

Stress Sensitization and Adolescent Depressive Severity as a Function of Childhood Adversity: A Link to Anxiety Disorders

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Abstract The goal of the present study was to determine whether exposure to adversity in childhood contributes to a differential threshold at which stressful life events provoke depressive reactions in adolescence. In addition, to address empirical and conceptual questions about stress effects, the moderating effect of anxiety disorder history was also explored. This examination was conducted in a sample of 816 children of depressed and nondepressed mothers, who were followed from birth to age 15. Information on adversities experienced in childhood was collected both from mothers during the first five years of their youth's life and from the youths themselves at age 15, and included information on the mother's relationship with her partner, maternal psychopathology, as well as youth-reported abuse. Results indicated that youths with both greater exposure to adversity in childhood and a history of an anxiety disorder displayed increased depressive severity following low levels of episodic stress compared to youths with only one or neither of these risk factors. The results are speculated to reflect the possibility that early anxiety disorders associated with exposure to adversity in childhood may be a marker of dysregulated stress responses, and may help to account for the comorbidity of depression and anxiety in some individuals.

Keywords Depression - Anxiety - Childhood adversity - Stress

Studies of psychiatric patients and community samples have consistently demonstrated that early childhood adversity is a major risk factor for depression (e.g., Brown & Harris, 1993; Faravelli et al., 1986; Kessler, Davis, & Kendler, 1997). Negative childhood experiences such as poor maternal care (Plantes, Prusoff, Brennan, & Parker, 1988), parental marital problems (Kessler & Magee, 1993), early death or separation from a parent (Harris, Brown, & Bifulco, 1986; Kendler, Sheth, Gardner, & Prescott, 2002), childhood physical and sexual abuse (Gibb, Butler, & Beck, 2003) and parental drinking and mental illness (Kessler & Magee, 1993) have all been linked to an increased risk of depression in adulthood. Studies have also linked childhood adversity with an increased risk of

adolescent depression (e.g. Kilpatrick et al., 2003; Marton & Maharaj, 1993; Mitchell et al., 1989). Given the robust associations, studies examining the mechanisms by which early childhood adversity can increase the risk for depression may have important conceptual and intervention implications.

One mechanism by which exposure to adversity in childhood may contribute to an increased risk of major depression is through a process of stress sensitization, wherein prior adversity contributes to an increased vulnerability to experience depressive reactions in response to lower levels of future stress. The concept of stress sensitization was originally proposed in models of the kindling effect of prior depressive episodes, whereby the etiological role of stressful life events is reduced in recurrences of depression compared to first lifetime episodes. In the seminal article in which the kindling hypothesis was outlined, Post (1992) proposed that episodes of mood disorder cause neurobiological changes such that less stress is required to precipitate subsequent episodes. Segal, Williams, Teasdale, and Gemar (1996) followed with a cognitive model of kindling and episode sensitization whereby the accessibility of negative patterns of information processing increases through repeated and frequent activation in depressed states, thereby increasing the likelihood of future activation to increasingly minor stressors. The kindling effects of prior depressive episodes have received reasonably strong empirical support (see Monroe & Harkness, 2005 for a review).

Similarly, exposure to prior adversity, particularly early in life, may also contribute to sensitization to subsequent stress. Researchers speculate that adverse events experienced early in life also lead to alterations in and sensitization of biological stress mechanisms (e.g., Heim & Nemeroff, 2001). The resulting alterations in the biological stress mechanisms may lead to a heightened reactivity to subsequent stress such that lower levels of stress can trigger the onset of a depressive episode in individuals who have experienced significant childhood adversity. In addition, cognitive models of vulnerability to depression have long hypothesized about the acquisition of maladaptive schemas in childhood, presumably in response to adverse experiences in the family environment (e.g., Beck, Rush, Shaw, & Emery, 1979; Nolen-Hoeksema, Girgus, & Seligman, 1992). Repeated and frequent exposure to adversity in childhood may increase the accessibility of negative schemas resulting in an increased likelihood of depressive reactions following minor negative events in the future. Empirical studies that can demonstrate a differential effect of current life stressors on depression as a function of adverse childhood experiences may stimulate further study of the mechanisms, both biological and psychosocial, by which early and recent stressors precipitate depression.

Hammen, Henry, and Daley (2000) tested stress sensitization as a function of childhood adversity in a sample of 121 young adult women using a 2-year longitudinal follow-up design. In accordance with the predictions of the sensitizing effects of early childhood adversity, the investigators hypothesized that those who had experienced one or more significant childhood adversities would have a lower threshold for developing a depressive reaction to recent stressors. The results indicated that women who were exposed to one or more adversities during childhood were more likely to experience a major depressive episode following less total stress than women without such adversity. Importantly, the results could not be accounted for by the experience of prior depression. The findings support a stress sensitization approach as a mechanism by which childhood adversity contributes to an increased risk of major depressive disorder. The Hammen et al. study was limited, however, in that the sample consisted entirely of young adult females, and it remains to be demonstrated if stress sensitization as a function of childhood adversity can be observed in a sample

of both males and females or in other age groups. A goal of the present study is to address these limitations by replicating this prior finding in a community sample that includes both male and female adolescents.

The present study also seeks to extend the findings of Hammen et al. (2000) by examining the possibility that stress sensitization as a function of childhood adversity is enhanced in individuals with a history of an anxiety disorder. Studies have shown that adversity experienced in childhood is associated with both depressive and anxiety disorders later in life (Brown & Harris, 1993; Kessler, Davis, & Kendler, 1997). In fact, Phillips, Hammen, Brennan, Najman, and Bor (2005), using the same community sample as the present study, demonstrated that adolescents with a history of pure anxiety disorders were more likely than adolescents with a history of pure depression to have been exposed to various childhood adversities. Other studies have found higher rates of childhood adversity in patients with co-morbid depression and anxiety than in patients with pure depression or pure anxiety (Alnæs & Torgerson, 1990; Mancini et al., 1995), suggesting that childhood adversity may place individuals particularly at risk to experience both anxiety and depression over the course of their lifetime. Given these commonalities, it is important to consider the possible moderating effect of anxiety disorder history in the investigation of stress sensitization as a function of childhood adversity.

