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Childhood Adversities and Depression in Adulthood: Current Findings and Future Directions

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Considerable support exists establishing a relationship between childhood adversities and adult depression. Consistent evidence has emerged linking early life adversities with a more chronic course for depression, as well as to poorer treatment outcomes. What remain decidedly less clear, however, are the moderators and mediating mechanisms underlying this association. This article provides a review of the existing research relating early adversities to adult depression, as well as recent studies suggestive of potential mediators and moderators of this relation. Advances in these areas are important for their potential to lead to the identification of new targets for clinical intervention for adults with a history of childhood adversities, as well as to the development of individually tailored prevention and treatment strategies.

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More than any other psychiatric disorder, depression is associated with the highest burden to society. When considered relative to all physical and mental health conditions, this disorder is the second leading cause of years living with disability (YLDs; Ferrari et al., 2013). Specifically, depression is responsible for approximately 9.6% of YLDs and 3.8% of global disability adjusted life years (DALYs; Ferrari et al., 2013). Given the considerable societal costs associated with this disorder, there is a critical need for a better understanding of the etiology of depression and thereby to improve early detection of risk, to inform clinical intervention strategies with at-risk individuals, and to identify potential modifiable targets for treatment.

One much-studied risk factor for depression is childhood adversity, a broad construct encompassing a range of difficulties experienced in childhood, including family dysfunction (e.g., parental criminality or substance abuse). Also falling under the term of childhood adversity is childhood maltreatment, which includes experiences formally defined as traumas (e.g., physical and sexual abuse), as well as other significant events (e.g., emotional abuse and neglect; for a discussion of definitional and operationalization issues regarding this construct, see McLaughlin, 2016). Adverse childhood events are notably prevalent in the general population, with 53.4% of adults in an epidemiological study experiencing at least one form of childhood adversity prior to age 18 (Green et al., 2010). Childhood adversities reflecting maladaptive family functioning (e.g., child maltreatment) appear to be associated with first lifetime onset of mood disorders (Green et al., 2010), a link that persists into late adulthood (Ege, Messias, Thapa, & Krain, 2015). Additionally, the well-documented association between certain forms of childhood adversity, particularly childhood traumas, and posttraumatic stress disorder (Cicchetti & Toth, 2005) may in part account for its frequent comorbidity with depression.

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The current article aims to present a review of the research to date on childhood adversity, with particular emphasis on childhood maltreatment, in relation to depression in adulthood. It then proceeds with a discussion of the much less established empirical literature on potential moderators and mediating mechanisms through which these adverse childhood experiences may exert their depressogenic effect. A diathesis–stress conceptual framework (i.e., childhood adversities interacting with moderating variables and leading to the development of vulnerability to future stressors) is adopted to guide discussion in these areas. Throughout this review, recommendations are provided to inform future research. Finally, this article concludes with a consideration of the clinical implications of our current understanding of the involvement of childhood adversity in the pathogenesis of depression in adulthood.

CHILDHOOD ADVERSITY AND DEPRESSION

Recently, several large-scale longitudinal studies have yielded insight into the relation between childhood adversity and the course of depression. In two long-term follow-up studies, chronic depression was associated with greater childhood adversity than was nonchronic depression (Angst, Gamma, Rössler, Ajdacic, & Klein, 2011; Klein & Kotov, 2016). Moreover, childhood adverse events were positively linked with severity of depressive course trajectory (i.e., symptom severity and time to remission) in a two-year follow-up study of depressed adults (Rhebergen et al., 2012). Childhood adversity also predicted longer time to depressive remission in a 12-year longitudinal, community-based study of adults (Fuller-Thomson, Battiston, Gadalla, & Brennenstuhl, 2014). All of these studies operationalized chronicity in terms of duration of depression. When depression chronicity is defined instead by its recurrence, this pattern of findings remains essentially unchanged, with childhood adversities being associated with an over 20% increase in risk for depressive recurrence over a three-year period in an epidemiological study (Gilman et al., 2013). Collectively, these studies suggest a history of adverse childhood events may be linked with a more negative and persistent course of this disorder.

