Oxford Handbooks Online

The Stress Sensitization Model

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The Oxford Handbook of Stress and Mental Health
Edited by Kate Harkness and Elizabeth P. Hayden

Subject: Psychology, Clinical Psychology Online Publication Date: Jun 2018
DOI: 10.1093/oxfordhb/9780190681777.013.16

Abstract and Keywords

The stress sensitization model was developed to explain the mechanism through which the relationship between stress and affective disorder onsets changes across the course of the disorder. The model posits that individuals become sensitized to stress over time, such that the level of stress needed to trigger episode onsets becomes increasingly lower with successive episodes. The stress sensitization model has accrued empirical support in the context of major depression and to a lesser extent in bipolar spectrum disorders. Furthermore, expanding upon the original stress sensitization model, research also indicates that early adversity (i.e., early childhood experiences) sensitizes individuals to subsequent proximal stress, increasing risk for psychopathology. In this chapter, the theoretical background underlying the stress sensitization model is reviewed, and research evidence investigating stress sensitization is evaluated. In addition, moderators and mechanisms of stress sensitization effects are reviewed, and recommendations for future research are provided.

Keywords: stress sensitization, kindling, early adversity, childhood maltreatment, life events

The nature of the relationship between stress and psychopathology has received considerable research attention. Central to this work is the observation that the relationship between stress and affective disorders changes across the course of the disorder. The stress sensitization model was formulated to explain the process through which this relationship changes: The model posits that in response to repeated exposure to affective episodes as well as external stress, individuals become sensitized to stress, such that minor (i.e., nonsevere) stressors become increasingly relevant with successive episodes (e.g., Harkness, Hayden, & Lopez-Duran, 2015; Monroe & Harkness, 2005). The stress sensitization model has accumulated support as a mechanism of the changing relationship between stress and episode onset in major depression and to a lesser extent

in bipolar spectrum disorders. Expanding upon the original stress sensitization model, research also suggests that early adversity (i.e., early childhood experiences) sensitizes individuals to subsequent proximal stress, increasing risk for psychopathology.

Importantly, stress-related forms of psychopathology, such as major depression and bipolar disorder, are often chronic, highly recurrent conditions, and are associated with significant impairment in work and in relationships, as well as high rates of morbidity and mortality (e.g., Kessler, 2012; Murray & Lopez, 1996). Thus, research evaluating the stress sensitization model has the potential to inform prevention and intervention efforts, with the goal of improving the course of illness and reducing the burdens associated with these conditions. Moreover, early adversity accounts for 30% of psychiatric disorder first onsets among US adolescents and adults (e.g., McLaughlin et al., 2012). As such, research focused on increasing our understanding of stress sensitization processes among those with a history of early adversity may inform efforts designed to prevent first onsets of stress-related forms of psychopathology. In this chapter, I will review the theoretical background underlying the stress sensitization model, examine research evidence investigating stress sensitization, review potential mechanisms underlying stress sensitization effects, and provide recommendations for future research.

Theoretical Background

Post’s Kindling Hypothesis

Post’s (1992) kindling hypothesis (herein called Post’s model) is the theoretical origin of the stress sensitization model (as applied to psychopathology). The core tenet of Post’s model (1992) is that the first episode of an affective disorder is more likely to be preceded by major psychological stressors than are subsequent episodes (Post, 1992). Post drew upon two distinct models to formulate the potential mechanisms underlying this observation: electrophysiological kindling and behavioral sensitization (e.g., Post, 1992; Post & Weiss, 1998). In the animal model of kindling, levels of electrical stimulation that were initially below the threshold needed to elicit seizures in brain tissue develop the capacity to elicit seizures after repeated applications due to progressive increases in behavioral and physiological reactivity (Goddard, McIntyre, & Leech, 1969). If electrical stimulation is repeated, seizures begin to occur autonomously of stimulation. The analog process in humans is the observation that after an initial period of sensitization to stressors, recurrences begin to occur autonomously, in the absence of stressors (e.g., Post & Weiss, 1998). In the animal model of stimulant-induced behavioral sensitization, when the same dose of a stimulant (e.g., cocaine) is repeatedly administered, animals begin to show *increased* behavioral responses (e.g., motor reactivity), with more robust increases observed when the stimulant is given in the same environmental context as prior doses

(Post, 1992). The analog process in humans is the observation that repeated stressors may elicit increasingly stronger affective and behavioral responses over time (Post, 1992).

Post (1992) drew upon research elucidating the neurobiological processes associated with kindling and sensitization to propose that changes in “gene expression,” which occur in response to electrical and chemical stimulation, as well as in response to psychosocial stressors, have long-term effects on the organism (e.g., changes in neurotransmitter and neuronal transmission), which serve to increase reactivity to future stressors as well as vulnerability to future affective episodes (p. 999). One long-term consequence of kindling and sensitization is the induction of transcription factors, including for example, the proto-oncogene c-fos, which binds at DNA sites and induces mRNAs for other substances, thereby altering gene expression (e.g., Post, 1992). Post proposed that the induction of c-fos and related transcription factors might result in long-term changes in neurotransmitters, neuropeptides, and receptors, which may lead to “long-term synaptic adaptations and memory that could last indefinitely” (p. 1002). Thus, in Post’s model, vulnerability to future stressors and affective episodes with successive recurrences was posited to occur because of “memory-like mechanisms” produced via environmentally induced changes in gene transcription (Post, 2016, p. 315). New research supporting epigenetic changes in response to the environment provides a framework for understanding these “memory-like mechanisms”—most relevant here is the assertion that epigenetic mechanisms “are likely the basis for long-term alterations in behavioral responsivity to recurrent events in sensitization” (p. 316).

