relationship between childhood maltreatment and alcohol abuse (156). Another study recently reported that sexual abuse increased risk of alcohol use and depression in adolescence, which then influenced risk for adult depression, anxiety, and substance abuse (157). In a longitudinal study investigating changes in patterns of substance use over time in 937 adolescents, childhood maltreatment was associated with an increased progression toward heavy polysubstance use (158). More research is needed looking at the interactions between childhood maltreatment and other drugs of abuse. This is especially true in light of the current opioid epidemic, as increased

rates of childhood maltreatment are also reported in individuals with opioid use disorders (159–161), and greater reported childhood maltreatment is associated with faster transmission from use to dependence (162) and with higher rates of suicide attempts in this population (163).

Interestingly, certain genes described above that exhibit gene–by–childhood maltreatment interactions on risk for mood disorders, including FKBP5 and the serotonin transporter promoter polymorphisms, also exhibit gene-by-childhood maltreatment interactions on risk for alcohol use disorders (164–168). Alterations in the stress hormone system are also associated with an increased risk for alcohol use disorders in individuals with a history of childhood maltreatment (169), and past-year negative life events have been reported to increase drinking and drug use, an effect that is dependent on genetic variation in the serotonin transporter gene (170). Childhood maltreatment has been found to be associated with an earlier age at initiation of alcohol and marijuana use, with this association mediated by externalizing behaviors (171). Impulsivity may mediate the relationship between childhood maltreatment and increased risk for developing alcohol or cannabis abuse (172). Etain et al. (173) conducted a path analysis in 485 euthymic patients with bipolar disorder and uncovered a significant association between impulsivity and emotional abuse, and impulsivity was associated with an increased risk for substance use disorders. These studies suggest that in some individuals with a history of childhood maltreatment, although not all, interventions that focus on alcohol or drug use problems, and specifically externalizing behaviors that may mediate the link between childhood maltreatment and alcohol or drug use problems (e.g., impulsivity), could decrease disease burden by decreasing risk for developing mood disorders or by improving illness course (e.g., decreasing symptom severity and risk for suicide).

Substance use disorders are also associated with increases in inflammatory markers (174, 175). Inflammation is suggested to contribute to comorbid alcohol use disorders and mood disorders (176), and it contributes to a variety of medical morbidities (177), and these in turn are associated with an increased risk for mood disorders (177). Speculatively, inflammation may be one mechanism by which childhood maltreatment increases risk for medical morbidity and through that pathway increases risk for mood disorders. While there is a paucity of studies on the pathways described above, the associations between childhood maltreatment, risky health behaviors, inflammation, and medical morbidities warrant more study, as identifying pathways (mediators and moderators) to illness outcomes could foster the development of more effective interventions and treatment strategies.

It should be noted that not all individuals who experience childhood maltreatment develop mood disorders. This may be related in part to genetics. However, other resiliency factors are likely of importance. In a recent meta-analysis, Braithwaite et al. (178) identified interpersonal relationships, cognitive vulnerabilities, and behavioral difficulties as modifiable predictors of depression following childhood maltreatment. Specifically, social support and secure attachments were reported to exert a buffering effect on risk for depression, brooding was suggested to be a cognitive marker of risk, and externalizing behavior was suggested to be a behavioral marker of risk. Other researchers have also reported that social support may be protective and that interventions directed toward enhancing social support may decrease disease vulnerability and improve illness course (179). Metacognitive beliefs, or beliefs about one's own cognition, are suggested to mediate the relationship between childhood maltreatment and mood-related and positive symptoms in individuals with psychotic or bipolar disorders (180). Specifically, beliefs about thoughts being uncontrollable or dangerous mediated the relationship between emotional abuse and depression or anxiety and positive symptom subscale score on the Positive and Negative Syndrome Scale. Affective lability was found to mediate the relationship between childhood maltreatment and several clinical features in bipolar disorder, including suicide attempts, anxiety, and mixed episodes (181), and social cognition was suggested to moderate the relationship between physical abuse and clinical outcome in an inpatient psychiatric rehabilitation program (182).

Childhood Maltreatment and Associated Alterations in Neural Structure and Function

Research on neurobiological consequences that may mediate the relationship between childhood maltreatment and risk for, and affect disease course in, mood disorders is clearly integral to addressing the question of whether the consequences of early-life stress are reversible. Although a comprehensive review of neuroimaging findings is beyond the scope of this review, over the past 5 years, review articles summarizing the neurobiological associations with childhood maltreatment have emphasized the long-lasting neurobiological structural and functional changes in the brain following maltreatment (21, 83, 183, 184). In brief, while null and conflicting findings have been reported, data are converging to suggest that childhood maltreatment is associated with lower gray matter volumes and thickness in the ventral and dorsal prefrontal cortex, including the orbitofrontal and anterior cingulate cortices, hippocampus, insula, and striatum, with more recent studies also suggesting an association with decreased white matter structural integrity within and between these regions (185–194). Smaller hippocampal and prefrontal cortical volumes following childhood maltreatment are consistently reported in unipolar depression and other psychiatric disorders (189, 195–199), with gene-by-environment interactions suggested (200–202). These studies suggest mechanisms that may cross diagnostic boundaries in conferring risk for psychopathology and genetic variation that may link neurobiology, childhood maltreatment, and vulnerability for detrimental outcomes.

Studies investigating differences in function within, and functional connectivity between, these regions following childhood maltreatment are emerging, with more recent results suggesting that these changes may relate to risk for psychopathology. It was recently reported that decreased prefrontal responses during a verbal working memory task mediated the relationship between childhood maltreatment and trait impulsivity in young adult women (203). In a study investigating functional responses to emotional faces in 182 adults with a range of anxiety symptoms (204), the authors found that increased amygdala and decreased dorsolateral prefrontal activity to fearful and angry faces—as well as increased insula activity to fearful and increased ventral but decreased dorsal and anterior cingulate activity to angry faces—mediated the relationship between childhood maltreatment and anxiety symptoms. Differences in functional connectivity, measured with multivariate network-based approaches, within the dorsal attention network and between task-positive networks and sensory systems have been reported in unipolar depression following childhood maltreatment (205). Altered reward-related functional connectivity between the striatum and the medial prefrontal cortex has also been reported in individuals with greater recent life stress and higher levels of childhood maltreatment, with increased connectivity associated with greater depressive symptom severity (206). Childhood maltreatment–associated changes in functional connectivity between the amygdala and the dorsolateral and rostral prefrontal cortex have been suggested to contribute to altered stress response and mood in adults (207). Additionally, childhood maltreatment has been reported to moderate the association between inhibitory control, measured with a Stroop color-word task, and activation in the anterior cingulate cortex while listening to personalized stress cues, an individual's recounting of his or her own stressful events (208). As discussed above, it has been hypothesized that childhood maltreatment may increase risk for mood disorders through alterations of the HPA axis and CRF circuits in the brain. Therefore, research aimed at identifying neurobiological changes in function of CRF circuits in the brain that may mediate the relationship between childhood maltreatment and risk for mood disorders and affect disease course, including interactions with recent life stress, is a promising area of investigation.