Importantly, this relation between childhood adverse events and chronicity of depression in adulthood appears not to be simply a function of homotypic continuity of child or adolescent onset of this disorder in adulthood. Childhood adversities are associated with sustained risk for depression, even among adults with no prior history of this condition. Specifically, adverse childhood events, in the form of poor parental care and sexual abuse, were found to be related to adult-onset depression (Hill, Pickles, Rollinson, Davies, & Byatt, 2004). In a recent longitudinal cohort study (Shanahan, Copeland, Costello, & Angold, 2011), childhood poverty and exposure to loss and violence, as well as family dysfunction in adolescence, were prospectively predictive of onset of this disorder in adulthood.

Taking a different approach to estimating the potential impact of adverse childhood experiences on risk for depression in adulthood, one epidemiological study found the population-attributable risk proportion for mood disorders was 22.9% (Kessler et al., 2010); completely preventing the occurrence of childhood adversities would be associated with a reduction of almost a fifth in terms of risk for this outcome.

In studies specifically focusing on childhood maltreatment, the evidence for long-term risk for depression appears to be very robust. In a meta-analysis of epidemiological studies ($k = 16$), experiencing any form of childhood maltreatment was linked with increased odds of recurrent and chronic depression (OR = 2.27, 95% CI = 1.80, 2.87; Nanni, Uher, & Danese, 2011). Moreover, a more recent meta-analysis focusing specifically on longitudinal cohort studies ($k = 8$) reported a small-to-medium effect size for the relation between any type of maltreatment and adult depression (OR = 2.03, 95% CI = 1.37, 3.01; Li, D'Arcy, & Meng, 2016).

Relative to other forms of maltreatment, childhood sexual abuse has received the most empirical attention, with several meta-analytic reviews (ks= 12–26) finding consistent evidence of an association with adult depression (OR = 2.42, 95% CI = 1.94, 3.02 and $d = 0.50$, 95% CI = 0.22, 0.78; Infurna et al., 2016; Mandelli, Petrelli, & Serretti, 2015). These same meta-analyses are also consistent in reporting links between depression and childhood emotional abuse (OR = 2.78, 95% CI = 1.89, 4.09 and $d = 0.93$, 95% CI = 0.93, 0.93), physical abuse (OR = 1.98, 95% CI = 1.68, 2.33 and

d = 0.81, 95% CI = 0.69, 0.93), and neglect (OR = 2.75, 95% CI = 1.59, 4.74 and d = 0.81, 95% CI = 0.61, 1.02). A third meta-analysis (k = 124) found the largest effect size (medium to large) for depression in relation to childhood emotional abuse (OR = 3.06, 95% CI = 2.43, 3.85), compared to physical abuse (OR = 1.54, 95% CI = 1.16, 2.04) and neglect (OR = 2.11, 95% CI = 1.61, 2.77), although the difference appears not to be significant in the latter case (Norman et al., 2012). Moreover, based on Bradford Hill criteria (i.e., strength of the association, childhood abuse temporally preceding depression, a dose–response gradient, biological plausibility of the association, and consideration of alternative explanations of the association), this review concluded the existing evidence is suggestive of a causal relation between these forms of childhood maltreatment and depression. Finally, greater vulnerability to childhood physical abuse (Norman et al., 2012) and exposure to sexual abuse may, in some measure, account for the greater prevalence of this disorder in women (Weiss, Longhurst, & Mazure, 1999).

Thus, there is consistent empirical evidence from studies across several different methodologies (e.g., epidemiological and longitudinal cohort studies) implicating childhood adversities, and childhood maltreatment particularly, in risk for adult depression. The longitudinal assessment of depression characteristic of many of these studies is a notable strength, especially given significant differences between prospectively and retrospectively measured prevalence rates of psychiatric illness (Wells & Horwood, 2004).