There are several reasons to suspect that the stress sensitization effect is linked to anxiety disorders. First, neurobiological changes, specifically alterations to the hypothalamic-pituitary-adrenal (HPA) axis, which are hypothesized to be associated with exposure to early childhood adversity, are speculated to underlie an increased risk for both depressive and anxiety disorders (Heim & Nemeroff, 2001). Consistent with this idea, Young, Abelson, and Cameron (2004) demonstrated that dysregulated HPA axis responding to a social stressor in a group of patients with major depression was exclusively due to a group of depressed patients with comorbid anxiety disorders. Interestingly, patients with pure depression or pure anxiety showed normal HPA axis responding. Second, pronounced exposure early in life to an uncontrollable environment, characterized by unpredictable stressors and/or parental overprotection, is hypothesized to lead to a psychological tendency to perceive future events as uncontrollable (see Chorpita & Barlow, 1998 for a review). While this tendency to perceive uncontrollability is hypothesized to represent a psychological vulnerability for anxiety, this same vulnerability may lead to enhanced perceptions of stress in the face of negative life events. As a result, minor stressors may have a greater impact on vulnerable individuals compared to individuals without such vulnerability (Hemenover, 2001; Schneider, 2004). Lastly, several studies have demonstrated that anxiety disorders increase the probability of subsequent depressive disorders (Cole, Peeke, Martin, Truglio, & Seroczynski, 1998; Pine, Cohen, Gurley, Brook, & Ma, 1988; Stein et al., 2001). It is possible that the increased risk for depression in individuals with a history of anxiety may, at least in part, be attributable to a psychological vulnerability resulting from childhood adversity that contributes to both stress sensitization and anxiety. Consistent with this idea, de Graaf, Bijl, ten Have, Beekman, and Vollebergh (2004) demonstrated that childhood adversity and recent life stress predicted the development of a comorbid depressive disorder among individuals with pure anxiety disorders. The findings of the current study may have important implications for future research on the risk for the lifetime co-morbidity of depression and anxiety as a consequence of exposure to childhood adversity.

The present study sought to replicate and extend the findings of Hammen et al. (2000) with a design well suited to also address some of the limitations of the prior finding. The present study included a much larger sample from a birth cohort of both male and female adolescents who differed in age from the participants in the Hammen et al. study. In addition, the current study retained many of the methodological strengths of the Hammen et al. study while also improving upon methodological weaknesses. For example, both studies used a longitudinal design with careful assessment of depressive experiences and stressful life events. But whereas Hammen et al. assessed childhood adversity solely through retrospective self-report, the current study included contemporaneous reports of adversities obtained from the participants' mothers in the participants' first 5 years of life, which were supplemented by the participants' retrospective reports at age 15.

The purpose of the present study was to determine whether exposure to adversity in childhood contributes to a differential threshold at which stressful life events provoke depressive reactions. An additional goal of the present study was to explore the potentially interactive role of anxiety disorder history in the stress sensitizing effects of childhood adversity. It was hypothesized that adolescents who have experienced greater amounts of recent episodic stress will demonstrate increased levels of depressive severity regardless of their history of exposure to early childhood adversity, but that those with a history of exposure to early childhood adversity will also demonstrate increased levels of depressive severity following lower amounts of recent stress in comparison to those who did not have such childhood experiences. It was further hypothesized that history of anxiety disorders will moderate the stress sensitization effect such that those with both a history of exposure to childhood adversity and a history of an anxiety disorder will demonstrate an increased level of depression severity following lower amounts of stress in comparison to those without such histories.

Method

Participants

The current sample consisted of 816 15-year-old adolescents, 414 males (50.7%) and 402 females (49.3%), drawn from a study of children born at the Mater Misericordiae Mothers' Hospital in Brisbane, Queensland, Australia, between 1981 and 1984. The original birth cohort participants were part of the Mater-University Study of Pregnancy (MUSP), which followed 7,775 mothers and their children, 4,038 males (51.9%) and 3,737 females (48.1%), from birth through age 5 (Keeping et al., 1989) in a study of child and mother health and development. In the MUSP, mothers were assessed at approximately 18 weeks gestation, 3 to 5 days after the birth of the child, at 6 months old, and at 5 years old. The present study is part of an investigation of children at risk for depression due to maternal depression, and commenced when the children reached age 15.

From the original sample, a subset of 816 mothers and adolescents was selected for follow-up based on the mother's self-report of depression on the Delusion-States Symptom Inventory (DSSI; Bedford, Foulds, & Sheffield, 1976) during the initial phases of the study, with the intention of including women with a range of depression experiences, including no depression, oversampling those with elevated and/or persisting levels of depressive symptoms. Selection of women with likely clinically

significant (or no) depression was verified by diagnostic evaluations when the child was 15 as noted below (44% of the women had diagnosed major depressive episodes or dysthymic disorder during the child's lifetime).

Families were included in the follow-up study when the youths were 15 (mean age 14.9 years old, $SD = .37$). The ethnicity of the adolescents in the sample was determined by the mothers' reports: 89.3% Caucasian ($N = 729$), 1.0% Asian ($N = 8$), .7% Maori or Aborigine ($N = 6$), and 6.2% mixed descent ($N = 51$). Overall, the families in this sample were lower middle to low SES. Compared to the children not selected for follow-up, the current sample did not differ on the basis of gender ($\chi^2(1, N = 7775) = .53, p = .47, ns$), family income ($\chi^2(6, N = 7149) = 1.61, p = .95, ns$), or mother's education level ($\chi^2(7, N = 7622) = 6.42, p = .49, ns$). However, the current sample contained marginally fewer ethnic minority members than the original sample ($\chi^2(4, N = 7438) = 8.87, p = .07$).

Procedure

In the initial phase of the MUSP, women at their first prenatal clinic visit at the Mater Misericordiae Public Hospital were invited to participate in a study on pregnancy. After consenting to participate, the women completed a self-report questionnaire on health problems, psychosocial factors, daily activities, and their attitudes toward their pregnancy. Additional self-report questionnaires were completed approximately 3 to 5 days after their child's birth, when the child reached the age of six months, and when the child reached the age of 5. Further details about the procedures used during the initial study are reported by Keeping et al. (1989).