Although an in-depth review of Post’s model and its mechanisms is beyond the scope of this chapter, a number of his assertions have particular relevance for understanding the stress sensitization model. First, expansions of Post’s model have implicated early adversity (i.e., early life experiences) as a mechanism through which individuals become sensitized to future proximal stressors in varied forms of psychopathology (e.g., Post, 2007, 2016; Post, Weiss, & Leverich, 1994). Specifically, given that many of the proposed changes that occur in kindling and sensitization correspond to those involved in the development of the nervous system, Post and colleagues (1994) proposed that the model could be used to understand “how early developmental experience could leave behind long-lasting residues and vulnerabilities to depression, post-traumatic stress disorder (PTSD), and other psychiatric disorders” (p. 782). Central to this formulation was the notion that long-term memory of early adversity was encoded in changes in “gene transcription,” which served to increase sensitization to subsequent stress and increase vulnerability to psychopathology. Indeed, using new research documenting the phenomenon of epigenetics and more specifically, how early adversity can give rise to epigenetic modifications, Post (2016) has refined his original formulation, positing that early adversity leads to epigenetic modifications (e.g., methylation of the gene for the glucocorticoid receptor) that serve to increase sensitivity to later stress.

Second, Post (e.g., Post, 1992; Post et al., 2003; Post et al., 1994) distinguished between two types of sensitization: (1) episode sensitization and (2) stress sensitization. Episode sensitization refers to the process through which the experience of episodes and their associated neurobiological changes result in trait vulnerabilities that predispose individuals to subsequent episodes, such that recurrences begin to emerge in the face of lower levels of stress. In stress sensitization, early life stress and stress occurring in adulthood can each serve to trigger episodes or leave behind neurobiological vulnerabilities that increase sensitivity to future stress. Importantly, in this process, each form of stress may or may not reach the threshold needed to trigger an episode, but nonetheless they can leave lasting vulnerabilities that engender stress sensitivity (e.g., Post, 2016). Thus, it is postulated that both episode sensitization and stress sensitization render individuals increasingly sensitive to lower levels of stress over time.

Third, although originally developed to explain the course of affective disorders, Post's model has been applied to anxiety disorders, including for example, panic disorder, PTSD, and obsessive-compulsive disorder, though the relevance of sensitization versus kindling processes varies across the disorders (e.g., Post & Weiss, 1998; Post, Weiss, Smith, & Li, 1997). For example, in PTSD, both kindling and stress sensitization processes may be useful in understanding the onset and progression of the disorder. Kindling processes may be used to explain the progression from flashbacks initially triggered by cues associated with the trauma to the emergence of flashbacks occurring in the absence of such cues. Stress sensitization processes may be used to explain the clinical observation that individuals who have experienced prior traumatic events tend to be more sensitive to subsequent trauma (Post & Weiss, 1998), consistent with emerging evidence (e.g., Shao et al., 2015) reviewed later in this chapter.

Fourth, Post postulated that qualities of the stressor (i.e., type, severity, and frequency) would likely shape its long-term effects (e.g., Post, 1992). For example, drawing upon the behavioral sensitization model, he proposed differences in sensitization effects as a function of the frequency of the stressor (single versus repeated); intermittent versus chronic course of the stressor; the interaction between magnitude and the frequency (repetition) of the stressor; and stressor type. Regarding the latter, Post (1992) posited that losses, particularly interpersonal ones, might have different consequences (i.e., behavioral, cognitive, neurobiological) than stressors involving threat of bodily harm, with the former most relevant for depression and the latter most relevant for PTSD. Consistent with this, research suggests that some of the stressor qualities Post proposed (e.g., type, severity, interpersonal nature) shape stress sensitization effects (see later), whereas others (e.g., repetition) remain to be investigated.

Monroe and Harkness's Critical Review of Research Supporting Post's Model

Post's model is perhaps the most influential theoretical framework guiding research on the course of affective disorders (Monroe & Harkness, 2005), as highlighted by the impressive body of empirical research evaluating it (reviewed later). In a critical examination of the research supporting the model, Monroe and Harkness (2005) called attention to the tendency for researchers in the field to misinterpret Post's model, which the authors postulated was in part due to the failure (with some exceptions) to distinguish between the two models underlying Post's model: stress sensitization and stress autonomy (see also Hlastala et al., 2000, for a similar argument). The stress sensitization model asserts that events of lower and lower severity develop the capacity to trigger episodes with successive recurrences (what Post, 1992, referred to as *sensitization*; e.g., Post & Weiss, 1998). The stress autonomy model asserts that episodes of depression occur autonomously of stress with repeated episodes (what Post, 1992, referred to as *kindling*).

To distinguish between the models, Monroe and Harkness (2005) argued that research needed to move beyond examining *whether* (or not) the relationship changes across successive episodes, but instead to examine *how* the role of stress changes. The authors distinguished between the *impact* of events, which refers to the likelihood an event will be followed by an episode (i.e., potency), versus the frequency of events, which refers to the likelihood an event will be present prior to an episode. Importantly, the stress sensitization and stress autonomy models provide a different set of predictions for how the impact and occurrence of major (i.e., severe) and minor (i.e., nonsevere) events change across the course of the disorder. The stress sensitization model predicts that the impact of major and minor events increases with successive episodes as individuals become sensitized to stress. Furthermore, the model predicts the frequency of major events decreases, whereas the frequency of minor events increases, as minor events begin to prevent major events from having the opportunity to affect episode onset due to their increasing impact along with their generally high base rate. In contrast, the stress autonomy model predicts that the impact of major and minor events decreases over the course of depression as stress loses the capacity to trigger episodes. In addition, the model predicts that the frequency of both major and minor events prior to episodes decreases as episodes become increasingly independent of events.