Also common across the studies in this literature, however, is a reliance on retrospective recall of adverse childhood events. Although there is some evidence recollection of childhood maltreatment tends to be reasonably reliable in adults (Bifulco, Brown, Lillie, & Jarvis, 1997), recent research has found significant differences between prospectively and retrospectively ascertained data on childhood adversities among adults (Colman et al., 2016; Patten et al., 2015). Of particular relevance to the study of depression, retrospectively recalled adverse childhood events, when compared to prospectively assessed adversities, were more strongly related to this disorder in adulthood (Patten et al., 2015). Moreover, depressed adults appear more likely to report retrospectively having experienced childhood adversities they did not endorse during childhood, and less likely to forget events they had previously endorsed in childhood (Colman et al., 2016). This pattern of findings is consistent with the broader literature on mood-congruent recall biases toward negative memories in depressed individuals (Mathews & MacLeod, 2005). Taken together, these findings suggest the magnitude of the observed association between childhood adverse events and adult depression in many of the studies in the literature may in some measure be inflated. It should be noted, however, that prospectively assessed childhood adversities are still significantly associated with adult depression, with a small-to-medium effect size, indicating that the relation consistently observed in prior studies between these two clinical phenomena is not simply an artifact of recall biases in depressed adults (Patten et al., 2015).

One solution to this methodological issue is for future studies to employ a fully prospective design, involving prospective measures of both adverse childhood experiences and depression. Given the attendant costs and resources required for adopting such an approach to assessing long-term risk, however, alternative strategies may also be considered. One such strategy that may be more feasibly employed would be to use semi-structured contextual interviews (e.g., the Childhood Experience of Care and Abuse Scale [CECA]; Bifulco, Brown, & Harris, 1994). Such measures, when contrasted to self-report methodologies, have been found to minimize recall biases (McQuaid, Monroe, Roberts, & Johnson, 1992), in large measure due to their incorporation of detailed probes for determining whether objective indicators exist in support of the occurrence of individual early adverse experiences (Harkness et al., 2015).

MEDIATING MECHANISMS OF RISK

In contrast to the well-established basic association between childhood adversities and adult depression in the empirical literature, the potential pathways through which these early adverse experiences exert their depressogenic effect remain relatively understudied (McLaughlin, 2016). In particular, there is a need for better characterization of the cognitive, interpersonal, and neurobiological mechanisms underlying the long-

term risk for depression that comes with experiencing early adversities. In addition to elucidating the etiology of depression, identifying these mechanisms may yield promising targets for preventive intervention with individuals with a history of childhood adversity and thus at risk for this illness. Although comparably few studies have directly examined mediators of the relation between adverse childhood experiences and adult depression, several potential candidates for future investigation may be drawn from the broader childhood adversity and depression literatures, respectively. What follows is a review of existing mediational studies, as well as a discussion of several of these potential candidates, which may serve as promising avenues for future research.

Cognitive Mediators

Several cognitive theories have placed importance on the influence of adverse childhood events, particularly dysfunctional parental relationships, on the development of cognitive vulnerability to depression (Beck, 1976; Lara & Klein, 1999; Rose & Abramson, 1992). Repeated negative feedback, especially in the form of verbal criticism or emotional abuse, has been hypothesized to lead to the development of depressogenic self-schemata because, in contrast to other adverse parental experiences, emotional abuse directly supplies negative cognitions to the individual (Rose & Abramson, 1992). Such a possibility may account for the aforementioned findings of a stronger relation between adult depression and childhood emotional abuse, relative to other forms of maltreatment. Congruent with this view, there appears to be substantial support for childhood emotional abuse, and to a lesser degree sexual abuse, being associated with cognitive vulnerability to depression (for a review, see Gibb, 2002). Furthermore, these depressogenic cognitive styles have been observed to mediate the relationship between childhood emotional abuse and depressive symptoms in an epidemiological study of adults (Sachs-Ericsson, Verona, Joiner, & Preacher, 2006), and this finding holds true for both implicit and explicit measures of cognitive vulnerability (van Harmelen et al., 2010). As an example of implicit indicators of cognitive risk for depression, attentional bias toward sad faces on a dot-probe task has been associated with childhood maltreatment history in adults with major depression (Günther, Dannlowski, Kersting, & Suslow, 2015). Among specific forms of depressogenic cognitive styles that have garnered interest within this context, rumination (Lara & Klein, 1999), a maladaptive thinking pattern characterized by a passive and perseverative focus on one's feelings of distress as well as their causes and consequences (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), has been found to mediate the relation between childhood emotional abuse and depressive symptoms in adulthood (Raes & Hermans, 2008). Support has also been reported for cognitive vulnerability as conceptualized within the hopelessness theory of depression (Hankin, 2005), experiential avoidance (Barnhofer, Brennan, Crane, Duggan, & Williams, 2014), and low self-esteem (Dunkley, Masheb, & Grilo, 2010) as mediators of this relation. A degree of caution should be taken in interpreting these findings, as most of the research in this area has relied on cross-sectional assessments of mediation and thus require replication in longitudinal studies (Maxwell & Cole, 2007).