When the child reached the age of 15, families selected for inclusion in the current study were contacted and asked to participate in a follow-up to the original MUSP. After obtaining consent/assent from the participants, trained clinicians, blind to maternal status on the DSSI, administered diagnostic and other semi-structured interviews separately and privately to both the adolescents and their parents in their homes; participants also completed a series of self-report questionnaires on a laptop computer. Procedures were completed in about 3.5 h (including 1.5–2 h for interviews), and the youth and parents received payment for their participation.

Measures obtained from the mother

Contemporaneous data on adverse conditions before youth age 5 were taken from the maternal self-report questionnaires administered during the first four waves of data collection by the MUSP. This data included measures of the mother's relationship with her current partner and information on various other adversities. Information on maternal history of psychopathology was collected from mothers at youth age 15.

Mother's relationship with current partner

The quality of the mother's relationship with her current partner was obtained at each of the four waves of data collection in MUSP from the mother's self-report on the eight satisfaction items of the Dyadic Adjustment Scale (DAS; Spanier, 1976). Alphas at each wave of data collection for the DAS were .86, .85, .88, and .97 respectively. DAS scores were averaged across the four time points. DAS scores were unavailable for at least one of the four time points for 18% of mothers ($N = 147$).

because they were not in relationships (single, separated/divorced, or widowed) at the time of the assessment. Where DAS scores were unavailable for one ($N = 98$; 12.0%) or two ($N = 20$; 2.5%) of the four time points, the average was based on the data points available. Where three or four data points were unavailable ($N = 29$; 3.5%), the mean DAS scores for the sample scores was imputed.¹ DAS scores were reversed scored so that higher scores indicate greater distress and less marital satisfaction.

Mother-reported adversities

A measure of various additional adversities experienced in the youth's first five years was created using the mothers' reports of negative circumstances across four domains: romantic relationship distress (maternal separation or divorce and changes in partner), death of the child's father, early childhood illness, and multiple early childhood hospitalizations. At the fourth wave of data collection in MUSP, the mothers reported the number of times they had been separated or divorced during the previous five years. This variable was dichotomized such that reporting one or more instances of separation or divorce was classified as the presence of the adversity. The mothers also reported the number of times they changed partners during the previous five years. This variable was similarly dichotomized such that reporting one or more instances of partner changes was classified as the presence of the adversity. Death of the child's father was defined as experiencing the death of the child's biological father during the first five years of the child's life. Presence of impairing chronic illnesses was defined as a maternal report indicating that the child's daily activity was impacted either "some" or "a lot" for one or more illnesses. "Multiple hospitalizations" was defined as a maternal report indicating that the child had two or more hospitalizations before age 5. The number of adversities experienced across these four domains in the first five years of the youth's life was summed. Where data were unavailable for one ($N = 20$; 2.5%), two ($N = 3$; 0.4%), or three ($N = 2$; 0.2%) of the five data points, the sum was pro-rated for the number of data points available.²

Maternal psychopathology in the first five years

Maternal psychopathology during the youth's first five years was assessed via the *Structured Clinical Interview for DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 1995). The SCID is a semi-structured interview used to diagnose current and past Axis I psychiatric disorders. The SCID for lifetime diagnoses was administered by trained clinicians to the mothers in the sample at participant age 15. For the present study, occurrence of a depressive disorder ($N = 125$; 15.4%), anxiety disorder ($N = 33$; 4.0%), alcohol abuse problem ($N = 10$; 1.2%), or substance abuse problem ($N = 12$; 1.4%) during the child's first 5 years of life was determined. Interrater reliabilities for lifetime diagnoses were determined using 52 of the SCID interview tapes randomly selected for rating by a second clinician blind to the original diagnoses. Overall, the weighted kappa for any past maternal depressive disorders was .84, and the weighted kappa for past maternal anxiety disorders was .85. Previous maternal substance abuse had a weighted kappa of .88. All other past maternal disorders had a kappa of .97. Additional analyses using contemporaneous MUSP data were conducted and confirmed the reliability of mother diagnoses dated to the first five years of the youth's life.³ Having a mother who met criteria for one or more disorders in the youth's first 5 years of life was classified as the presence of this adversity.

Measures obtained from the youth

Youth-reported adversities

At age 15, youths completed a checklist of adverse events experienced in their lives. The list included: death of father, death of sibling, parental substance abuse, physical abuse in the family, parental psychopathology, parental marital conflict, serious illness or accident to family member, serious illness or accident to participant, parent divorce or separation, and participant victim of violence (physical or sexual assault). History of physical or sexual abuse was also assessed separately via questionnaire. No specific information on the child's age at the time the adversity occurred or the duration of the adversity was obtained. A youth-reported adversity score was created by summing the number of adversities endorsed by the participants.

Stressful life events

At age 15, youths were administered an episodic life stress interview modeled after, but briefer than, the contextual threat assessment methods of Brown and colleagues (e.g., Brown & Harris, 1978). The episodic life stress interview has been used extensively by Hammen and colleagues in populations of diverse ages and mood disorders (e.g., Hammen, 1991; Hammen, Ellicott, Gitlin, & Jamison, 1989). Questionnaire checklists and self-report ratings have been criticized because they may either elicit distorted perceptions of the significance of an event as a function of the individual's current mood state or fail to characterize the unique meaning of an event for an individual. The goal of the interview approach is to obtain sufficient information about the circumstances surrounding an event's occurrence to characterize its impact on the person's life as objectively as possible. The interviewer inquires about the various areas of the person's life, identifying and carefully dating events that have occurred in the past period (for the present study, the previous 12-months). Each reported event is probed to obtain information about what happened, how long it continued, whether it was expected, whether the person had ever experienced similar events, what resources were available to the person, what the consequences were, and any other relevant background. Narrative accounts of each event containing this information were then prepared by the interviewer and presented to an independent rating team, omitting any information about the individual's actual reaction to the event. The team then rates how much impact an event would have for a typical person under the same conditions, and an objective impact, or threat rating, is assigned on a scale ranging from 1 (*no negative impact*) to 5 (*extremely severe negative impact*). Interrater reliabilities based on the independent ratings by Australian and U.S. teams for approximately 20% of cases in the first two years of data collection (approximately 12% of the total cases) yielded intraclass correlations of 0.92.

For the present study, the primary stress variable was the total episodic stress score for the 12-month interval prior to the age 15 interview. The total episodic stress score was generated by adding the objective impact ratings for all events (excluding those with an impact of 1, i.e., not at all stressful) occurring in that period.