Thus, perhaps most important here, in defining stress sensitization in this manner and distinguishing it from the stress autonomy model, Monroe and Harkness (2005) refined the theory of stress sensitization. In doing so, the authors highlighted that although most of the extant literature supported Post's model, it could not distinguish between the stress sensitization and the stress autonomy models, suggesting a major gap in our understanding of the extent to which research supported the stress sensitization model. Moreover, Monroe and Harkness (2005) provided a lens through which to evaluate

existing research investigating the stress sensitization model, which will be adopted in the literature review presented later. Importantly, although their review focused exclusively on major depression, the concepts have been investigated in the context of other disorders (e.g., Weiss et al., 2015) and apply transdiagnostically.

Evidence for Stress Sensitization: Effect of Prior Episodes

Support for the stress sensitization model is emerging in the context of depression and bipolar spectrum disorders. In this section, research investigating the sensitizing effect of progressive episodes, as well as moderators of these effects, will be reviewed.

Depression

Early research examined Post's model using two main strategies. First, early studies focused on investigating "differences in the *proportion* [italics added]" (Monroe & Harkness, 2005, p. 424) of individuals experiencing a prior major life event in first onsets versus recurrences. Supporting Post's model, this work suggested that a greater proportion of individuals experiencing first onsets had a prior major life event, as compared to the proportion of individuals experiencing a recurrence (for reviews, see Mazure, 1998; Monroe & Harkness, 2005). Second, later studies investigated the "differential *prediction* [italics added] by [major] life stress of a first onset versus a recurrence" (Monroe & Harkness, 2005, p. 424) using the odds ratio and other statistical indices of strength. Also supporting the model, this work suggested that there was a decline in the strength of the relationship between major life stress and major depression with successive recurrences (Mazure, 1998; Monroe & Harkness, 2005).

In one of the most methodologically sophisticated and informative studies using the latter approach, Kendler and colleagues (2000) showed that the strength of the major stress–major depression association declined over the course of the first nine episodes, with the strength declining approximately 13% per episode. Interestingly, after nine episodes, the strength of the association continued to decline, but at a much slower rate of approximately 1% per episode. Importantly, follow-up analyses suggested that the decline in the association (a) reflected within-person changes rather than systematic differences between individuals with few versus many episodes; and (b) held when accounting for genetic risk and when examining exclusively major independent (i.e., uncontrollable) events.

In their critical review of the literature, Monroe and Harkness (2005) called attention to two major limitations in this field of research. First, the authors argued that as a consequence of testing Post's model using these two different strategies (i.e., differences in proportion versus differential strength), earlier and later lines of research were testing two different questions. Specifically, the authors highlighted concerns with the manner in which the odds-ratio was used and interpreted, arguing that the first-onset odds-ratio would always be larger than the recurrence odds-ratio, regardless of real changes in the relationship between major stress and major depression in first onsets versus recurrences (for details, see Monroe & Harkness, 2005). Thus, to unify the literature, Stroud and colleagues (2008) conducted a meta-analysis using a proportion difference effect size, converting the results of studies using the odds-ratio (and other indices of strength) to differences in the proportion of individuals with a prior major life event in first onsets versus recurrences. Overall, the meta-analysis provided support for Post's model (1992) model, with 11% more individuals in the first-onset group reporting a prior major life event than in the recurrence group. Of course, the 11% difference was significant, but small, leaving questions of its clinical significance. Moreover, support for the model was most evident among certain groups or under certain conditions (discussed later).

Second, Monroe and Harkness (2005) argued that few studies could distinguish between the two models underlying Post's model (1992): the stress autonomy model and the stress sensitization model (see also Hlastala et al., 2000). Thus, although Stroud and colleagues' (2008) meta-analysis unified the literature examining Post's model, the findings did not explicitly support the stress sensitization model, as both models predict that the proportion is greater in first onsets versus recurrences, but for different reasons. For the stress autonomy model, the smaller proportion for recurrences, as well as the decline in strength of the association with successive recurrences, is evidence that episodes begin to occur in the absence of stress. In contrast, for the stress sensitization model, both findings are evidence that individuals become sensitized to stress with successive recurrences, such that minor stress develops the capacity to trigger recurrences (resulting in a smaller role for major stress with successive recurrences). Thus, at the time of Monroe and Harkness's (2005) review, although the existing literature supported Post's (1992) model, most research was equivocal with regard to whether it supported stress sensitization (see also Hlastala et al., 2000).

Following Monroe and Harkness's (2005) seminal review, results supporting the stress sensitization model (over the stress autonomy model) began to emerge (Morris, Ciesla, & Garber, 2010; Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011). For example, in a 5-year longitudinal study of young adult women, Stroud and colleagues (2011) separately investigated the impact (i.e., likelihood of a major depressive episode given an event; Monroe & Harkness, 2005) and frequency (i.e., likelihood of an event given a major depressive episode; Monroe & Harkness, 2005) of major and minor events. As predicted by both models, major events were less likely to present in the 3 months prior to recurrences (versus first onsets), but there was no change in the impact of major events or the frequency of minor events (contradicting both models). Importantly, however, the impact of minor events was greater for recurrences than first onsets, providing robust support for the stress sensitization model. Notably, follow-up analyses indicated the increased impact of minor events held when accounting for the presence of a major event in the past 3 months, and when excluding months in which major events had occurred in the past 3 months from analyses (Stroud, Davila, Vrshek-Schallhorn, & Hammen, 2017), ruling out the possibility that this effect was due to the presence of recent major events (S. M. Monroe, personal communication, March 17, 2017). Thus, the increased impact of minor events observed in those with a history of depression provides robust support for the stress sensitization model.