The developmental period in which these childhood adversities occur appears to define the nature of their relation with cognitive risk for depression. According to several cognitive models of depression (e.g., Rose & Abramson, 1992), cognitive schemata tend to be fairly malleable in early childhood and to solidify during adolescence. This view has received empirical support (Hankin, 2008). An implication of this phenomenon is depressogenic cognitive styles that may function as mediators between adversities experienced in childhood and subsequent depression, with these adverse childhood experiences leading to the development of more negative cognitive styles, which in turn result in greater risk for depression.

Additionally, these cognitive risk factors may transition to a more moderational relation with adversities experienced in adolescence predicting later depressive onset, with now-stable cognitive vulnerability interacting with adversities to confer risk for depression. Although prior research has yielded evidence in support of this position with negative life events in general (Cole et al., 2001; Hoffman, Cole, Martin, Tram, & Seroczynski, 2000), future research is needed to evaluate this possibility with adverse childhood events specifically.

Importantly, even in seemingly healthy adults with no history of mental illness, childhood abuse has been linked to notable elevations on both implicit and explicit indices of cognitive vulnerability to depression (Wells, Vanderlind, Selby, & Beevers, 2014). This finding suggests even adults with an early abuse history, but no history of psychopathology, remain at long-term risk for this disorder, which is consistent with prior findings of an association between childhood adversities and adult-onset depression (Hill et al., 2004; Shanahan et al., 2011).

Although the empirical research on cognitive mediators of childhood predictors of adult depression has focused largely on childhood abuse specifically, there is reason to suspect cognitive vulnerabilities may similarly mediate the depressogenic risk of childhood adversities more generally. For instance, adverse childhood events have been related to depressogenic cognitions in adulthood (Klein et al., 2009). These early life adversities have also been linked to executive functioning deficits, such as in working memory (Majer, Nater, Lin, Capuron, & Reeves, 2010), which, in turn, have been found also to be related to depression (Snyder, 2013). Further research is needed to determine the extent to which these cognitive risk factors mediate the relation between childhood adversities and adult depression.

Interpersonal Mediators

As with potential cognitive mechanisms underlying the association between childhood adverse events and depression, the research on depressogenic interpersonal styles has focused primarily on childhood abuse. Maladaptive interpersonal styles, and the social stressors that are often associated with them (Hankin, Kassel, & Abela, 2005), may be of especial etiological relevance to depression (Hammen, 2005), and prior research has linked childhood abuse with the formation of difficulties in interpersonal functioning (Huh, Kim, Yu, & Chae, 2014).

Insecure attachment style has received cross-sectional support as a mediating mechanism of a link between childhood emotional abuse and depression (Hankin, 2005). In a recent study, the tendency to excessively seek reassurance from close others and sensitivity to social rejection uniquely mediated the relation between childhood emotional abuse and depressive symptoms in young adults (Massing-Schaffer, Liu, Kraines, Choi, & Alloy, 2015). These interpersonal styles have been linked with risk for depression through prospectively elevated rates of dependent life stress (i.e., stress at least partly influenced by the individual's own thoughts and behavior; Liu, Kraines, Massing-Schaffer, & Alloy, 2014). Further, past research has found life stress in adulthood partially accounts for the relation between childhood adversity and adult depression (Korkeila et al., 2010). Therefore, interpersonal abuse during adulthood appears to mediate the relation between childhood abuse and depressive symptoms (Salwen, Hymowitz, Vivian, & O'Leary, 2014). Collectively, these findings are consistent with the view that childhood abuse may lead to long-term risk for depression through the mediational role of these interpersonal styles and associated risk for dependent life stress.