Recent studies investigating altered function could suggest neurobiological mechanisms of risk but may also suggest possible mechanisms underlying resilience (183). Functional studies, such as those discussed above, that link functional changes in the brain following childhood maltreatment to mood-related symptoms can provide some clues to help identify mechanisms underlying risk. However, in the absence of longitudinal study of outcomes, these results must still be interpreted with caution. While the majority of studies have been cross-sectional, longitudinal studies are beginning to emerge. Opel et al. (209) recently reported that reduced insula surface area mediated the association between childhood maltreatment and relapse of depression among 110 patients with unipolar depression followed prospectively. A longitudinal study incorporating structural MRI in 51 adolescents (37% of whom had a history of childhood maltreatment) found that reduced cortical thickness in prefrontal and temporal cortices was associated with psychiatric symptoms at follow-up (210). Swartz et al. (211) followed 157 adolescents over a 2-year period and reported results suggesting that early-life stress is associated with amygdala hyperactivity during threat processing, with this finding preceding syndromal mood or anxiety. Longitudinal study of outcomes following childhood maltreatment and underlying neurobiology (predictors and trajectories) is critically needed to identify modifiable targets that confer risk and disentangle mechanisms of risk and resilience.

Only recently have studies investigating childhood maltreatment in bipolar disorder and neurobiological associations begun to emerge. Similar to unipolar depression and other psychiatric disorders, decreased ventral and dorsolateral prefrontal, insula, and hippocampal gray matter volume are reported in individuals with bipolar disorder with a history of childhood maltreatment compared with individuals with bipolar disorder without childhood maltreatment (202, 212, 213). Decreased white matter structural integrity across the whole brain, including lower structural integrity in the corpus callosum and uncinate fasciculus, have been reported in individuals with bipolar disorder who reported having experienced child abuse compared with those who did not and a healthy comparison group (214, 215). Interestingly, one study (214) found that the effects of childhood maltreatment on white matter structural integrity were specific to individuals with bipolar disorder; decreased structural integrity was not observed in healthy comparison individuals with a history of childhood maltreatment compared with healthy individuals without maltreatment. In light of this finding, along with recently published data from other groups (216–218), it is possible that some consequences following childhood maltreatment may be more robust or distinct in some individuals—or that perhaps individuals with a genetic predisposition for mood disorders may be more vulnerable to the detrimental effects of childhood maltreatment.

Altered amygdala and hippocampal volumes are suggested to be differentially modulated following childhood maltreatment in patients with bipolar disorder compared with a healthy comparison group (216), although interactions with history of treatment (e.g., duration of lithium exposure) cannot be ruled out, as this was not investigated. Souza-Queiroz et al. (217) found that childhood maltreatment was associated with decreased amygdala volume, decreased ventromedial prefrontal connectivity with the amygdala and hippocampus, and decreased structural integrity in the uncinate fasciculus—the main white matter fiber tract connecting these regions. The bipolar group primarily drove these effects, with only smaller amygdala volume associated with childhood maltreatment in the healthy comparison group. While these findings could be driven by higher rates of

maltreatment reported in the bipolar disorder group, or other clinical factors such as medication exposure and history of depressed or manic episodes, they could also suggest interactions between genetic vulnerability to bipolar disorder (or other environmental factors) and neurobiological consequences following childhood maltreatment.

More research is needed to identify genes that may influence neurobiological vulnerability following childhood maltreatment. An example of a potential gene that may mediate this relationship is the serotonin transporter promoter. Genetic variation in the serotonin transporter promoter is associated with differences in structural integrity of white matter in bipolar disorder (219). Because a large number of studies support the interaction between early-life stress, the serotonin transporter promoter, and disease vulnerability and illness course in depression and bipolar disorder (106–111), this example highlights the potential of genes to contribute to long-lasting structural consequences in the brain following childhood maltreatment in mood disorders. Genetic imaging studies are emerging and suggest gene-by-environment interactions on structural and functional alterations following childhood maltreatment. For example, one study found that hippocampal volume differences following childhood maltreatment are mediated by genetic variation in bipolar disorder (202). Additionally, polymorphisms in stress system genes, including FKBP5 and NR3C1, are suggested to moderate the effects of childhood maltreatment on amygdala reactivity (220–222) and hippocampal volumes (223). Studies investigating interactions between familial risk for mood disorders and childhood maltreatment and associated structural and functional changes in the brain would be useful to test whether familial factors (genetic and environmental vulnerability) may interact with childhood maltreatment to alter brain structure and function while avoiding confounders such as medication exposure.

LIMITATIONS AND FUTURE DIRECTIONS

A sizable percentage of patients with mood disorders have a history of childhood maltreatment. While the devastating consequences of childhood maltreatment cannot be disavowed, several limitations in research should be noted. Research groups often assess childhood maltreatment differently, and this can result in a measurement bias. Demographic characteristics and differences in assessments (age and sex ratio of participants; clinical versus nonclinical populations being studied; observer-rated versus self-rated depression measures) are all suggested to contribute to differences in prevalence of childhood maltreatment and relation with illness severity (12). For example, studies using the Childhood Trauma Questionnaire report higher rates of emotional abuse compared with studies using other measures to investigate childhood maltreatment (12). Further study is warranted investigating the neurobiological mechanisms, underlying genetics, familial factors, and modifiable targets

that may drive development of mood disorders following childhood maltreatment. A promising area is network-based approaches to understand this link (224). Additionally, consequences following different types of maltreatment require further investigation, as different forms of childhood maltreatment may be associated with distinct neural consequences, and a better understanding of these relations is critical for the development of more effective interventions and prevention strategies. For example, Heim et al. (225) reported that victims of sexual abuse exhibit more alterations in the somatosensory area, whereas victims of emotional abuse exhibit differences in areas mediating emotional processing and self-awareness, including the anterior cingulate and parahippocampal gyrus. More work is needed to investigate whether there are sensitive periods in development when maltreatment has more robust consequences on neurobiology. Humphreys et al. (226) recently reported that hippocampal volume differences were associated with stress severity during early childhood (≤5 years of age), but there was no association between hippocampal volumes and stress occurring during later childhood. Studies investigating interactions between childhood maltreatment and genetic variation or familial risk for mood disorders could identify mechanisms underlying risk and resiliency in the absence of some study-related confounders (e.g., medication).

Longitudinal studies are critically needed to distinguish what behaviors and mechanisms (genetic and neurobiological) may contribute to risk and whether alterations in behaviors or neurobiology are secondary to mood disorder onset. It is important to emphasize that sex differences likely contribute to outcomes following childhood maltreatment (227). These include females, compared with males, having a higher risk for internalizing disorders (depression and anxiety) (228, 229), greater deficits in neural systems underlying emotional regulation (187, 230), and being more susceptible to stress-induced changes in the HPA axis (231) following maltreatment. Males, compared with females, may be more vulnerable to developing externalizing disorders (conduct disorders and substance use disorders) (232). However, few studies have investigated sex differences following childhood maltreatment. More research on sex differences is critically needed, including on the underlying neurobiology. As previously reviewed (21), early-life adversity is associated with increased vulnerability to several major medical disorders, including coronary artery disease and myocardial infarction, cerebrovascular disease and stroke, type 2 diabetes, asthma, and certain forms of cancer. More work is needed on medical morbidities that may increase risk for early mortality following early-life adversity. Additionally, more research is needed on disparities that contribute to, and minority communities that show, elevated rates of early-life adversity. As discussed above, rates of early-life adversity are higher among individuals with developmental disabilities (138–140). Rates of trauma are also higher in youths in the lesbian, gay, bisexual, transgender, and questioning (LGBTQ) community (233). Few studies have been published in this

area. Youths in the LGBTQ community show higher rates of mood disorders, anxiety, suicide, and alcohol and drug use (234). In a recent study, Rhoades et al. (235) investigated the relationship between parental rejection, homelessness, and mental health outcomes in LGBTQ youths. Parental rejection was associated with higher rates of homelessness, with experience of homelessness associated with greater feelings of hopelessness, PTSD and depressive symptoms, and greater prevalence of past suicide attempts and more individuals saying they are likely to attempt suicide in the future. More work is critically needed in vulnerable populations, including work focused on interventions that may improve mental health outcomes, for example, interventions that focus on the family unit and interpersonal relationships to foster support and educational interventions, which may decrease peer victimization and cyberbullying (236, 237).