Beck depression inventory (BDI; Beck & Steer, 1987)

At age 15, the 21-item self-report BDI was administered to the youths as a measure of the current presence and severity of depressive symptoms. This measure has been widely used in the study of depression with internal consistency estimates ranging from .73 to .95 for the BDI (Beck, Steer, & Garbin, 1988). Coefficient alpha is .86 in the present sample.

Schedule for Affective Disorders and Schizophrenia in School-Aged Children (K-SADS-E; Orvaschel, 1995)

At age 15, youths were administered the K-SADS-E by trained clinicians. The K-SADS-E is a semi-structured interview for diagnosing the current presence or past history of Axis I psychiatric disorders for children and adolescents. A clinical interview team assigned best estimate diagnoses, based on reviews by the research team of mother and child interviews and any additional available information. In order to capture a range of current depressive severity, the K-SADS was modified to include criteria for Minor Depressive Disorder as specified in the Diagnostic and Statistical Manual, Fourth Edition (American Psychiatric Association, 1994) and depression diagnoses were transformed into a 4-point scale indicating severity of symptoms or diagnoses: 0 = no diagnosis ($N = 721$; 88.4%), 1 = sub-clinical Minor Depressive Disorder, Dysthymia, or Major Depressive Disorder ($N = 55$; 5.3%), 2 = diagnosis of Minor Depressive Disorder or Dysthymia ($N = 22$; 1.6%), 3 = diagnosis of Major Depressive Disorder or Major Depressive Disorder and Dysthymia ("double-depression") ($N = 18$; 2.2%). The mean BDI scores and the standard deviations for the 4 groups were as follows: 0 ($M = 5.07$, $SD = 5.53$), 1 ($M = 11.65$, $SD = 9.50$), 2 ($M = 13.42$, $SD = 10.46$), and 3 ($M = 17.56$, $SD = 10.77$). The correlation between interview-rated depressive severity and BDI scores was .39 ($p < .0001$).

Clinically, 13.1% ($N = 107$) of the total had a history of past Major Depressive Disorder or Dysthymia. A total of 100 (12.3%) youths had a lifetime history (current or past) of an anxiety disorder: Generalized Anxiety Disorder ($N = 13$; 1.6%), Obsessive-Compulsive Disorder ($N = 4$; 0.5%), Agoraphobia with Panic ($N = 2$; 0.2%), Post-Traumatic Stress Disorder ($N = 12$; 1.5%), Acute Stress Disorder ($N = 2$; 0.2%), Social Phobia ($N = 30$; 3.7%), Specific Phobia ($N = 33$; 4.0%), and Separation Anxiety Disorder ($N = 28$; 3.4%). Among adolescents who had a lifetime history of Major Depressive Disorder or Dysthymia, 25.5% ($n = 28$) also had a lifetime history of anxiety disorder.

Seventy-five of the KSADS-E interview tapes were randomly selected for reliability ratings by a second clinician blind to the original diagnoses. Overall, the weighted kappa for any depressive disorders was .82 for current disorders and .73 for past disorders. The weighted kappa for any anxiety disorders was .76 for current disorders and .79 for past disorders.

Composite indices of childhood adversity and current depression severity

Principal components analysis was used to create a composite measure of childhood adversity and a composite measure of depression severity from the multiple indicators of each construct available for this study. A goal of principal components analysis is to provide a simpler representation of a set of intercorrelated variables by reducing them down to principal components (Afifi & Clark, 1996). Principal component scores can be estimated for each participant representing the scores the

participant would have received had the component been measured directly (Tabachnick & Fidell, 2001). The first principal component is the linear combination of the observed variables that maximally separates participants by maximizing the variance of their component scores. Principal component scores are adjusted for the inter-correlations among the observed variables that are contributing to the component, thus, the component scores are adjusted for redundancies in the information measured across the individual observed variables. Component scores are often more reliable than scores on individual observed variables.

Childhood adversity component

To formulate a composite index of childhood adversity utilizing data from all available sources, principal components analysis was performed using four indicators of childhood adversity: maternal psychopathology in the first five years, mean maternal DAS scores, number of mother-reported adversities, and number of youth-reported adversities. Descriptive statistics and the intercorrelations amongst these four variables are listed in Table 1. With the initial criterion that the number of factors extracted have an eigenvalue greater than one, a one factor solution was produced. As an additional criterion, a scree test was conducted and a one factor solution was confirmed. The childhood adversity component accounted for 42.2% of the total variance of the four indicators of childhood adversity. The component loadings for the four original variables were .55 for maternal psychopathology in the first five years, .65 for mean maternal DAS scores in the first five years, .72 for mother-reported adversities, and .66 for youth-reported adversities. A principal component score was then calculated by first standardizing the original variables, weighting the standard scores by the component loading for that variable, and then adding the results for each participant.

Table 1 Correlations and descriptive statistics for childhood adversity and depressive severity variables^a

	1	2	3	4	5	6	7	<i>M(SD)</i> or Freq. (%)
Childhood adversity								
1. Maternal psychopathology in 1st 5 years								40.85 (4.81)
2. Mean maternal DAS score in 1st 5 years	.19**							148 (18.1%)
3. Mother-reported adversities by age 5	.20**	.29**						0.60 (0.95)
4. Youth-reported adversities at age 15	.16**	.22**	.30**					1.53 (1.60)
5. Childhood Adversity Component	.55**	.65**	.72**	.66**				—
Depressive severity at age 15								
6. Interviewer-rated	.16**	.09*	.15**	.32**	.27**			0.19 (0.58)
7. BDI score	.05	.08*	.07*	.23**	.16**	.39**		6.02 (6.75)
8. Depressive severity component	.12**	.10**	.13**	.31**	.26**	.84**	.84**	—

^aThe childhood adversity and depressive severity components were standardized in the process of creating these variables. Thus, the mean and standard deviation for these variables are not reported.

+ $p < .10$; * $p < .05$; ** $p < .01$.

Depression severity component

To formulate a composite index of current depression severity, principal components analysis was performed using two indicators of current depression severity: interviewer-rated depressive severity and BDI scores. Descriptive statistics and the correlations between these two variables are listed in Table 1. Using the initial criterion of an eigenvalue greater than one, a one component solution was produced and was confirmed in a scree test. The depressive severity component accounted for 69.7% of the total variance of the two indicators of depression severity with each variable loading .84 to the component. A principal component score for depressive severity was then calculated using the same procedures listed above.