When childhood adversities are considered more generally, there is reason to suspect maladaptive interpersonal processes may similarly underlie their relation with later-life depression. For example, adverse childhood events have been associated with violent interpersonal tendencies in adolescence (Duke, Pettingell, McMorris, & Borowsky, 2010). Such tendencies, in turn, have been linked with depression (Wolitzky-Taylor et al., 2008). However, as with candidate cognitive mediators, potential interpersonal mediators for long-term risk for depression associated with early adversities await confirmation in future studies.

When interpreting the literature in this area, care should be taken not to misattribute responsibility for later interpersonal dysfunction to individuals with childhood adversities. Rather, it should be noted that these adversities often involve severe disruptions in family and social environments (e.g., childhood abuse, parental divorce, and physical or sexual assault). For example, although individual differences certainly exist in trajectories following parental divorce, the often resulting perturbations in parental relationships can lead to the development of unstable interpersonal styles (Fraley & Heffernan, 2013). Finally, it should be noted that insecure attachment is just one of several maladaptive interpersonal styles that may result from childhood adversities (see Doyle & Cicchetti, 2017, for a thorough treatment of this issue).

Neurobiological Mediators

Perhaps the subject of greatest empirical attention in this area in recent years are potential neurobiological pathways linking early adversities to adult depression. The finding that childhood adversities are associated with pathophysiological correlates of depression seems clear across a growing number of neuroimaging studies. Among the most consistent findings in this area is the hippocampal atrophy often associated with depression (MacQueen & Frodl, 2011). The hippocampus is part of a complex network of cortical regions involved in emotion regulation, various aspects of which evidence abnormality in depression. Interestingly, this appears particularly to be the case in depressed individuals with a history of childhood maltreatment (Vythilingam et al., 2002). When considered together with separate findings of reduced hippocampal volume in individuals with experiences of early life adversities (McCrory, De Brito, & Viding, 2010), these studies are suggestive of the possibility that reduced hippocampal volume may temporally mediate the association between childhood maltreatment and depression later in adulthood. Indeed, one study has found preliminary support for this possibility, with smaller hippocampal volume functioning as a partial mediator of the association between early life adversities and depression in early adulthood (Rao et al., 2010).

Also of potential relevance to both childhood adversities and depression is atypical amygdala activity in response to emotion-laden stimuli. Depression is associated with increased amygdala activation in response to negative stimuli (Price & Drevets, 2010). This has similarly been demonstrated to be the case for adults with a history of childhood maltreatment (McCrory et al., 2010). Whether heightened amygdala reactivity to negative stimuli may mediate the relation between early maltreatment experiences and depression in adulthood is currently unclear. Findings suggestive of this possibility, however, come from a study in which elevated amygdala response to negative stimuli was found to be associated with childhood maltreatment history (Grant, Cannistraci, Hollon, Gore, & Shelton, 2011). Furthermore, among depressed adults, greater amygdala reactivity was found to be specific to those with a maltreatment history.

Similarly, prefrontal cortex abnormalities have been associated with early adverse experiences and depression (Tyrka, Burgers, Philip, Price, & Carpenter, 2013). For example, in one study of adults, childhood emotional maltreatment was linked with reduced volume in the medial prefrontal cortex (mPFC), a cortical region also implicated in emotion regulation (van Harmelen et al., 2010). Although this finding was independent of participants' psychopathology, resting-state functional imaging research has noted abnormalities in the mPFC in relation to depression (e.g., Shansky & Morrison, 2009). Nonetheless, more research is needed to assess its potential role in the link between early adversities and later depression.

In addition to these findings, the dorsal lateral prefrontal cortex (DLPFC) also appears to be involved in modulating amygdala reactivity to emotional stimuli (Banks, Eddy, Angstadt, Nathan, & Phan, 2007). Aberrations in this pathway have been implicated in depression, with heightened amygdala activity and blunted DLPFC evident in this disorder (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Early life adversities have also been associated with impairments in this circuitry, and this deficit was not observed in depressed individuals without childhood adversities (Grant et al., 2014), suggesting a degree of specificity in dysfunction of this neural pathway to a subset of depressed individuals with early life exposure to adversities.