In summary, studies converge on and consistently support the finding that childhood maltreatment increases disease vulnerability for mood disorders, as well as a more pernicious disease course. A reduction in the prevalence of childhood maltreatment would have a substantial impact on decreasing disease burden (238). Studies suggesting modifiable targets are only just beginning to emerge and point to behavioral and environmental factors that could be focused on for early interventions.

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REFERENCES

1. US Department of Health and Human Services, Administration for Children and Families, Administration on Children, Youth and Families, Children's Bureau: Child Maltreatment 2016. Washington, DC, US Department of Health and Human Services, 2018 (https://www.acf.hhs.gov/cb/research-data-technology/statistics-research/child-maltreatment)

2. Maniglio R: Child sexual abuse in the etiology of depression: a systematic review of reviews. Depress Anxiety 2010; 27:631–642

3. Maniglio R: Prevalence of child sexual abuse among adults and youths with bipolar disorder: a systematic review. Clin Psychol Rev 2013; 33:561–573

4. Lindert J, von Ehrenstein OS, Grashow R, et al: Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. Int J Public Health 2014; 59:359–372

5. Scott KM, Smith DR, Ellis PM: Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. Arch Gen Psychiatry 2010; 67:712–719

6. Green JG, McLaughlin KA, Berglund PA, et al: Childhood adversities and adult psychiatric disorders in the National Comorbidity Survey Replication I: associations with first onset of DSM-IV disorders. Arch Gen Psychiatry 2010; 67:113–123

7. Widom CS, DuMont K, Czaja SJ: A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch Gen Psychiatry 2007; 64:49–56

8. Benjet C, Borges G, Medina-Mora ME: Chronic childhood adversity and onset of psychopathology during three life stages: childhood, adolescence, and adulthood. J Psychiatr Res 2010; 44:732–740

9. Chapman DP, Whitfield CL, Felitti VJ, et al: Adverse childhood experiences and the risk of depressive disorders in adulthood. J Affect Disord 2004; 82:217–225

10. Zavaschi ML, Graeff ME, Menegassi MT, et al: Adult mood disorders and childhood psychological trauma. Br J Psychiatry 2006; 28:184–190

11. Kessler RC: The effects of stressful life events on depression. Annu Rev Psychol 1997; 48:191–214

12. Nelson J, Klumparendt A, Doebler P, et al: Childhood maltreatment and characteristics of adult depression: meta-analysis. Br J Psychiatry 2017; 210:96–104

13. Romero S, Birmaher B, Axelson D, et al: Prevalence and correlates of physical and sexual abuse in children and adolescents with bipolar disorder. J Affect Disord 2009; 112:144–150

14. Hyun M, Friedman SD, Dunner DL: Relationship of childhood physical and sexual abuse to adult bipolar disorder. Bipolar Disord 2000; 2:131–135

15. Post RM, Altshuler L, Leverich G, et al: More stressors prior to and during the course of bipolar illness in patients from the United States compared with the Netherlands and Germany. Psychiatry Res 2013; 210:880–886

16. Bernet CZ, Stein MB: Relationship of childhood maltreatment to the onset and course of major depression in adulthood. Depress Anxiety 1999; 9:169–174

17. Comijs HC, van Exel E, van der Mast RC, et al: Childhood abuse in late-life depression. J Affect Disord 2013; 147:241–246

18. Nanni V, Uher R, Danese A: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry 2012; 169:141–151

19. Wiersma JE, Hovens JG, van Oppen P, et al: The importance of childhood trauma and childhood life events for chronicity of depression in adults. J Clin Psychiatry 2009; 70:983–989

20. Withers AC, Tarasoff JM, Stewart JW: Is depression with atypical features associated with trauma history? J Clin Psychiatry 2013; 74:500–506

21. Nemeroff CB: Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. Neuron 2016; 89:892–909

22. Quilty LC, Marshe V, Lobo DS, et al: Childhood abuse history in depression predicts better response to antidepressants with higher serotonin transporter affinity: a pilot investigation. Neuropsychobiology 2016; 74:78–83

23. Scott KM, McLaughlin KA, Smith DA, et al: Childhood maltreatment and DSM-IV adult mental disorders: comparison of prospective and retrospective findings. Br J Psychiatry 2012; 200: 469–475

24. Fergusson DM, Horwood LJ, Boden JM: Structural equation modeling of repeated retrospective reports of childhood maltreatment. Int J Methods Psychiatr Res 2011; 20:93–104

25. Baldwin JR, Reuben A, Newbury JB, et al: Agreement between prospective and retrospective measures of childhood maltreatment: a systematic review and meta-analysis. JAMA Psychiatry (Epub ahead of print, March 20, 2019)

26. Ellis RER, Seal ML, Simmons JG, et al: Longitudinal trajectories of depression symptoms in adolescence: psychosocial risk factors and outcomes. Child Psychiatry Hum Dev 2017; 48:554–571

27. Gilman SE, Trinh NH, Smoller JW, et al: Psychosocial stressors and the prognosis of major depression: a test of axis IV. Psychol Med 2013; 43:303–316

28. Daruy-Filho L, Brietzke E, Lafer B, et al: Childhood maltreatment and clinical outcomes of bipolar disorder. Acta Psychiatr Scand 2011; 124:427–434

29. Anand A, Koller DL, Lawson WB, et al: Genetic and childhood trauma interaction effect on age of onset in bipolar disorder: an exploratory analysis. J Affect Disord 2015; 179:1–5

30. Jansen K, Cardoso TA, Fries GR, et al: Childhood trauma, family history, and their association with mood disorders in early adulthood. Acta Psychiatr Scand 2016; 134:281–286

31. Gilman SE, Ni MY, Dunn EC, et al: Contributions of the social environment to first-onset and recurrent mania. Mol Psychiatry 2015; 20:329–336

32. Noto MN, Noto C, Caribé AC, et al: Clinical characteristics and influence of childhood trauma on the prodrome of bipolar disorder. Br J Psychiatry 2015; 37:280–288

33. Agnew-Blais J, Danese A: Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 2016; 3:342–349

34. Dienes KA, Hammen C, Henry RM, et al: The stress sensitization hypothesis: understanding the course of bipolar disorder. J Affect Disord 2006; 95:43–49

35. Leverich GS, McElroy SL, Suppes T, et al: Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol Psychiatry 2002; 51:288–297

36. Erten E, Funda Uney A, Saatçioğlu Ö, et al: Effects of childhood trauma and clinical features on determining quality of life in patients with bipolar I disorder. J Affect Disord 2014; 162:107–113