RESULTS

Correlations among relevant variables in the current analyses were computed to evaluate potentially confounding relationships between demographic factors and current depression severity. These correlations as well as descriptive statistics are presented in Table 2. Family income was modestly but significantly associated with youth depression severity, $r(776) = -.13, p < .001$. In addition, a significant difference in depression severity was found based on gender, $t(803) = 4.42, p < .001$, with higher current depression severity for females ($M = 0.15, SD = 1.15$) than for males ($M = -0.15, SD = 0.80$). As expected, a significant difference in current depression severity was also found based on maternal depression history, $t(803) = 3.32, p < .001$, with higher depression severity for youths whose mother had a history of depression ($M = 0.13, SD = 1.18$) than for youths whose mother did not ($M = -0.10, SD = 0.82$). Additionally, a significant difference in depression severity was found on the basis of past depression history, $t(803) = 13.00, p < .001$, such that the current depression severity of youths with a past history of depression ($M = 1.07, SD = 1.73$) was higher than that for youths without a past history of depression ($M = -0.16, SD = 0.71$). Given these differences, family income, gender, maternal depression history, and youth past depression were controlled in the regression analyses evaluating hypothesized predictors of current depression severity.⁴

Table 2 Correlations and descriptive statistics

	1	2	3	4	5	6	7	<i>M(SD)</i> or Freq. (%)
1. Youth gender (male)								414 (50.7%)
2. Family income	<.01							2.97 (2.04)
3. Maternal depression history	>-.01	-.14**						358 (43.9%)
4. Youth past depression	.16**	-.08*	.12**					107 (13.1%)
5. Childhood adversity component	-.01	-.30**	.41**	.17**				—
6. Youth total episodic stress	.19**	-.04	.11**	.23**	.18**			6.00 (3.99)
7. Youth anxiety history	.06 ⁺	-.05	.07*	.15**	.16**	.08*		100 (12.3%)
8. Depressive severity component	.15**	-.13**	.12**	.42**	.26**	.21**	.20**	—

⁺ $p < .10$; * $p < .05$; ** $p < .01$.

Because this study was, in part, an attempt to replicate the findings of Hammen et al. (2000), the effects of childhood adversity, total episodic stress, and their interaction were examined in the prediction of current depressive severity before considering the effect of anxiety disorder history. Hierarchical linear regression was used to predict depression severity at age 15 from childhood adversity component scores, total episodic stress in the prior 12 months, and the interaction of childhood adversity and total episodic stress. The total episodic stress variable was centered prior to forming the interaction term to eliminate nonessential multicollinearity (Cohen, Cohen, West, & Aiken, 2003). Demographic and control variables were entered simultaneously on the first step of the analysis. The main effects of childhood adversity and total episodic stress were entered on the second step. To examine the incremental prediction of depressive severity after controlling for the main effects of childhood adversity and total episodic stress, their interaction was entered on the third step.

Level of childhood adversity was a significant incremental predictor of depression severity after controlling for gender, family income, maternal depression history, and youth past depression ($b = .19$, $t(769) = 5.24$, $p < .001$). Total episodic stress in the previous 12 months also contributed significantly to the prediction of depression severity ($b = .02$, $t(769) = 2.52$, $p < .05$). The interaction between childhood adversity and total episodic stress was not a significant incremental predictor of current depression severity ($b = 0.01$, $t(768) = 1.26$, $p = .21$, *ns*), such that the effect of stress on levels of current depression severity did not vary as a function of exposure to childhood adversity.

In preparation for an examination of anxiety disorder history modifying the interaction between childhood adversity and total episodic stress, the main effect of anxiety history, the interaction of anxiety history and total episodic stress, and the interaction of childhood adversity and anxiety history were each added in subsequent steps of the regression equation predicting depressive severity. The main effect of anxiety disorder history and its interactions with both total episodic stress and childhood adversity were added on separate steps so that their individual contributions to the prediction of depressive severity could be examined. In the fourth step, anxiety history was a significant incremental predictor of current depression severity ($b = 0.33$, $t(767) = 3.36$, $p < .001$). In the fifth step, the interaction between anxiety history and total episodic stress was non-significant ($b = .01$, $t(766) = 0.50$, $p = .62$, *ns*), indicating that the effect of stress on current depression severity did not vary as a function of anxiety history. In the sixth step, the interaction between early adversity and anxiety history was also non-significant ($b = .08$, $t(765) = 1.03$, $p = .31$, *ns*).

Finally, to examine the incremental prediction of the interaction of childhood adversity, total episodic stress and anxiety history, their 3-way interaction was added in the seventh and final step. Results of the final regression analysis are presented in Table 3. After entering all main effects and interactions, level of childhood adversity remained a significant predictor of depression severity ($b = .15$, $t(764) = 3.77$, $p < .001$). Total episodic stress also remained a significant predictor of depression severity ($b = .02$, $t(764) = 2.21$, $p < .05$). The interaction between childhood adversity and total episodic stress became a significant incremental predictor of current depression severity ($b = .20$, $t(764) = 2.297$, $p < .05$). Anxiety history was also a significant incremental predictor of current depression severity at age 15 ($b = .33$, $t(764) = 3.14$, $p < .01$). The interaction between anxiety history and total episodic stress became marginally significant ($b = .04$, $t(764) = 1.73$, $p < .10$), while the interaction between childhood adversity and anxiety history remained non-significant

($b = .07$, $t(764) = 0.87$, $p = .38$, *ns*). Finally, the hypothesized 3-way interaction of childhood adversity, total episodic stress, and anxiety history was a highly significant predictor of depression severity at age 15 ($b = -.06$, $t(764) = -2.93$, $p < .005$).