Other evidence for the stress sensitization model comes from research demonstrating that minor events predict recurrences of major depression (Lenze, Cyranowski, Thompson, Anderson, & Frank, 2008; Monroe et al., 2006; Ormel, Oldehinkel, & Brilman, 2001). For example, Lenze and colleagues (2008) showed that the accumulation of minor events significantly predicted time to recurrence, with each additional minor event experienced increasing risk by approximately 37%. In addition, Ormel and colleagues (2001) found that minor life events were associated with increased risk of recurrences, but not first onsets (but this difference only approached significance). Thus, consistent with the stress sensitization model, this work suggests that minor events become

increasingly important with successive recurrences (Monroe & Harkness, 2005). This work, however, cannot ascertain whether this reflects an increase in the impact of minor events (i.e., as individuals become sensitized to stress, the threshold needed to trigger a recurrence is lowered), an increase in the frequency of minor events (i.e., as individuals become sensitized to stress, minor events become more likely to be present prior to episodes), or both (e.g., Stroud et al., 2011). Thus, additional research investigating changes in the impact and frequency of minor events is needed.

Few studies have investigated whether the stress sensitization model is relevant for understanding the link between chronic stress and major depression in first onsets versus recurrences. In a notable exception, Monroe and colleagues (2007) found that chronic stress was more likely to occur among individuals with many prior episodes of depression than among those experiencing first onsets. Importantly, such findings emerged when accounting for the presence of major events (which were less likely to occur prior to recurrences versus first onsets), with major events and chronic stress each independently predicting depression history. Collectively, such findings suggest that chronic stress might play a greater etiological role with successive episodes, consistent with the stress sensitization model. In contrast, however, in a sample of young adult women, chronic stress significantly predicted first onsets, but not recurrences of major depression, suggesting a diminished role for chronic stress with successive recurrences (Daley, Hammen, & Rao, 2000). Thus, research evaluating how the role of chronic stress changes with the course of depression is limited and mixed, underscoring the need for further research (e.g., Hammen, 2005).

In sum, although over a decade has passed since Monroe and Harkness's (2005) seminal review, one of their central conclusions continues to reflect the extant literature: Most research examining how the stress-depression association changes with successive recurrences is equivocal with regards to whether the findings support stress sensitization or stress autonomy interpretations. Importantly, however, of those studies that can distinguish between the stress sensitization and stress autonomy models, findings have predominately supported the stress sensitization model (e.g., Morris et al., 2010; Stroud et al., 2011). Moreover, there are hints of support from research demonstrating that minor events predict recurrences of depression (e.g., Monroe et al., 2006). These promising findings underscore the need to continue to test the stress sensitization model using prospective longitudinal studies wherein individuals are followed across first onsets and recurrences so that within-person changes in the impact and frequency of stressful life events can be examined over the course of the disorder. Given that 50% of people who have a first onset of depression will never develop a recurrence (Monroe & Harkness, 2011), conducting this type of within-person investigation with individuals who experience first onsets *and* at least one recurrence will also permit the evaluation of whether observed changes in the stress-depression association do indeed reflect stress sensitization, as opposed to spurious differences that emerge as a result of comparing individuals experiencing first onsets to those experiencing recurrences, and including

individuals in the first-onset group who will never go on to experience a recurrence (K. L. Harkness, personal communication, July 10, 2017).

Moderators of Stress Sensitization Effects

Surprisingly, few studies have investigated factors that moderate stress sensitization effects, and most of the existing studies cannot speak to whether the factors identified moderate stress sensitization or stress autonomy mechanisms (exceptions are highlighted).

Characteristics of the Sample

In a meta-analytic review that tested Post's model by comparing the proportion of individuals experiencing first onsets who experienced a severe life event prior to episode onset to the proportion of individuals experiencing recurrences who experienced a severe life event prior to episode onset (i.e., the first onset/recurrence differential), three sample characteristics—age, gender, and sample type (clinical versus community sample)—were identified as moderators (Stroud et al., 2008). First, Post's model was supported to a greater extent as the mean age of the sample increased, suggesting that perhaps developmental stage or age moderates changes in the stress-depression association across successive episodes. However, this finding may have been an artifact of comparing a group of individuals experiencing a first onset to a group of individuals experiencing any number of recurrences: given that episode number likely increases with age, Post's model would predict that the first onset/recurrence differential would be larger in older samples simply because the recurrence group will have experienced a greater mean number of episodes. Second, as the percentage of women in the sample increased, support for Post's model weakened. This may indicate that Post's model is less applicable to women than men, thereby suggesting that the mechanisms through which the stress-depression association changes across successive episodes varies according to gender. Alternatively, women may have experienced higher rates of severe life events prior to episode onsets (versus men; a hypothesis supported by prior work; e.g., Kendler, Thornton, & Prescott, 2001). As a result, if severe events retained their capacity to trigger episodes, consistent with the stress sensitization model, the first onset/recurrence differential would be smaller in women than in men, not because of gender differences in the underlying mechanisms, but due to gender differences in rates of precipitating events. Third, support for Post's model was found in patient, but not community samples, an effect that may have been driven by patient samples experiencing a higher mean number of recurrences or more severe depression, as compared to community samples, or biases associated with treatment seeking. Thus, it will be important for future work to investigate whether age, gender, and sample type moderate Post's model, or whether such moderators reflect methodological concerns. In addition, the meta-analytic findings do not distinguish between the stress sensitization and stress autonomy models, and thus,

whether such factors moderate stress sensitization effects remains an important question for future research (see Stroud et al., 2008).