Also potentially implicating neural abnormalities associated with early adversities in the pathophysiology of depression, one study found that adults with childhood maltreatment, when compared to nonmaltreated counterparts, reported experiencing greater symptoms of anhedonia and depression and were less responsive to reward cues in regions of basal ganglia associated with reward-related learning and motivation (Dillon et al., 2009). This finding builds on prior studies suggestive of the possibility that childhood adversities, particularly maltreatment experiences, may relate to risk for later-life depression through increased anhedonia (Agrawal et al., 2012). It is also consistent with findings from the adolescent literature of stunted ventral striatum development being reflective of emotional maltreatment history and predictive of depressive symptoms (Hanson, Hariri, & Williamson, 2015).

In an imaging study comparing resting-state functional connectivity in healthy controls and depressed individuals with and without childhood neglect, both depressed groups exhibited diminished functional connectivity strength in bilateral ventral medial prefrontal cortex and ventral anterior cingulate cortex (Wang et al., 2014). Depressed individuals who had been neglected in childhood also differed notably from those with no history of childhood neglect, evidencing widespread attenuations in functional connectivity strength in the prefrontal–limbic–thalamic–cerebellar circuitry. What remains to be determined is the precise nature of the relation between aberrant resting-state functional connectivity, early adversities, and depression.

In addition to these neuroimaging findings, processes relating to cellular aging may underlie the association between childhood adversities and depression. Shortening of telomere length, for example, which occurs with cellular aging, has come to be regarded as a biomarker of chronic stress (Epel, 2009). In particular, early life adversities, including childhood maltreatment, are negatively correlated with telomere length (Price, Kao, Burgers, Carpenter, & Tyrka, 2013). Telomere length similarly has been inversely associated with depression (Schutte & Malouff, 2015). No studies to date, however, have directly examined whether accelerated erosion of telomeres mediates the relation between early life adversities and later-life depression. A subject of emerging interest in this area is whether mitochondrial biogenesis, another index of cellular aging, may also be associated with adverse childhood experiences and adult depression. Thus far, one study has found higher mitochondrial biogenesis to be associated with both early adversities and lifetime history of depression in a sample of adults (Tyrka et al., 2016).

Collectively, these findings are generally consistent with the view espoused by several researchers that depression in individuals with a history of childhood adversities may be a distinct subtype of this disorder with its own unique etiology (Grant et al., 2011). The research in this area has been predominantly cross-sectional. Fully prospective studies are required to adequately assess the temporal relation between adverse childhood experiences, depression in adulthood, and putative neurobiological mediators. Such work is particularly important for disentangling several potential accounts of the associations between childhood adversities, adult depression, and its neurobiological correlates. Competing explanations for some of the aforementioned findings could include (i) early life adversities interact with neurobiological risk factors to heighten risk for later-life depression; (ii) early adversities interact with depression to confer risk for neurobiological dysfunction; (iii) these neurobiological correlates are a consequence of depression, which mediates their relation with early adverse experiences; and (iv) childhood adversities function as a common third variable, with both neurobiological aberrations and depression as their pathological sequelae. In the absence of longitudinal research, such alternatives to neurobiological risk factors mediating the depressogenic effect of adverse childhood experiences cannot be eliminated from consideration.

HPA Axis and Stress Sensitivity

Early life adversities, particularly in the form of childhood maltreatment, may confer long-term risk for depression by increasing sensitivity to future stressors. Indeed, prior research has documented a stress sensitization effect in adults with a history of childhood adversities (Kendler, Kuhn, & Prescott, 2004). These individuals appear to be more vulnerable to the depressogenic effects of stressors in adulthood than counterparts with no childhood adversities.

Although these findings are collectively consistent with the possibility that adverse childhood experiences may lead to the development of diatheses for depression that interact with later-life stressors to predict the occurrence of this disorder, there have yet to be any studies directly testing what is essentially a moderated mediation model of the relation between early adversities and subsequent depression. In particular, no studies of stress sensitization to date have assessed why individuals with a history of adversity in childhood are more susceptible to the depressogenic effects of stressors experienced in adulthood.