37. Carballo JJ, Harkavy-Friedman J, Burke AK, et al: Family history of suicidal behavior and early traumatic experiences: additive effect on suicidality and course of bipolar illness? J Affect Disord 2008; 109:57–63

38. Park YM: Relationship between childhood maltreatment, suicidality, and bipolarity: a retrospective study. Psychiatry Investig 2017; 14:136–140

39. Pavlova B, Perroud N, Cordera P, et al: Anxiety disorders and childhood maltreatment as predictors of outcome in bipolar disorder. J Affect Disord 2018; 225:337–341

40. Pavlova B, Perroud N, Cordera P, et al: Childhood maltreatment and comorbid anxiety in people with bipolar disorder. J Affect Disord 2016; 192:22–27

41. Cakir S, Tasdelen Durak R, Ozyildirim I, et al: Childhood trauma and treatment outcome in bipolar disorder. J Trauma Dissociation 2016; 17:397–409

42. Post RM, Leverich GS, Kupka R, et al: Clinical correlates of sustained response to individual drugs used in naturalistic treatment of patients with bipolar disorder. Compr Psychiatry 2016; 66:146–156

43. Short AT, Nemeroff CB: Early life trauma and suicide, in Suicide: Phenomenology and Neurobiology. Edited by Cannon KE, Hudzik TJ. Basel, Springer, 2014, pp 187–205

44. Castellví P, Miranda-Mendizábal A, Parés-Badell O, et al: Exposure to violence, a risk for suicide in youths and young adults: a meta-analysis of longitudinal studies. Acta Psychiatr Scand 2017; 135: 195–211

45. Liu J, Fang Y, Gong J, et al: Associations between suicidal behavior and childhood abuse and neglect: a meta-analysis. J Affect Disord 2017; 220:147–155

46. Miller AB, Esposito-Smythers C, Weismoore JT, et al: The relation between child maltreatment and adolescent suicidal behavior: a systematic review and critical examination of the literature. Clin Child Fam Psychol Rev 2013; 16:146–172

47. Norman RE, Byambaa M, De R, et al: The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med 2012; 9: e1001349

48. Dube SR, Anda RF, Felitti VJ, et al: Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. JAMA 2001; 286:3089–3096

49. Gomez SH, Tse J, Wang Y, et al: Are there sensitive periods when child maltreatment substantially elevates suicide risk? Results from a nationally representative sample of adolescents. Depress Anxiety 2017; 34:734–741

50. Miller AB, Jenness JL, Oppenheimer CW, et al: Childhood emotional maltreatment as a robust predictor of suicidal ideation: a 3-year multi-wave, prospective investigation. J Abnorm Child Psychol 2017; 45:105–116

51. Peyre H, Hoertel N, Stordeur C, et al: Contributing factors and mental health outcomes of first suicide attempt during childhood and adolescence: results from a nationally representative study. J Clin Psychiatry 2017; 78:e622–e630

52. Behr Gomes Jardim G, Novelo M, Spanemberg L, et al: Influence of childhood abuse and neglect subtypes on late-life suicide risk beyond depression. Child Abuse Negl 2018; 80:249–256

53. Dunn EC, Nishimi K, Powers A, et al: Is developmental timing of trauma exposure associated with depressive and post-traumatic stress disorder symptoms in adulthood? J Psychiatr Res 2017; 84: 119–127

54. Teicher MH, Samson JA: Annual research review: enduring neurobiological effects of childhood abuse and neglect. J Child Psychol Psychiatry 2016; 57:241–266

55. Dunn EC, Nishimi K, Gomez SH, et al: Developmental timing of trauma exposure and emotion dysregulation in adulthood: are there sensitive periods when trauma is most harmful? J Affect Disord 2018; 227:869–877

56. Sanchez MM: The impact of early adverse care on HPA axis development: nonhuman primate models. Horm Behav 2006; 50: 623–631

57. Roque S, Mesquita AR, Palha JA, et al: The behavioral and immunological impact of maternal separation: a matter of timing. Front Behav Neurosci 2014; 8:192

58. Goldstein JM, Holsen L, Huang G, et al: Prenatal stress-immune programming of sex differences in comorbidity of depression and obesity/metabolic syndrome. Dialogues Clin Neurosci 2016; 18: 425–436

59. Heim CM, Entringer S, Buss C: Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. Psychoneuroendocrinology 2019; 105:123–137

60. Cowell RA, Cicchetti D, Rogosch FA, et al: Childhood maltreatment and its effect on neurocognitive functioning: timing and chronicity matter. Dev Psychopathol 2015; 27:521–533

61. Dunn EC, McLaughlin KA, Slopen N, et al: Developmental timing of child maltreatment and symptoms of depression and suicidal

ideation in young adulthood: results from the National Longitudinal Study of Adolescent Health. Depress Anxiety 2013; 30:955–964

62. Schalinski I, Teicher MH, Nischk D, et al: Type and timing of adverse childhood experiences differentially affect severity of PTSD, dissociative, and depressive symptoms in adult inpatients. BMC Psychiatry 2016; 16:295

63. Khan A, McCormack HC, Bolger EA, et al: Childhood maltreatment, depression, and suicidal ideation: critical importance of parental and peer emotional abuse during developmental sensitive periods in males and females. Front Psychiatry 2015; 6:42

64. Copeland WE, Wolke D, Angold A, et al: Adult psychiatric outcomes of bullying and being bullied by peers in childhood and adolescence. JAMA Psychiatry 2013; 70:419–426

65. Lereya ST, Copeland WE, Costello EJ, et al: Adult mental health consequences of peer bullying and maltreatment in childhood: two cohorts in two countries. Lancet Psychiatry 2015; 2:524–531

66. Campbell-Sills L, Kessler RC, Ursano RJ, et al: Associations of childhood bullying victimization with lifetime suicidal behaviors among new US Army soldiers. Depress Anxiety 2017; 34:701–710

67. Jaye Capretto J: Developmental timing of childhood physical and sexual maltreatment predicts adult depression and post-traumatic stress symptoms. J Interpers Violence (Epub ahead of print, April 1, 2017)

68. Harpur LJ, Polek E, van Harmelen AL: The role of timing of maltreatment and child intelligence in pathways to low symptoms of depression and anxiety in adolescence. Child Abuse Negl 2015; 47:24–37

69. Alameda L, Ferrari C, Baumann PS, et al: Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. Psychol Med 2015; 45:2727–2736

70. Carr CP, Martins CM, Stingel AM, et al: The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. J Nerv Ment Dis 2013; 201:1007–1020

71. Chen LP, Murad MH, Paras ML, et al: Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. Mayo Clin Proc 2010; 85:618–629

72. Maniglio R: The role of child sexual abuse in the etiology of suicide and non-suicidal self-injury. Acta Psychiatr Scand 2011; 124:30–41

73. Humphreys KL, Zeanah CH: Deviations from the expectable environment in early childhood and emerging psychopathology. Neuropsychopharmacology 2015; 40:154–170

74. Shaffer A, Yates TM, Egeland BR: The relation of emotional maltreatment to early adolescent competence: developmental processes in a prospective study. Child Abuse Negl 2009; 33:36–44

75. Wright MO, Crawford E, Del Castillo D: Childhood emotional maltreatment and later psychological distress among college students: the mediating role of maladaptive schemas. Child Abuse Negl 2009; 33:59–68