Table 3 Predicting depressive severity at age 15 from childhood adversity, 12-month total episodic stress, and youth anxiety history

	Hierarchical regression results		
	<i>b</i>	<i>R</i> ²	ΔR^2
1. Gender	0.17**		
Family income	-0.02		
Maternal depression history	0.02		
Youth past depression	1.02**	.208	.208**
2. Childhood adversity component	0.15***		
Total episodic stress	0.02*	.247	.039**
3. Childhood Adversity×Total Episodic Stress	0.02*	.249	.002
4. Anxiety History	0.33**	.260	.011**
5. Anxiety History×Total Episodic Stress	0.04 ⁺	.260	.000
6. Childhood Adversity×Anxiety History	0.07	.261	.001
7. Childhood Adversity×Anxiety History×Total Episodic Stress	-0.06**	.269	.008**

⁺ $p < .10$; * $p < .05$; ** $p < .01$; *** $p < .001$.

To illustrate the interaction effect graphically, we used the final regression equation to calculate predicted depression severity at a level of stress one standard deviation above the mean (high stress—a total episodic stress score approximately equal to 10) and at a level of stress one standard deviation below the mean (low stress—a total episodic stress score approximately equal to 2), and at a level of childhood adversity one standard deviation above the mean (high adversity) and at one standard deviation below the mean (low adversity) for both youths with and youths without an anxiety disorder history. To enhance interpretability, simple slope analyses were conducted at the values depicted in the graph using procedures outlined by Aiken and West (1991).⁵ In addition, predicted depression severity scores were converted to BDI scores ($M = 6.02$, $SD = 6.75$). The interaction is illustrated in Fig. 1.

Additional analyses

To examine the impact of only those adversities occurring in the first five years of the youth's life, a childhood adversity component score comprised only of the data collected from the mothers (i.e., mean maternal DAS scores, maternal psychopathology, and number of mother-reported adversities) was computed using principal components analysis. This childhood adversity component accounted for 48.4% of the total variance of the three variables with the following component loadings: .63 for maternal psychopathology in the first five years, .72 for mean maternal DAS scores, and .73 for mother-reported adversities. The correlation between youth-reported adversities and the childhood adversity component with youth-reported adversities excluded was .33 ($p < .00001$). The correlation between the childhood adversity component with youth-reported adversities included and the childhood adversity component with youth-reported adversities excluded was .93 ($p < .00001$). Hierarchical linear regression analyses were run following the same procedures as depicted above using the childhood adversity component with youth-reported adversities excluded. The results were largely similar to the results depicted above. The 3-way interaction of childhood adversity,

total episodic stress, and anxiety history was again a highly significant predictor of depression severity at age 15 ($b = -.08$, $t(764) = -4.18$, $p < .00005$).

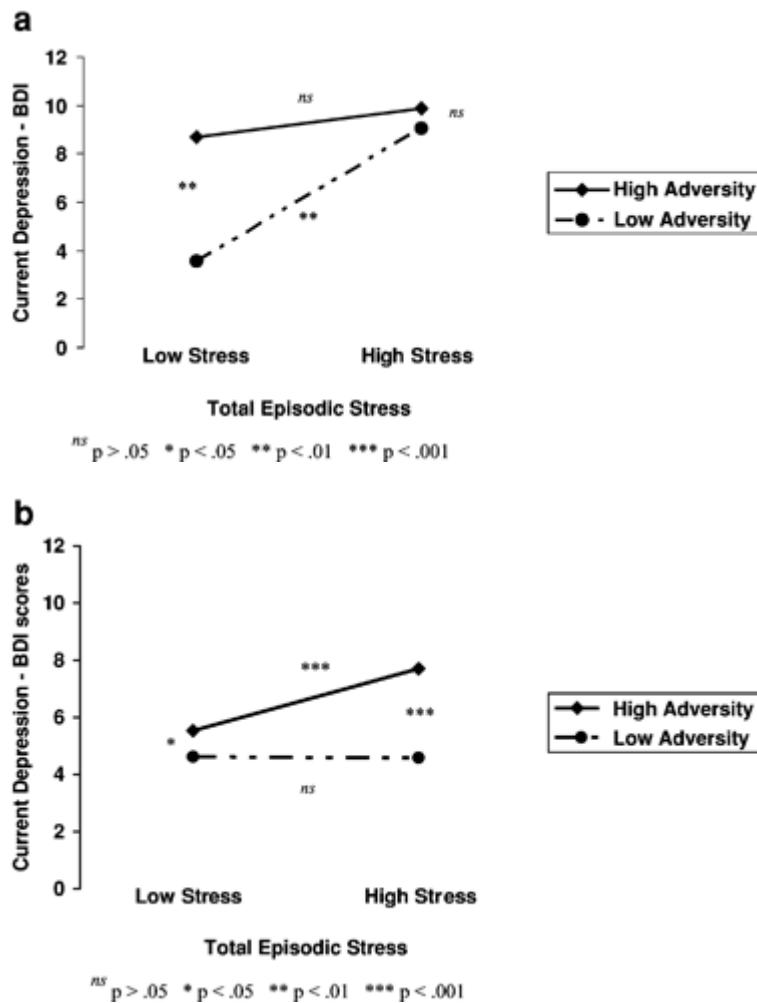


Fig. 1 The interaction of total episodic stress at age 15 and childhood adversity in predicting age 15 depressive severity among a) youths with a history of an anxiety disorder and among b) youths without a history of an anxiety disorder. The results of simple slope analyses are indicated in the figure. In addition, depressive severity differed by anxiety disorder history status among youths with high childhood adversity and low recent stress ($p < .01$), among youths with high childhood adversity and high recent stress ($p < .05$), and among youths with low childhood adversity and high recent stress ($p < .01$). Depressive severity did not differ by anxiety disorder history status among youths with low childhood adversity and low recent stress ($p = ns$).

Discussion

The goal of the present study was to determine whether exposure to adversity in childhood contributes to a differential threshold at which stressful life events provoke depressive reactions in adolescence. It was hypothesized that youths who were exposed to a greater degree of adverse experiences in childhood would display a high degree of reactivity to even low levels of stress, as reflected in higher levels of current depression severity following lower exposure to stress in

comparison to those without such histories. In contrast to the findings reported by Hammen et al. (2000), recent stress did not interact with childhood adversity history to predict depressive severity prior to examining the moderating effect of anxiety disorder history. Upon considering the interaction of childhood adversity, recent stress, and anxiety disorder history, the interaction of recent stress and childhood adversity became significant in the prediction of current depression severity. Moreover, the hypothesized 3-way interaction of childhood adversity, recent stress, and anxiety history was highly significant. Slope analyses confirmed that youths with a higher degree of adverse experiences in childhood displayed higher levels of current depression severity following lower exposure to recent stress compared to youths with less exposure to childhood adversity in *both* the anxiety history and the no anxiety history groups. However, among youths who had a high degree of childhood adversity, the level of depressive severity following conditions of low stress was much higher in youths who *also* had an anxiety disorder history compared to those who did not have an anxiety disorder history.