Two studies have examined whether genetic risk/family history affects the stress–depression relationship across successive episodes. Although both studies have found that changes in the relationship occur as a function of genetic risk/family history (defined differently in each study), the results conflict with regards to whether stress sensitization and stress autonomy mechanisms are most relevant to those at high versus low risk. Kendler et al. (2001) found that strength of the stress-depression association declined with successive recurrences among all women, with the exception of those at highest genetic risk (defined as having a monozygotic co-twin with a lifetime history of major depression), suggesting that individuals with high genetic risk may be "prekindled" even prior to a first onset. However, given that a decline in the strength of the major stress-major depression association could reflect a stress sensitization or stress autonomy pattern (Monroe & Harkness, 2005), whether those with highest genetic risk are "prekindled" (episodes occur independently of stress even in the absence of a prior history of depression) or "presensitized" (episodes occur at low levels of stress even in the absence of a prior history of depression) remains an important question for future research. Contradicting these findings, a cross-sectional study found that individuals with major depression who had a *positive* family history of major depression (i.e., immediate family member with major depression) and who did not have a major preonset life event had experienced significantly more lifetime episodes than depressed individuals with a *positive* family history and *with* a major preonset life event (Monroe, Slavich, & Gotlib, 2014). Interestingly, however, among individuals with a *negative* family history, those with and without a major preonset event did not differ in number of lifetime episodes. This suggests that kindling (stress autonomy) and stress sensitization mechanisms may be most relevant for those with a positive family history of depression (and as discussed by the authors, perhaps, but not necessarily among those at higher genetic risk). Thus, although the extant literature does not provide a consistent picture of how genetic risk/family history shapes stress sensitization effects, and does not distinguish between the stress sensitization and stress autonomy models, there are hints that genetic risk/family history may modify stress sensitization effects.

Characteristics of the Events

In accord with Post's (1992) model, most research has focused on whether the relationship between stress and depression in first onsets versus recurrences varies according to event type, including severity level, independence (i.e., controllability), focus, and interpersonal nature. In terms of event independence, two studies have examined whether the etiological significance of major events for first onsets versus recurrences varies for independent (i.e., uncontrollable) versus dependent (i.e., caused in part by the person's actions or behaviors) events. First, Monroe et al. (2007) showed that the frequency of major dependent events decreased with a history of depression (supporting the stress sensitization and stress autonomy models), but the frequency of major independent events was unrelated to a history of depression. Second, Stroud et al.

(2011) showed that the impact of major independent events was greater than the impact of major dependent events, regardless of history of depression (contradicting both models). In addition, although all major events were less likely to be present prior to first onsets than recurrences (consistent with both models), the frequency of major independent events *increased* relative to the frequency of dependent major events (for recurrences versus to first onsets). Rather than indicating that the frequency of independent major events increased with a history of depression, this finding suggests that the frequency of major independent events declined less from first onsets to recurrences, as compared to the frequency of major dependent independent events. Taken together, findings from both studies indicate that major independent events may be particularly relevant for recurrences (Monroe et al., 2006; Stroud et al., 2011), but they do not provide evidence that individuals may be especially sensitized to independent events.

For minor events, results are also mixed and limited with regard to whether stress sensitization effects are stronger for independent or dependent events. Supporting the stress sensitization model, results of a longitudinal study of young adult women showed that the impact of minor independent events increased significantly more strongly than the impact of minor dependent events with a history of depression (Stroud et al., 2011). Such findings suggest that as individuals become sensitized to stress, events of lower severity develop the capacity to trigger episodes, with the threshold lowered more substantially for independent relative to dependent events. In addition, findings from two studies suggest that independence may shape the relevance of minor events for recurrences, but such studies did not directly test whether independence moderated stress sensitization effects (i.e., whether changes in the impact of minor events across successive recurrences were modified by independence). Monroe et al. (2006) found that minor independent, but not dependent, events predicted recurrences of depression (effects were also modified by focus [see later] and medication status). In contrast, other evidence suggests that sensitization effects may be stronger for minor dependent events, with one investigation showing that minor dependent, but not independent, events predicted time to recurrence in psychotherapy patients (Lenze et al., 2008).

Two other dimensions of events may affect sensitization effects. First, for minor events, evidence suggests that minor subject-focused (i.e., events that directly occur to the participant or jointly to the participant and someone else), but not other-focused, events predict recurrences (effects were further modified by independence in both studies and medication status in one study; Lenze et al., 2008; Monroe et al., 2006). Although such findings suggest that subject-focused events may have implications for recurrences, because changes in the impact and occurrence of events across successive episodes were not examined, whether individuals may be particularly sensitized to subject-focused events remains a question for future work (e.g., Monroe et al., 2006). Second, the interpersonal nature of events, including specifically whether the event is a relationship loss (or not), may influence sensitization effects. For example, Slavich and colleagues (2011) showed that individuals with a history of depression may be *selectively sensitized* to events involving interpersonal loss (e.g., death of a close other or relationship

dissolution): Individuals with a greater number of prior depressive episodes developed a recurrence following lower levels of stress involving interpersonal loss (but not following lower levels of nonloss stress). In contrast, however, a second study showed that the impact and frequency of major and minor interpersonal events, and relationship loss events specifically, did not vary as a function of depression history (Stroud et al., 2011).