76. Mandelli L, Petrelli C, Serretti A: The role of specific early trauma in adult depression: a meta-analysis of published literature: childhood trauma and adult depression. Eur Psychiatry 2015; 30:665–680

77. Infurna MR, Reichl C, Parzer P, et al: Associations between depression and specific childhood experiences of abuse and neglect: a meta-analysis. J Affect Disord 2016; 190:47–55

78. Spertus IL, Yehuda R, Wong CM, et al: Childhood emotional abuse and neglect as predictors of psychological and physical symptoms in women presenting to a primary care practice. Child Abuse Negl 2003; 27:1247–1258

79. Teicher MH, Samson JA, Polcari A, et al: Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. Am J Psychiatry 2006; 163:993–1000

80. Dualibe AL, Osório FL: Bipolar disorder and early emotional trauma: a critical literature review on indicators of prevalence rates and clinical outcomes. Harv Rev Psychiatry 2017; 25:198–208

81. Saleptsi E, Bichescu D, Rockstroh B, et al: Negative and positive childhood experiences across developmental periods in psychiatric patients with different diagnoses: an explorative study. BMC Psychiatry 2004; 4:40

82. Putnam KT, Harris WW, Putnam FW: Synergistic childhood adversities and complex adult psychopathology. J Trauma Stress 2013; 26:435–442

83. Anda RF, Felitti VJ, Bremner JD, et al: The enduring effects of abuse and related adverse experiences in childhood: a convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci 2006; 256:174–186

84. Sala R, Goldstein BI, Wang S, et al: Childhood maltreatment and the course of bipolar disorders among adults: epidemiologic evidence of dose-response effects. J Affect Disord 2014; 165:74–80

85. McCrory E, De Brito SA, Viding E: Research review: the neurobiology and genetics of maltreatment and adversity. J Child Psychol Psychiatry 2010; 51:1079–1095

86. Danese A, Pariante CM, Caspi A, et al: Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci USA 2007; 104:1319–1324

87. Toft H, Neupane SP, Bramness JG, et al: The effect of trauma and alcohol on the relationship between level of cytokines and depression among patients entering psychiatric treatment. BMC Psychiatry 2018; 18:95

88. Aas M, Dieset I, Hope S, et al: Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. Brain Behav Immun 2017; 65:342–349

89. Berk M, Kapczinski F, Andreazza AC, et al: Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress, and neurotrophic factors. Neurosci Biobehav Rev 2011; 35:804–817

90. Leboyer M, Soreca I, Scott J, et al: Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 2012; 141:1–10

91. Danese A, Moffitt TE, Pariante CM, et al: Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry 2008; 65:409–415

92. Syed SA, Beurel E, Loewenstein DA, et al.: Defective inflammatory pathways in never-treated depressed patients are associated with poor treatment response. Neuron 2018; 99:914–924e3

93. Miller AH, Raison CL: Are anti-inflammatory therapies viable treatments for psychiatric disorders? Where the rubber meets the road. JAMA Psychiatry 2015; 72:527–528

94. Bandoli G, Campbell-Sills L, Kessler RC, et al: Childhood adversity, adult stress, and the risk of major depression or generalized anxiety disorder in US soldiers: a test of the stress sensitization hypothesis. Psychol Med 2017; 47:2379–2392

95. La Rocque CL, Harkness KL, Bagby RM: The differential relation of childhood maltreatment to stress sensitization in adolescent and young adult depression. J Adolesc 2014; 37:871–882

96. Brietzke E, Mansur RB, Soczynska J, et al: A theoretical framework informing research about the role of stress in the pathophysiology of bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2012; 39:1–8

97. Alloy LB, Abramson LY, Walshaw PD, et al: A cognitive vulnerability-stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. Dev Psychopathol 2006; 18:1055–1103

98. Heim C, Newport DJ, Mletzko T, et al: The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 2008; 33:693–710

99. Heim C, Newport DJ, Wagner D, et al: The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. Depress Anxiety 2002; 15:117–125

100. Abercrombie HC, Frost CP, Walsh EC, et al: Neural signaling of cortisol, childhood emotional abuse, and depression-related memory bias. Biol Psychiatry Cogn Neurosci Neuroimaging 2018; 3:274–284

101. Klengel T, Mehta D, Anacker C, et al: Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci 2013; 16:33–41

102. Binder EB, Bradley RG, Liu W, et al: Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA 2008; 299:1291–1305

103. Appel K, Schwahn C, Mahler J, et al: Moderation of adult depression by a polymorphism in the FKBP5 gene and childhood physical abuse in the general population. Neuropsychopharmacology 2011; 36:1982–1991

104. Roy A, Gorodetsky E, Yuan Q, et al: Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. Neuropsychopharmacology 2010; 35:1674–1683

105. Zimmermann P, Brückl T, Nocon A, et al: Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: results from a 10-year prospective community study. Am J Psychiatry 2011; 168:1107–1116

106. Caspi A, Sugden K, Moffitt TE, et al: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003; 301:386–389

107. Haberstick BC, Boardman JD, Wagner B, et al: Depression, stressful life events, and the impact of variation in the serotonin transporter: findings from the National Longitudinal Study of Adolescent to Adult Health (Add Health). PLoS One 2016; 11:e0148373

108. Brezo J, Bureau A, Mérette C, et al: Differences and similarities in the serotonergic diathesis for suicide attempts and mood disorders: a 22-year longitudinal gene-environment study. Mol Psychiatry 2010; 15:831–843

109. Karg K, Burmeister M, Shedden K, et al: The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch Gen Psychiatry 2011; 68:444–454

110. Etain B, Lajnef M, Henrion A, et al: Interaction between SLC6A4 promoter variants and childhood trauma on the age at onset of bipolar disorders. Sci Rep 2015; 5:16301

111. Provenzi L, Giorda R, Beri S, et al: SLC6A4 methylation as an epigenetic marker of life adversity exposures in humans: a systematic review of literature. Neurosci Biobehav Rev 2016; 71:7–20

112. Culverhouse RC, Saccone NL, Horton AC, et al: Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. Mol Psychiatry 2018; 23:133–142

113. Bradley RG, Binder EB, Epstein MP, et al: Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. Arch Gen Psychiatry 2008; 65:190–200

114. Heim C, Bradley B, Mletzko TC, et al: Effect of childhood trauma on adult depression and neuroendocrine function: sex-specific moderation by CRH receptor 1 gene. Front Behav Neurosci 2009; 3:41

115. Ben-Efraim YJ, Wasserman D, Wasserman J, et al: Gene-environment interactions between CRHR1 variants and physical assault in suicide attempts. Genes Brain Behav 2011; 10:663–672

116. Gatt JM, Nemeroff CB, Dobson-Stone C, et al: Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry 2009; 14:681–695

117. Savitz J, van der Merwe L, Stein DJ, et al: Genotype and childhood sexual trauma moderate neurocognitive performance: a possible role for brain-derived neurotrophic factor and apolipoprotein E variants. Biol Psychiatry 2007; 62:391–399

118. Oliveira J, Etain B, Lajnef M, et al: Combined effect of TLR2 gene polymorphism and early life stress on the age at onset of bipolar disorders. PLoS One 2015; 10:e0119702