One prominent possibility is that neuroendocrinological processes involving emotion regulation in response to life stress may be altered by early life experiences. In particular, the role of the hypothalamic–pituitary–adrenal (HPA) axis in regulating response to stress appears well established (Gunnar & Quevedo,

2007). Although brief HPA axis activation is adaptive, chronic activation appears to be deleterious, being associated with hippocampal atrophy (Cicchetti & Toth, 2005), such as has been observed in the aforementioned neuroimaging studies of childhood adversities. Indeed, prior research has found HPA axis dysregulation to be linked with a history of adverse childhood experiences, as well as with depression (Cicchetti & Toth, 2005). However, it remains unclear whether this potential pathway between childhood adversities and adult depression may account for the stress sensitization observed in the previously mentioned studies, with HPA axis dysregulation in response to early adversities interacting with stressors in adulthood to predict the occurrence of depression.

MODERATORS OF RISK

Genetic Influences

Not every child who experiences adversities goes on to develop depression later in life. Instead, these adverse childhood experiences likely interact with existing vulnerabilities to account for the development of this disorder. Among the most widely studied vulnerabilities that may share a moderating relationship with early life adversities in predicting depression in adulthood are genetic diatheses. Indeed, a number of candidate genes have been investigated in recent years, including brain-derived neurotrophic factor (BDNF; Kudinova, McGeary, Knopik, & Gibb, 2015) and serotonin transporter polymorphisms (5-HTTLPR; Kudinova et al., 2015).

Additionally, genetic diathesis and adverse childhood experiences interactions have been implicated in the pathophysiology of depression. For example, the interaction between FKBP5 polymorphisms and childhood maltreatment in a diffusion tensor imaging study predicted structural differences in brain regions associated with emotional processing and regulation and implicated in depression (Tozzi et al., 2016). In another study, BDNF Val66Met polymorphism interacted with childhood adversities in predicting reduced volume in the hippocampus and lateral PFC (Gatt et al., 2009). A similar interaction between 5-HTTLPR polymorphisms and childhood maltreatment has been associated with hippocampal atrophy (Frodl et al., 2010).

A degree of caution may be exercised in interpreting these findings, as research on candidate genes has become the focus of some controversy in recent years; however, the accumulating literature appears to be quite mixed, raising concerns of replicability, with some arguing several methodological limitations, theoretical considerations, and publication bias may in part account for the state of the literature (Dick et al., 2015). Reductions in the cost of genotyping over the years have led to genomewide association studies (GWAS) becoming increasingly considered a viable alternative, simultaneously assessing multiple single nucleotide polymorphisms instead of single candidate genes. GWAS studies come with formidable challenges of their own, however, perhaps chief among which is the necessity of large sample sizes (e.g., on the order of tens of thousands) to have sufficient power to detect the small effects that appear common in such work (Dick et al., 2015). This is not to say that candidate gene studies are without their place in this field of research. Rather, several important considerations and recommendations have been put forth to advance future such studies in this area (for a more thorough discussion of this issue, see Dick et al., 2015).

Developmental Influences

Moderator influences on the link between early life adversities and adult depression may occur in other ways; particularly, developmental considerations may be relevant. For example, the manner in which mediators of the risk for depression associated with early life adversities manifest at the neurobiological level may be heavily dependent on the developmental period during which the individual experienced these adversities (Lupien, McEwen, Gunnar, & Heim, 2009). Specifically, the brain regions most vulnerable to early adversity may be those experiencing a growth spurt at the time of exposure. The hippocampus appears to be most sensitive to adversities between birth and age 2, whereas the same is true for the amygdala in the case of adversities during early childhood and for the PFC and adversities in adolescence (Lupien et al., 2009). An important implication of this pattern of findings is the need for future research to be particularly attentive, from a neurodevelopmental perspective, to the timing of exposure to adverse events. It is also worth noting, as previously mentioned, that these brain regions have

all been implicated in childhood adversities, which may be reflective of the often chronic or recurrent nature of these early life experiences. It remains to be determined whether these neurobiological changes mediate the depressogenic risk of childhood adversities, or whether neurobiological abnormalities and depression separately occur as a result of early adversity.