Interestingly, among those youths with both greater exposure to adversity in childhood and a history of an anxiety disorder there was no evidence for a differential effect of level of recent stress on current depression severity. That is, although they were reactive to low levels of stress, such youths did not show more depression in response to high exposure to recent stress. Thus, it does not appear that youths who are vulnerable due to both high adversity and anxiety disorders are simply more reactive to stress of any kind. The pattern reflects “sensitization” to low levels of stress but no greater reactivity to high levels of stress. The failure to demonstrate higher levels of depression severity at high levels of stress than at lower levels of stress was likely not the result of a ceiling effect limiting detection of increased symptoms, as predicted levels of depressive symptoms were low overall in this study. Whether the pattern of outcomes was affected by other factors—or whether there are truly no differential patterns of depressive response to high and low recent stress levels among those who are vulnerable by virtue of childhood adversity exposure plus anxiety disorders is a question for further study. In any case, the patterns of stress response are abnormal compared to those lacking high adversity experiences in childhood or history of anxiety disorders.

The current study extends the findings of the Hammen et al. (2000) suggesting that depressive sensitization to stressors as a function of early childhood adversity is linked with anxiety disorder history. Anxiety disorder history was not assessed in the Hammen et al. study, but given the high rates of co-morbidity between these two disorders it is possible that the stress-sensitization effect demonstrated in that study were also due to a group with a co-morbid history of anxiety disorder. The link to anxiety disorder history in the current study is consistent with several studies that have found childhood adversity to place individuals at particular risk for co-morbid depression and anxiety (e.g. Alnæs & Torgerson, 1990; Mancini et al., 1995; de Graaf et al., 2004). We note that youths with a history of anxiety and lower exposure to adversity in childhood did not demonstrate increased depressive reactivity at low levels of stress, suggesting the critical contribution of childhood adversity, not just anxiety disorder-based stress sensitivity.

One might speculate that a unique pathway to depression in adolescents results from abnormal HPA alterations due to early adversity, possibly leading to anxiety disorders that reflect or potentiate further sensitivity, ultimately displaying depression in response to even low levels of stressors. Furthermore, early adversity may confer increased depressive susceptibility through its effects on

personality factors, such as neuroticism (Roy, 2002), a point that has also been offered to explain the sensitizing effects of prior depressive episodes (see Monroe & Harkness, 2005). Chorpita (2001) proposed that the experience of uncontrollable stressors, especially in early childhood, may contribute to the formation of a psychological vulnerability that acts to amplify the effects of negative events experienced in late childhood and adulthood. The findings of the current study suggest that this psychological vulnerability may exert its amplifying effects particularly at low levels of stress in contributing to depression. The findings further suggest that early anxiety disorders in response to adversity may be a marker of this vulnerability process. Further study is clearly needed to examine the impact of childhood adversity on the experience of future stressors in predicting depression, the biological and psychosocial variables mediating these processes, and the role that anxiety may play as a marker and potential mediator in vulnerability processes.

The findings of the current study point to the potential benefit of targeting the early family environment as a major prevention aim. The childhood adversity component was constructed with an emphasis on the first five years of the youths' lives, which is suggestive of the high impact experiences within this developmental period may have in the formation of psychological vulnerabilities to future stress (Chorpita, 2001). In fact, constructing the child adversity component to include only those variables measuring circumstances occurring in the first five years produced more highly significant findings. Maternal psychopathology and maternal marital problems in these early years appear to be markers of an environment that may confer psychological vulnerability to experience depression in response to future stress and may serve as targets for future prevention programs. It might be pointed out that youths in the current study with low exposure to childhood adversity and no history of anxiety disorders did not display depressive reactions to high levels of stress, and appeared to be relatively resistant or resilient. This suggests that improving circumstances early in child development may have long lasting protective effects in the face of stressors experienced later in life. Further study is clearly needed to demonstrate the degree to which the absence of adversity in the early family environment can continue to confer resilience to the depressive effects of stress. A longitudinal follow-up of the youths in the current study may help to address this issue.

It is acknowledged that although the 3-way interaction of childhood adversity, total stress, and anxiety disorder history was highly significant, the incremental variance accounted for by this 3-way interaction was less than 1%. However, as depicted in Fig. 1 and confirmed by simple slope analyses, it is clear that the 3-way interaction is important in the prediction of current depressive severity and can inform further examination of stress processes in depression. It is further acknowledged that the full model in the current study accounted for only 26.9% of the total variance of current depressive severity and that depressive severity levels predicted by the final regression equation were on the lower end of the depressive severity spectrum. Clearly, other factors not measured in the current study are also contributing in the etiology of depression and must be considered in predicting more severe forms of depression. Moreover, to verify the clinical significance of the current findings, future research should determine whether the current patterns of depressive vulnerability also apply in the prediction of major depressive episodes.

A limitation of the present study is that some of the information on adversities was collected by retrospective report. Retrospective reports of childhood experiences have been questioned for their

reliability and validity, especially as they may be influenced by specific mood-congruent memory biases associated with current psychopathology. Evidence suggests, however, that retrospective reports of major adversities, when clearly defined, are generally valid (Hardt & Rutter, 2004), and that there is little reason to link psychiatric status with less valid or less reliable recall of early experiences (Brewin, Andrews, & Gotlib, 1993). Because the reports of adversity in the current study focused on the occurrence of specific events or facts and were mostly behavioral and non-subjective, reports of adversities are likely to be reasonably accurate. In addition, although youth-reported adversity had the largest association with current depression severity amongst the early adversity indicators (see Table 1), excluding the youths' retrospective reports from the early adversity component did not alter the findings of the current study.

Reports of adversities were also limited in that maternal reported adversities assessed in this study were limited to those occurring by youth's age 5, the age of occurrence for youth-reported adversities was not obtained, and the information gathered for each domain of interest may not be sensitive to differences in the actual severity or chronic nature of negative conditions. Each of these factors may have independent influence on the stress sensitization process. A strength of the childhood adversity data, however, is that maternal-reported adversities were obtained contemporaneously and combined with youth-reported adversities using principal component analyses to strengthen both the validity and the reliability of the childhood adversity measure.