119. Myers AJ, Williams L, Gatt JM, et al: Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress, and depression in individuals with a history of exposure to early life stress. J Psychiatr Res 2014; 59:93–100

120. Cohen-Woods S, Fisher HL, Ahmetspahic D, et al: Interaction between childhood maltreatment on immunogenetic risk in depression: discovery and replication in clinical case-control samples. Brain Behav Immun 2018; 67:203–210

121. Lok A, Bockting CL, Koeter MW, et al: Interaction between the MTHFR C677T polymorphism and traumatic childhood events predicts depression. Transl Psychiatry 2013; 3:e288

122. Tollenaar MS, Molendijk ML, Penninx BWJH, et al: The association of childhood maltreatment with depression and anxiety is not moderated by the oxytocin receptor gene. Eur Arch Psychiatry Clin Neurosci 2017; 267:517–526

123. Peyrot WJ, Milaneschi Y, Abdellaoui A, et al: Effect of polygenic risk scores on depression in childhood trauma. Br J Psychiatry 2014; 205:113–119

124. Mullins N, Power RA, Fisher HL, et al: Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. Psychol Med 2016; 46:759–770

125. Peyrot WJ, Van der Auwera S, Milaneschi Y, et al: Does childhood trauma moderate polygenic risk for depression? A meta-analysis of 5765 subjects from the Psychiatric Genomics Consortium. Biol Psychiatry 2018; 84:138–147

126. Kundakovic M, Champagne FA: Early-life experience, epigenetics, and the developing brain. Neuropsychopharmacology 2015; 40:141–153

127. Checknita D, Ekström TJ, Comasco E, et al: Associations of monoamine oxidase A gene first exon methylation with sexual abuse and current depression in women. J Neural Transm (Vienna) 2018; 125:1053–1064

128. McGowan PO, Sasaki A, D'Alessio AC, et al: Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009; 12:342–348

129. Perroud N, Zewdie S, Stenz L, et al: Methylation of serotonin receptor 3A in ADHD, borderline personality, and bipolar disorders: link with severity of the disorders and childhood maltreatment. Depress Anxiety 2016; 33:45–55

130. Brown A, Fiori LM, Turecki G: Bridging basic and clinical research in early life adversity, DNA methylation, and major depressive disorder. Front Genet 2019; 10:229

131. Braun K, Champagne FA: Paternal influences on offspring development: behavioural and epigenetic pathways. J Neuroendocrinol 2014; 26:697–706

132. Gudsnuk K, Champagne FA: Epigenetic influence of stress and the social environment. ILAR J 2012; 53:279–288

133. Galler J, Rabinowitz DG: The intergenerational effects of early adversity. Prog Mol Biol Transl Sci 2014; 128:177–198

134. Champagne F, Meaney MJ: Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. Prog Brain Res 2001; 133:287–302

135. Roth TL, Lubin FD, Funk AJ, et al: Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry 2009; 65:760–769

136. Yehuda R, Halligan SL, Grossman R: Childhood trauma and risk for PTSD: relationship to intergenerational effects of trauma, parental PTSD, and cortisol excretion. Dev Psychopathol 2001; 13:733–753

137. Yehuda R, Bell A, Bierer LM, et al: Maternal, not paternal, PTSD is related to increased risk for PTSD in offspring of Holocaust survivors. J Psychiatr Res 2008; 42:1104–1111

138. Ammerman RT, Hersen M, van Hasselt VB, et al: Maltreatment in psychiatrically hospitalized children and adolescents with developmental disabilities: prevalence and correlates. J Am Acad Child Adolesc Psychiatry 1994; 33:567–576

139. McDonnell CG, Boan AD, Bradley CC, et al: Child maltreatment in autism spectrum disorder and intellectual disability: results from a population-based sample. J Child Psychol Psychiatry 2019; 60:576–584

140. Perrigo JL, Berkovits LD, Cederbaum JA, et al: Child abuse and neglect re-report rates for young children with developmental delays. Child Abuse Negl 2018; 83:1–9

141. Mill J, Tang T, Kaminsky Z, et al: Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. Am J Hum Genet 2008; 82:696–711

142. Brunoni AR, Lopes M, Fregni F: A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol 2008; 11:1169–1180

143. Springer KW, Sheridan J, Kuo D, et al: Long-term physical and mental health consequences of childhood physical abuse: results from a large population-based sample of men and women. Child Abuse Negl 2007; 31:517–530

144. Sachs-Ericsson NJ, Sheffler JL, Stanley IH, et al: When emotional pain becomes physical: adverse childhood experiences, pain, and the role of mood and anxiety disorders. J Clin Psychol 2017; 73:1403–1428

145. Springer KW, Sheridan J, Kuo D, et al: The long-term health outcomes of childhood abuse: an overview and a call to action. J Gen Intern Med 2003; 18:864–870

146. Hughes K, Bellis MA, Hardcastle KA, et al: The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health 2017; 2:e356–e366

147. Shin SH, Chung Y, Rosenberg RD: Identifying sensitive periods for alcohol use: the roles of timing and chronicity of child physical abuse. Alcohol Clin Exp Res 2016; 40:1020–1029

148. Anda RF, Croft JB, Felitti VJ, et al: Adverse childhood experiences and smoking during adolescence and adulthood. JAMA 1999; 282:1652–1658

149. Marangoni C, Hernandez M, Faedda GL: The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. J Affect Disord 2016; 193:165–174

150. Faedda GL, Serra G, Marangoni C, et al: Clinical risk factors for bipolar disorders: a systematic review of prospective studies. J Affect Disord 2014; 168:314–321

151. Merikangas KR, Gelernter CS: Comorbidity for alcoholism and depression. Psychiatr Clin North Am 1990; 13:613–632

152. Goldstein BI, Diamantouros A, Schaffer A, et al: Pharmacotherapy of alcoholism in patients with co-morbid psychiatric disorders. Drugs 2006; 66:1229–1237

153. Goldstein BI, Velyvis VP, Parikh SV: The association between moderate alcohol use and illness severity in bipolar disorder: a preliminary report. J Clin Psychiatry 2006; 67:102–106

154. Potthast N, Neuner F, Catani C: The contribution of emotional maltreatment to alcohol dependence in a treatment-seeking sample. Addict Behav 2014; 39:949–958

155. Enoch MA: The role of early life stress as a predictor for alcohol and drug dependence. Psychopharmacology (Berl) 2011; 214:17–31

156. Salokangas RKR, From T, Luutonen S, et al: Effect of childhood adversities on alcohol problems is mainly mediated by depression. Am J Addict (Epub ahead of print, May 15, 2018)

157. Skinner ML, Hong S, Herrenkohl TI, et al: Longitudinal effects of early childhood maltreatment on co-occurring substance misuse and mental health problems in adulthood: the role of adolescent alcohol use and depression. J Stud Alcohol Drugs 2016; 77:464–472

158. Hyucksun Shin S: A longitudinal examination of the relationships between childhood maltreatment and patterns of adolescent substance use among high-risk adolescents. Am J Addict 2012; 21:453–461

159. Garami J, Valikhani A, Parkes D, et al: Examining perceived stress, childhood trauma and interpersonal trauma in individuals with drug addiction. Psychol Rep 2019; 122:433–450

160. Lei Y, Xi C, Li P, et al: Association between childhood maltreatment and non-medical prescription opioid use among Chinese senior high school students: the moderating role of gender. J Affect Disord 2018; 235:421–427