CLINICAL CONSIDERATIONS

Elucidating mediating pathways linking early adversities to depression in adulthood is important for its potential to yield promising targets for clinical intervention. If depression in adults with adverse childhood experiences is indeed a distinct subtype of this disorder with its own etiology, as has been suggested (Grant et al., 2011), advancements in this area may lend to the development of a more personalized fit between treatment and individual risk profile. Such work is especially needed in the current context, given consistent evidence of poorer treatment course for depression co-occurring with a history of childhood adversities. Depressed adults with adverse childhood experiences are less likely than counterparts with no experiences of early adversities to achieve remission in response to pharmacotherapy (Klein et al., 2009). Consistent with these findings, a childhood maltreatment history was associated with treatment nonresponse (OR = 1.43, 95% CI = 1.11, 1.83) in a meta-analysis of clinical trials for depression for psychotherapy, pharmacotherapy, and these two modalities combined (Nanni et al., 2011). It is also associated with a shorter time to recurrence, regardless of treatment modality (i.e., CBT, IPT, and medication; Harkness, Bagby, & Kennedy, 2012). Furthermore, a recent review of psychological interventions aimed at preventing relapse and recurrence of depression observed that a history of adverse childhood events was one of the strongest risk factors for depressive relapse and recurrence (Bockting, Hollon, Jarrett, Kuyken, & Dobson, 2015).

Despite the poorer treatment course associated with a history of childhood adversities, it should not be assumed that current treatments for depression are entirely without benefit. In comparisons between specific forms of psychotherapy and pharmacotherapy in depressed patients with adverse childhood experiences, notable differences emerge. These individuals appear less likely to respond to interpersonal therapy (IPT) than to medication or cognitive behavior therapy (CBT; Harkness et al., 2012). Additionally, cognitive behavioral analysis system of psychotherapy (CBASP), which integrates elements of IPT into CBT, has been associated with better treatment outcomes than medication (48.3% vs. 32.9% remission rate), and this finding held true across different types of childhood adversity (Korotana, Dobson, Pusch, & Josephson, 2016). CBASP was also superior in the short term to IPT for depressed adults with childhood maltreatment history (57.1% vs. 20.0% remission), although differences across these treatments were no longer significant a year after treatment. Collectively, these findings suggest that CBT may be the best currently available treatment for depression for individuals with childhood adversities. Nonetheless, the low remission rate for CBASP specifically and the poorer long-term gains associated with available treatments, more generally, are indicative of the need for the development of new therapies for this population.

Given the generally poorer treatment course for depression in adults with childhood adversities, early screening for these adversities is important to optimize the window for preventive efforts, before the onset of depression and its often poorer prognosis and treatment course (Wiersma, 2015). Primary care settings may be especially valuable in this regard, as most youth make annual visits to their primary care physician, and these are the settings in which psychosocial issues are often first detected (Fordwood, Asarnow, Huizar, & Reise, 2007). Early detection of childhood adversities through routine screening in these settings may facilitate intervention implementation before adversities assume a chronic, and thus more deleterious, course (Nanni et al., 2011). Although this strategy may hold promise for limiting the negative trajectory linked with childhood adversities, given the dose–response nature of its relation to depression (Wiersma, 2015), research is needed to evaluate its efficacy.

CONCLUSION

The finding that diversities experienced in early childhood are associated with long-term risk for depression has received consistent empirical support. Moreover,

adverse childhood events seem to be linked with a poorer prognosis and treatment response among adults with this disorder. There is a particular need, however, for contextual interviews and prospective assessments of childhood adversities in studies linking this phenomenon with adult depression. In addition, there are several potential avenues for further refinement of our understanding of this association. Although some empirical evidence exists pointing to the possible mediating role of cognitive risk factors, maladaptive interpersonal styles, abnormalities in brain structure, functioning, and connectivity, particularly in areas related to memory and emotion regulation (hippocampus, amygdala, and regions of the PFC), and markers of cellular aging, longitudinal studies testing for temporal mediation are particularly needed in this area. Future work is also needed to better understand moderating influences accounting for why some individuals with childhood adversities go on to develop depression whereas others do not. Advancing beyond first-wave research documenting the association between adverse childhood experiences and adult depression toward second-wave research involving more nuanced models of mediators and moderators of this association is of translational value insofar as they may yield meaningful targets for clinical intervention and lead to the development of personalized treatment protocols.

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