Additional limitations of the present study are also acknowledged. First, the study oversampled families with maternal depression, and therefore may not be generalizable to unselected community samples. At the same time, however, the sample was large and provided ample variation in levels of exposure to childhood adversity, recent life stress, and anxiety history to study their combined effects in the prediction of current depressive severity. Finally, although the present study included a naturalistic design with the careful assessment of stressors occurring over a 12-month period prior to current depressive severity, precise details of the timing of stressful events relative to the onset of current depression severity could not be determined. It should be noted, however, that despite controlling for several variables which were all individually strong predictors of current depression severity, including maternal depression, past youth depression, gender, income and the main effects of childhood adversity, stress, and anxiety disorders, results showed significant incremental effects of the interaction of anxiety disorder history, childhood adversity, and recent stress levels.

In conclusion, this study offers promising leads toward understanding the mechanisms by which adverse experiences occurring early in life can increase the risk for depression. It suggests that adversity experienced in childhood is associated with abnormal depressive reactions to recent stressors, potentially increasing the likelihood of experiencing a depressive episode under low stress conditions. It further suggests that early anxiety disorders in response to childhood adversity may be markers of this vulnerability process. Thus, one might speculate that the stress sensitization process and early anxiety disorders are linked by a common causal mechanism, possibly related to biological and/or cognitive changes associated with childhood adversity exposure. Uncovering the link between stress sensitization and anxiety may not only implicate potential mechanisms of depressive vulnerability associated with dysregulated stress responding; it may also help facilitate understanding of common risk factors in the etiology of anxiety and depression.

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Footnotes

¹ It was decided not to exclude the 29 mothers who were missing DAS data for three or four time points because analyses indicated that they were not a random subsample, differing significantly in depression history ($\chi^2(1, N = 816) = 4.04, p < .05$) and their youths' reports of total episodic stress ($t(814) = 2.233, p < .05$). Therefore, a conservative method of imputation of the missing DAS scores was used that consisted of assigning them the mean of the total sample.

² Final analyses excluding those 25 youths whose mothers were missing data points in the computation of the "mother-reported adversities" variable were largely the same. The 3-way interaction of childhood adversity, total episodic stress, and anxiety history remained highly significant ($b = -.06, t(743) = -2.93, p < .005$).

³ Reliability of the dating of maternal diagnoses in the first 5 years was examined in the following ways: Mothers' contemporaneous self-reports of depression on the DSSI were averaged across the 4 waves of MUSP in the first 5 years of the child's life. Mothers who met DSM criteria for a depressive diagnosis in the first five years of the child's life endorsed significantly more depressive symptoms than did mothers who did not meet criteria over that time period ($t(810) = 7.052, p < .0001$).

Mothers' self-reports of anxiety on the DSSI were also averaged across the 4 waves of MUSP.

Mothers who met criteria for an anxiety disorder in the first five years of the child's life reported significantly more anxious symptoms than did mothers who did not meet criteria over that time period ($t(813) = 4.393, p < .0001$).

At the fourth wave of data collection in MUSP, mothers reported on both the frequency with which they drank alcohol since the time of their child's birth and the amount of alcohol they consumed at those times. Mothers who met diagnostic criteria for alcohol abuse in the first five years of the child's life reported greater frequency of consuming alcohol ($t(811) = 4.413, p < .0001$) and greater amount of alcohol consumed ($t(811) = 4.095, p < .0001$) than did mothers who did not meet criteria over that time period.

Finally, at the fourth wave of data collection in MUSP, mothers also reported on the frequency with which they used any "sedatives, sleeping pills, tranquilizers, anti-depressants, or other drugs" to help them relax in the last week. Mothers who met criteria for substance abuse in the first five years of the child's life reported greater frequency of using drugs to help them relax than did mothers who did not meet criteria over that time period ($t(804) = 2.589, p < .01$).

⁴ Eleven youths were missing BDI scores, thus, depressive severity component scores could not be computed for these individuals. An additional 29 youths did not have family income information available. These 40 youths did not differ from the remainder of the sample in terms of any of the relevant study variables ($p = ns$) and were omitted from remaining analyses. Thus, the sample size for final analyses was 776.

⁵ Results of simple slope analyses indicated that depressive severity differed by level of recent stress among youths with a history of an anxiety disorder and low adversity in childhood ($b = .11, t(764) = 2.76, p < .01$) and among youths without a history of an anxiety disorder and high adversity in childhood ($b = .04, t(764) = 3.31, p < .001$). Both indicated higher levels of recent stress predicting higher depressive severity. Depressive severity did not differ by level of recent stress among youths with a history of an anxiety disorder and high adversity in childhood ($b = .02, t(764) = .95, p = .35, ns$) nor among youths without a history of an anxiety disorder and low adversity in childhood ($b = .01, t(764) = .99, p = .32, ns$).

Depressive severity differed by level of childhood adversity among youths with a history of an anxiety disorder and low recent stress ($b = .11, t(764) = 2.76, p < .01$), among youths without a history of an anxiety disorder and low recent stress ($b = .11, t(764) = 2.067, p < .05$), and among youths without a history of an anxiety disorder and high recent stress ($b = .21, t(764) = 4.50, p < .001$), each indicating higher levels of childhood adversity predicting higher depressive severity. Depressive severity did not differ by level of childhood adversity among youths with a history of an anxiety disorder and high levels of recent stress, ($b = .02, t(764) = .96, p = .72, ns$).

Finally, depressive severity differed by anxiety history status among youths with high childhood adversity and low recent stress ($b = .47, t(764) = 2.96, p < .01$), among youths with high childhood adversity and high recent stress ($b = .33, t(764) = 2.536, p < .05$), and among youths with low childhood adversity and high recent stress ($b = .66, t(764) = 2.94, p < .01$), each indicating higher depressive severity among those with a history of anxiety disorder than among those without an

anxiety disorder history. Depressive severity did not differ as a function of anxiety disorder history among youths with low childhood adversity and low recent stress ($b = -.15$, $(t(764) = -.752$, $p = .45$, *ns*).