Summary

In sum, given the mixed and limited evidence, it is clear that research designed to elucidate moderators of stress sensitization effects is needed. In terms of sample characteristics, although potential moderators have been identified, including age, gender, sample type, and family history/genetic risk, the extant literature cannot distinguish between the stress autonomy versus stress sensitization models, and thus, whether such characteristics moderate stress sensitization effects is unknown. In terms of event characteristics, for major events, limited, but converging, evidence suggests that although independent events may be etiologically relevant for recurrences, individuals do not appear to be especially sensitized to independent events (Monroe et al., 2007; Stroud et al., 2011). For minor events, however, individuals appear to be particularly sensitized to independent events (Stroud et al., 2011). In addition, although minor subject-focused (versus other-focused; Monroe et al., 2006) events appear to predict recurrences, whether event focus shapes sensitization effects remains to be examined. Finally, for both major and minor events, findings are mixed regarding whether interpersonal status, and relationship loss specifically, shape sensitization effects, as some evidence suggests that individuals may be particularly sensitized to such events (Slavich et al., 2011), whereas other work suggests that such events retain their etiological significance with a history of depression (Stroud et al., 2011). It will be important for future work to continue to identify who is most vulnerable to stress sensitization, and under what circumstances, with the goal of informing efforts to prevent recurrences of depression.

Bipolar Spectrum Disorders

Overall, the literature examining whether and how the stress–episode relationship changes across successive episodes among individuals with bipolar disorder has produced mixed findings and is relatively small (Bender & Alloy, 2011; Hlastala et al., 2000). In the most recent critical review of the literature, Bender & Alloy (2011) noted that only 8 of 14 studies supported Post’s model. Furthermore, among the four studies that were the strongest methodologically, three did not support Post’s model (Dienes, Hammen, Henry, Cohen, & Daley, 2006; Hammen & Gitlin, 1997; Hlastala et al., 2000; Swendsen, Hammen, Heller, & Gitlin, 1995). Findings from two of those studies, however, are relevant for understanding the potential role of stress sensitization in bipolar disorders. First, in a 2-year longitudinal study of outpatients with bipolar 1 disorder, among those with a higher number of lifetime episodes (9 or more), 76% had a major life event in the 6 months prior to onset, compared to 45% among those with a lower number

of lifetime episodes (0–8 episodes), contradicting Post's model (Hammen & Gitlin, 1997). However, the impact of major events (defined as time between the occurrence a major event and episode onset) was also *greater* among individuals with a *greater* number of lifetime episodes than among those with fewer lifetime episodes. Consistent with the stress sensitization hypothesis, this suggests that major events may have become more potent with successive episodes (for a similar interpretation, see Hlastala et al., 2000). Second, in a cross-sectional study of patients with bipolar 1 disorder unique in its examination of major and minor stressors, and consequently particularly informative with regards to testing stress sensitization (versus stress autonomy), lifetime episode number did not predict stress levels (defined as high [presence of at least one major event], moderate [presence of at least one minor event, no major events], low [no major or minor events]) prior to episodes, contradicting both the stress sensitization and stress autonomy models (Hlastala et al., 2000).

Importantly, however, in their review, Bender and Alloy (2011) argued that it was too early to draw conclusions from this body of work, because most of the "literature suffers from serious methodological limitations," such as using self-report checklist measures of stress, relying on long retrospective recall intervals, and examining unipolar and bipolar patients within the same analyses (p. 393). Furthermore, the authors noted that existing research had not examined depressive and (hypo)manic episodes separately, and as a result, it was unclear whether effects were specific to episode type and/or specific types of events (i.e., positive versus negative events). Finally, at the time of the review, because only one study had examined the role of minor events (Hlastala et al., 2000), few findings could differentiate between the stress autonomy and stress sensitization models.

Weiss and colleagues (2015) addressed many of these concerns in a prospective longitudinal study of young adults with bipolar spectrum disorders. Consistent with the stress sensitization model, more lifetime depressive episodes predicted a higher level of minor *negative* events prior to depressive episodes (accounting for the number of events in the within-person control period). Similarly, more lifetime hypomanic episodes predicted a higher level of minor *positive* events prior to hypomanic episodes (accounting for the number of events in the within-person control period). Contradicting both the stress sensitization and stress autonomy models, however, the impact of major and minor events did not change across successive episodes. Thus, the findings were partially consistent with the stress sensitization model, and they suggested that effects varied according to event type and episode polarity.

Research on additional moderators of stress sensitization effects in the context of bipolar disorder is scarce. Bender and Alloy (2011) identified three potential moderators that merit investigation based upon preliminary evidence: age, age of initial bipolar disorder onset, and genetic risk for bipolar disorder. Regarding the latter, one study found that patients with bipolar disorder who had a family history of affective disorder had significantly lower levels of stress in the year prior to initial onset, as compared to patients with bipolar disorder who did not have this history (Johnson, Andersson-

Lundman, Aberg-Wistedt, & Mathe, 2000). Clearly, research examining factors that modify stress sensitization effects in the context of bipolar disorder is an important question for future work.

In sum, although support for the stress sensitization model is emerging (Weiss et al., 2015), few studies (a) can distinguish between the stress sensitization and stress autonomy models; (b) can speak to how the role of stress changes across successive episodes (i.e., changes in impact, frequency, or both); (c) can address whether effects differ according to episode polarity (depressive versus hypo[manic] episodes) and event type (e.g., positive versus negative events); and (d) can elucidate moderators of stress sensitization effects (e.g., genetic risk; see Bender & Alloy, 2011). A priority for future research will be to conduct studies that evaluate each of these questions with the goal of rigorously testing the stress sensitization model in the context of bipolar disorder (e.g., Bender & Alloy, 2011).

Evidence for Stress Sensitization in Different Forms of Psychopathology: Effect of Early Adversity

Consistent with the stress sensitization model, research suggests that early adversity (i.e., early childhood experiences; e.g., childhood abuse and neglect, parental loss) increases individuals' sensitivity to later proximal stress, thereby increasing risk for depression, bipolar disorder, anxiety disorders, and substance-related outcomes, as well as the broad dimensions of internalizing and externalizing psychopathology. In this section, research exploring the sensitizing effect of early adversity, and factors that shape this effect, will be reviewed.