161. Conroy E, Degenhardt L, Mattick RP, et al: Child maltreatment as a risk factor for opioid dependence: comparison of family characteristics and type and severity of child maltreatment with a matched control group. Child Abuse Negl 2009; 33:343–352

162. Larance B, Gisev N, Cama E, et al: Predictors of transitions across stages of heroin use and dependence prior to treatment-seeking among people in treatment for opioid dependence. Drug Alcohol Depend 2018; 191:145–151

163. Maloney E, Degenhardt L, Darke S, et al: Suicidal behaviour and associated risk factors among opioid-dependent individuals: a case-control study. Addiction 2007; 102:1933–1941

164. Handley ED, Rogosch FA, Cicchetti D: From child maltreatment to emerging adult problem drinking: identification of a multilevel internalizing pathway among African American youth. Dev Psychopathol 2017; 29:1807–1821

165. Young-Wolff KC, Enoch MA, Prescott CA: The influence of gene-environment interactions on alcohol consumption and alcohol use disorders: a comprehensive review. Clin Psychol Rev 2011; 31:800–816

166. Keyes KM, Hatzenbuehler ML, Hasin DS: Stressful life experiences, alcohol consumption, and alcohol use disorders: the epidemiologic evidence for four main types of stressors. Psychopharmacology (Berl) 2011; 218:1–17

167. Kaufman J, Yang BZ, Douglas-Palumberi H, et al: Genetic and environmental predictors of early alcohol use. Biol Psychiatry 2007; 61:1228–1234

168. Oo KZ, Aung YK, Jenkins MA, et al: Associations of 5HTTLPR polymorphism with major depressive disorder and alcohol dependence: a systematic review and meta-analysis. Aust N Z J Psychiatry 2016; 50:842–857

169. Young-Wolff KC, Kendler KS, Prescott CA: Interactive effects of childhood maltreatment and recent stressful life events on alcohol consumption in adulthood. J Stud Alcohol Drugs 2012; 73:559–569

170. Covault J, Tennen H, Armeli S, et al: Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. Biol Psychiatry 2007; 61:609–616

171. Proctor LJ, Lewis T, Roesch S, et al: Child maltreatment and age of alcohol and marijuana initiation in high-risk youth. Addict Behav 2017; 75:64–69

172. Kim ST, Hwang SS, Kim HW, et al: Multidimensional impulsivity as a mediator of early life stress and alcohol dependence. Sci Rep 2018; 8:4104

173. Etain B, Lajnef M, Henry C, et al: Childhood trauma, dimensions of psychopathology, and the clinical expression of bipolar disorders: a pathway analysis. J Psychiatr Res 2017; 95:37–45

174. Henriques JF, Portugal CC, Canedo T, et al: Microglia and alcohol meet at the crossroads: microglia as critical modulators of alcohol neurotoxicity. Toxicol Lett 2018; 283:21–31

175. Nennig SE, Schank JR: The role of NFkB in drug addiction: beyond inflammation. Alcohol Alcohol 2017; 52:172–179

176. Neupane SP: Neuroimmune interface in the comorbidity between alcohol use disorder and major depression. Front Immunol 2016; 7:655

177. Kaptoge S, Di Angelantonio E, Lowe G, et al: C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010; 375:132–140

178. Braithwaite EC, O'Connor RM, Degli-Esposti M, et al: Modifiable predictors of depression following childhood maltreatment: a systematic review and meta-analysis. Transl Psychiatry 2017; 7:e1162

179. Cheong EV, Sinnott C, Dahly D, et al: Adverse childhood experiences (ACEs) and later-life depression: perceived social support as a potential protective factor. BMJ Open 2017; 7:e013228

180. Østefjells T, Lystad JU, Berg AO, et al: Metacognitive beliefs mediate the effect of emotional abuse on depressive and psychotic symptoms in severe mental disorders. Psychol Med 2017; 47:2323–2333

181. Aas M, Henry C, Bellivier F, et al: Affective lability mediates the association between childhood trauma and suicide attempts, mixed episodes and co-morbid anxiety disorders in bipolar disorders. Psychol Med 2017; 47:902–912

182. Choi KH, Davidson C, Spaulding WD: Social cognition moderates the influence of child physical abuse on inpatient psychiatric rehabilitation. J Nerv Ment Dis 2011; 199:465–470

183. Teicher MH, Samson JA, Anderson CM, et al: The effects of childhood maltreatment on brain structure, function, and connectivity. Nat Rev Neurosci 2016; 17:652–666

184. Heany SJ, Groenewold NA, Uhlmann A, et al: The neural correlates of Childhood Trauma Questionnaire scores in adults: a meta-analysis and review of functional magnetic resonance imaging studies. Dev Psychopathol 2018; 30:1475–1485

185. Hanson JL, Chung MK, Avants BB, et al: Structural variations in prefrontal cortex mediate the relationship between early childhood stress and spatial working memory. J Neurosci 2012; 32:7917–7925

186. Cohen RA, Grieve S, Hoth KF, et al: Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. Biol Psychiatry 2006; 59:975–982

187. Edmiston EE, Wang F, Mazure CM, et al: Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. Arch Pediatr Adolesc Med 2011; 165:1069–1077

188. Van Dam NT, Rando K, Potenza MN, et al: Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. JAMA Psychiatry 2014; 71:917–925

189. Sheffield JM, Williams LE, Woodward ND, et al: Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. Schizophr Res 2013; 143:185–191

190. Lim L, Hart H, Mehta M, et al: Grey matter volume and thickness abnormalities in young people with a history of childhood abuse. Psychol Med 2018; 48:1034–1046

191. Lim L, Radua J, Rubia K: Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. Am J Psychiatry 2014; 171:854–863

192. Yamada K, Suzuki Y, Okuyama M, et al: Developmental abnormalities of the brain exposed to childhood maltreatment detected by diffusion tensor imaging. Neurol Res 2019; 41:19–25

193. McCarthy-Jones S, Oestreich LKL, Lyall AE, et al: Childhood adversity associated with white matter alteration in the corpus callosum, corona radiata, and uncinate fasciculus of psychiatrically healthy adults. Brain Imaging Behav 2018; 12:449–458

194. Puetz VB, Parker D, Kohn N, et al: Altered brain network integrity after childhood maltreatment: a structural connectomic DTI-study. Hum Brain Mapp 2017; 38:855–868

195. Bonne O, Vythilingam M, Inagaki M, et al: Reduced posterior hippocampal volume in posttraumatic stress disorder. J Clin Psychiatry 2008; 69:1087–1091

196. Vythilingam M, Heim C, Newport J, et al: Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 2002; 159:2072–2080

197. Driessen M, Herrmann J, Stahl K, et al: Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry 2000; 57:1115–1122

198. Frodl T, Reinhold E, Koutsouleris N, et al: Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. J Psychiatr Res 2010; 44:799–807

199. Opel N, Redlich R, Zwanzger P, et al: Hippocampal atrophy in major depression: a function of childhood maltreatment rather than diagnosis? Neuropsychopharmacology 2014; 39:2723–2731

200. Frodl T, Skokauskas N, Frey EM, et al: BDNF Val66Met genotype interacts with childhood adversity and influences the formation of hippocampal subfields. Hum Brain Mapp 2014; 35:5776–5783