Depression

Supporting the stress sensitization model, research indicates that, as compared to individuals without a history of early adversity, those who have experienced early adversity are more likely to develop depression in the face of recent stress (e.g., Harkness & Lumley, 2008). For example, in a large epidemiological national sample of adults, the association between past-year major stressors and major depression was stronger among those who had experienced early adversity, such that major stressors were associated with a two-fold increase in the 12-month risk of depression onset among those who had experienced three or more early adversities as compared to those who not experienced early adversity (McLaughlin, Conron, Koenen, & Gilman, 2010). Although examined in fewer investigations, early adversity also appears to render individuals more sensitive to recent chronic stress. For instance, one study showed that the association between past-year chronic stress and depressive symptoms at age 20 was stronger among adults who had experienced higher levels early adversity, as compared to those who had experienced lower levels of early adversity (Starr, Hammen, Conway, Raposa, & Brennan, 2014). Similar findings for the sensitizing effect of early adversity have been obtained in the context of depressive symptoms (Shapero et al., 2014) and dysthymic disorder (Dougherty, Klein, & Davila, 2004).

Importantly, research also indicates that adolescents and adults who have experienced early adversity are more likely to develop depression in the face of lower levels of recent stress (e.g., Hammen, Henry, & Daley, 2000; Harkness, Bruce, & Lumley, 2006; La Rocque, Harkness, & Bagby, 2014; Rudolph & Flynn, 2007), providing robust support for the stress sensitization model. For example, Hammen and colleagues (2000) demonstrated that young women with a history of early adversity were more likely to experience a subsequent onset of major depression in the context of low levels of recent acute stress, as compared to women without such a history. In contrast, under high levels of recent stress, individuals had an increased likelihood of a major depressive episode onset, regardless of level of early adversity. This suggests that, in accord with the stress sensitization model, low levels of recent stress were sufficient to trigger depression among those with a history of early adversity, but severe stress retained the capacity to do so when it occurred (Monroe & Harkness, 2005). Notably, evidence for the relation between lower levels of stress and depression has emerged (a) in the context of varied types of early adversity, including for example, childhood maltreatment (e.g., Harkness et al., 2006; La Rocque et al., 2014) and family disruption (e.g., Rudolph & Flynn, 2007); (b) when conceptualizing recent acute stress continuously (sum of severity scores; e.g., Hammen et al., 2000; Harkness et al., 2006; La Rocque et al., 2014) and categorically (i.e., presence or absence of event; e.g., La Rocque et al., 2014); and (c) when accounting for the effects of recent chronic stress (e.g., Hammen et al., 2000; Harkness et al., 2006) and history of prior depressive episodes (e.g., Hammen et al., 2000; La Rocque et al.,

2014), ruling out the possibility that the observed stress sensitization effects were due to depression history or high levels of recent chronic stress.

Interestingly, the sensitizing effect of early adversity may vary according to several factors, including, for example, developmental stage (La Rocque et al., 2014; Rudolph & Flynn, 2007) and gender (Rudolph & Flynn, 2007). In one study, evidence for sensitization effects were observed among depressed adolescents (aged 12–17), but not among depressed emerging adults (aged 18–29), with a history of emotional maltreatment (La Rocque et al., 2014). In a second study, stress sensitization effects were evident in pubertal girls (but not pubertal boys) and prepubertal boys (but not prepubertal girls) who had experienced family disruption, suggesting that during adolescence, developmental stage and gender may shape sensitization effects.

Early adversity also appears to sensitize individuals to certain types of recent stress. Notably, results of two studies indicated that early adversity might sensitize individuals to independent, but not dependent, events. Harkness and colleagues (2006) found that adolescents with a history of childhood maltreatment (i.e., childhood abuse or neglect) reported lower levels of independent, but not dependent, recent acute stress, prior to first onsets of depression, as compared to those without such a history. Similarly, La Rocque et al. (2014) demonstrated that adolescents with a history of emotional abuse reported a lower severity level of recent independent acute stress, prior to depression onset, and were less likely to have experienced an independent event prior to onset, as compared to adolescents without a history of emotional abuse. In contrast, there was not evidence that emotional abuse sensitized adolescents to the effects of recent dependent stress. Importantly, however, such findings may be unique to the developmental period of adolescence given that adolescents report significantly higher levels of independent events than adults (Harkness et al., 2010), and that many of the major events faced by adolescents occur to their parents (e.g., parental divorce), independent of adolescents' behavior (e.g., Harkness et al., 2006). Thus, whether early adversity sensitizes older adults to independent, but not dependent, stress is an important question for future research.

Sensitization effects have also been found to be unique to recent interpersonal acute stress, such that pubertal girls and prepubertal boys with a history of family disruption were more likely to experience depression in the face of low levels of recent interpersonal, but not noninterpersonal, acute stress. Of interest, given that the early adverse experience (i.e., family disruption) was interpersonal, such findings fit with the notion that individuals may be *selectively sensitized* to recent stress (Slavich et al., 2011), with sensitization effects limited to recent stressors that match the early adverse experience. Consistent with this, Slavich and colleagues (2011) demonstrated that individuals who experienced early parental loss or prolonged separation became depressed following lower levels of stress prior to onset, but sensitization effects were unique to stressors involving interpersonal loss. In light of such findings, it is tempting to speculate that selective sensitization effects may provide an additional explanation for

why adolescents who experience early adversity are sensitized to independent (Harkness et al., 2006; La Rocque et al., 2014) and interpersonal stress (Rudolph & Flynn, 2007), given early adversity is also often interpersonal and independent.