201. Marusak HA, Kuruvadi N, Vila AM, et al: Interactive effects of BDNF Val66Met genotype and trauma on limbic brain anatomy in childhood. Eur Child Adolesc Psychiatry 2016; 25:509–518

202. Poletti S, Locatelli C, Radaelli D, et al: Effect of early stress on hippocampal gray matter is influenced by a functional polymorphism in EAAT2 in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2014; 51:146–152

203. Hallowell ES, Oshri A, Liebel SW, et al: The mediating role of neural activity on the relationship between childhood maltreatment and impulsivity. Child Maltreat (Epub ahead of print, March 27, 2019)

204. Fonzo GA, Ramsawh HJ, Flagan TM, et al: Early life stress and the anxious brain: evidence for a neural mechanism linking childhood emotional maltreatment to anxiety in adulthood. Psychol Med 2016; 46:1037–1054

205. Yu M, Linn KA, Shinohara RT, et al: Childhood trauma history is linked to abnormal brain connectivity in major depression. Proc Natl Acad Sci USA 2019; 116:8582–8590

206. Hanson JL, Knodt AR, Brigidi BD, et al: Heightened connectivity between the ventral striatum and medial prefrontal cortex as a biomarker for stress-related psychopathology: understanding interactive effects of early and more recent stress. Psychol Med 2018; 48:1835–1843

207. Kaiser RH, Clegg R, Goer F, et al: Childhood stress, grown-up brain networks: corticolimbic correlates of threat-related early life stress and adult stress response. Psychol Med 2018; 48:1157–1166

208. Zhai ZW, Yip SW, Lacadie CM, et al: Childhood trauma moderates inhibitory control and anterior cingulate cortex activation during stress. Neuroimage 2019; 185:111–118

209. Opel N, Redlich R, Dohm K, et al: Mediation of the influence of childhood maltreatment on depression relapse by cortical structure: a 2-year longitudinal observational study. Lancet Psychiatry 2019; 6:318–326

210. Busso DS, McLaughlin KA, Brueck S, et al: Child abuse, neural structure, and adolescent psychopathology: a longitudinal study. J Am Acad Child Adolesc Psychiatry 2017; 56:321–328.e1

211. Swartz JR, Williamson DE, Hariri AR: Developmental change in amygdala reactivity during adolescence: effects of family history of depression and stressful life events. Am J Psychiatry 2015; 172:276–283

212. Duarte DG, Neves MdeC, Albuquerque MR, et al: Gray matter brain volumes in childhood-maltreated patients with bipolar disorder type I: a voxel-based morphometric study. J Affect Disord 2016; 197:74–80

213. Poletti S, Vai B, Smeraldi E, et al: Adverse childhood experiences influence the detrimental effect of bipolar disorder and schizophrenia on cortico-limbic grey matter volumes. J Affect Disord 2016; 189:290–297

214. Stevelink R, Abramovic L, Verkooijen S, et al: Childhood abuse and white matter integrity in bipolar disorder patients and healthy controls. Eur Neuropsychopharmacol 2018; 28:807–817

215. Benedetti F, Bollettini I, Radaelli D, et al: Adverse childhood experiences influence white matter microstructure in patients with bipolar disorder. Psychol Med 2014; 44:3069–3082

216. Janiri D, Sani G, Rossi P, et al: Amygdala and hippocampus volumes are differently affected by childhood trauma in patients with bipolar disorders and healthy controls. Bipolar Disord 2017; 19:353–362

217. Souza-Queiroz J, Boisgontier J, Etain B, et al: Childhood trauma and the limbic network: a multimodal MRI study in patients with bipolar disorder and controls. J Affect Disord 2016; 200:159–164

218. Quidé Y, O'Reilly N, Rowland JE, et al: Effects of childhood trauma on working memory in affective and non-affective psychotic disorders. Brain Imaging Behav 2017; 11:722–735

219. Benedetti F, Bollettini I, Poletti S, et al: White matter microstructure in bipolar disorder is influenced by the serotonin transporter gene polymorphism 5-HTTLPR. Genes Brain Behav 2015; 14:238–250

220. White MG, Bogdan R, Fisher PM, et al: FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. Genes Brain Behav 2012; 11:869–878

221. Bogdan R, Williamson DE, Hariri AR: Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. Am J Psychiatry 2012; 169:515–522

222. Di Iorio CR, Carey CE, Michalski LJ, et al: Hypothalamic-pituitary-adrenal axis genetic variation and early stress moderates amygdala function. Psychoneuroendocrinology 2017; 80:170–178

223. Malhi GS, Das P, Outhred T, et al: Effect of stress gene-by-environment interactions on hippocampal volumes and cortisol secretion in adolescent girls. Aust N Z J Psychiatry 2019; 53:316–325

224. Ho TC, Dennis EL, Thompson PM, et al: Network-based approaches to examining stress in the adolescent brain. Neurobiol Stress 2018; 8:147–157

225. Heim CM, Mayberg HS, Mletzko T, et al: Decreased cortical representation of genital somatosensory field after childhood sexual abuse. Am J Psychiatry 2013; 170:616–623

226. Humphreys KL, King LS, Sacchet MD, et al: Evidence for a sensitive period in the effects of early life stress on hippocampal volume. Dev Sci 2019; 22:e12775

227. Sweeney S, Air T, Zannettino L, et al: Gender differences in the physical and psychological manifestation of childhood trauma and/or adversity in people with psychosis. Front Psychol 2015; 6:1768

228. Gallo EAG, De Mola CL, Wehrmeister F, et al: Childhood maltreatment preceding depressive disorder at age 18 years: a prospective Brazilian birth cohort study. J Affect Disord 2017; 217: 218–224

229. Gault-Sherman M, Silver E, Sigfúsdóttir ID: Gender and the associated impairments of childhood sexual abuse: a national study of Icelandic youth. Soc Sci Med 2009; 69:1515–1522

230. Herringa RJ, Birn RM, Ruttle PL, et al: Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. Proc Natl Acad Sci USA 2013; 110: 19119–19124

231. Weiss EL, Longhurst JG, Mazure CM: Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. Am J Psychiatry 1999; 156:816–828

232. Kendler KS, Gardner CO: Sex differences in the pathways to major depression: a study of opposite-sex twin pairs. Am J Psychiatry 2014; 171:426–435

233. Andersen JP, Blosnich J: Disparities in adverse childhood experiences among sexual minority and heterosexual adults: results from a multi-state probability-based sample. PLoS One 2013; 8: e54691

234. Rodgers SM: Transitional age lesbian, gay, bisexual, transgender, and questioning youth: issues of diversity, integrated identities, and mental health. Child Adolesc Psychiatr Clin N Am 2017; 26: 297–309

235. Rhoades H, Rusow JA, Bond D, et al: Homelessness, mental health, and suicidality among LGBTQ youth accessing crisis services. Child Psychiatry Hum Dev 2018; 49:643–651

236. Proulx CN, Coulter RWS, Egan JE, et al: Associations of lesbian, gay, bisexual, transgender, and questioning-inclusive sex education with mental health outcomes and school-based victimization in US high school students. J Adolesc Health 2019; 64: 608–614

237. Wiederhold BK: Cyberbullying and LGBTQ youth: a deadly combination. Cyberpsychol Behav Soc Netw 2014; 17:569–570

238. Li M, D'Arcy C, Meng X: Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychol Med 2016; 46:717–730