Findings also suggest that the sensitizing effect of childhood maltreatment may vary according to the type of maltreatment. Indeed, two separate investigations provide converging evidence that emotional, but not physical or sexual, abuse sensitizes individuals to recent acute stress (LaRocque et al., 2014; Shapero et al., 2014). Whether the sensitizing effect of early adversity varies for other types of early adversity (e.g., parental loss, parental divorce) beyond childhood maltreatment remains a question for future research.

The sensitizing effect of early adversity has also been found to vary as a function of the presence of a history of anxiety disorder (Espejo et al., 2007), depression history (Harkness et al., 2006), and neuroticism (Kendler et al., 2004). Although existing research has largely focused on whether early adversity increases vulnerability to subsequent acute stress, one investigation showed that the sensitizing effect of early adversity on recent chronic stress was moderated by genetic variation, such that the association between past-year chronic stress and depressive symptoms was stronger among those with a history of high levels of early adversity (versus low levels), but only among those who were A homozygotes on the CRHR1 genotype or short-allele homozygotes on 5-HTTLPR genotype (Starr et al., 2014). More research is needed to understand whether early adversity sensitizes individuals to recent chronic stress and to elucidate factors that modify this effect.

Bipolar Spectrum Disorders

Surprisingly, only two studies have examined the sensitizing effect of early adversity (after accounting for the number of prior episodes) using objective contextual stress interviews. In one investigation, adults with a diagnosis of bipolar 1 disorder who had experienced early adversity reported lower levels of acute stress prior to recurrence, as compared to those without this history (Dienes et al., 2006). In a second investigation of adults who predominately had a diagnosis of bipolar II disorder, early adversity did not accelerate time to onset following recent majors and minor events, but those who had experienced more early adverse events had fewer negative events prior to a depressive episode (when considering all events regardless of severity), suggesting that greater early adversity was associated with developing depression in the context of fewer events (Shapero et al., 2017). However, when the frequency of major and minor events was examined separately, those who had experienced more early adverse experiences had fewer minor (but not major) events prior to depressive episode onset, contradicting the stress sensitization model. Interestingly, there was not evidence for an association between early adverse events and the frequency of positive events prior to hypomanic episodes. Thus, there is some limited support for stress sensitization, though the effects

appear to vary according to the type of recent stress, episode polarity, and the role of stress investigated.

Anxiety Disorders

Little research has addressed whether early adversity sensitizes individuals to recent stress in the context of anxiety disorders. In a notable exception, one investigation found support for the sensitizing effect of early adversity, though effects varied for men and women. For men and women, the association between past-year major stressors and 12-month risk for PTSD and other anxiety disorders (e.g., social phobia, panic disorder) onset was stronger among those who had experienced early adversity, supporting stress sensitization; however, early adversity was associated with increased risk of onset following recent minor events among men, but not women (McLaughlin, Conron, et al., 2010). Early adversity may also sensitize individuals to subsequent traumatic events (i.e., pipeline explosion), with greater PTSD symptoms following the event among those with a history of adversity, as compared to those without this history (Shao et al., 2015).

Substance-Related Outcomes

Limited evidence suggests that stress sensitization processes may be relevant to understanding the role of recent stress in substance-related outcomes. For example, one investigation showed that childhood maltreatment may render individuals more sensitive to chronic stressors, such as neighborhood physical disorder (i.e., presence of vacant and damaged buildings), with the presence of neighborhood disorder associated with greater risk for at-risk alcohol use, but only among those with greater exposure to childhood maltreatment (Keyes, McLaughlin, et al., 2012). In addition, research indicates that childhood maltreatment may have implications for the relation of stress to other substance-related outcomes, including at-risk alcohol use (Young-Wolff, Kendler, & Prescott, 2012), likelihood of smoking cessation (Smith, Oberleitner, Smith, & McKee, 2016), and disordered drug use (Myers, McLaughlin, Wang, Blanco, & Stein, 2014), particularly among women (Myers et al., 2014; Smith et al., 2016; Young-Wolff et al., 2012). An important question for future research in this area will be to examine whether childhood adversity is associated with higher risk in the context of *lower* levels of stress, consistent with the stress sensitization model.

Internalizing and Externalizing Psychopathology

Recent work has implicated stress sensitization as a mechanism through which early adversity contributes to the broad dimensions of externalizing and internalizing psychopathology. Meyers and colleagues (2015) demonstrated that childhood maltreatment potentiated the effect of subsequent exposure to 9/11 during adulthood on risk for developing internalizing and externalizing psychopathology. Although research on

moderators is scarce, results of one investigation showed that two genetic polymorphisms (the CRHR1 genotype and 5-HTTLPR genotype) moderated the sensitizing effect of early adversity on internalizing symptoms (Starr et al., 2014). Stress sensitization effects may also have relevance for intimate partner violence, with results from a large epidemiological study suggesting that early adversity increased the potency of past-year stressful life events on risk of perpetrating among adult men and women (Roberts, McLaughlin, Conron, & Koenen, 2011).

Summary

In sum, the sensitizing effect of early adversity has received support in the context of several disorders. Despite this, there are significant gaps in our understanding of the ways in which early adversity impacts the stress-depression association. First, akin to the literature addressing the changes in the stress-depression association with successive episodes (e.g., Monroe & Harkness, 2005), with few exceptions, the extant literature cannot ascertain whether early adversity increases the impact of stress, the likelihood that stress is present prior to episodes (i.e., frequency), or both. For example, research demonstrating that there is a stronger association of stress and depression among those with versus without a history of early adversity does not reveal whether this reflects increases in impact, frequency, or both. Second, most existing research demonstrating that individuals with early adversity develop psychopathology in the face of lower levels of stress has collapsed major and minor events into one score reflecting total stress either by summing the severity ratings of events (e.g., Dienes et al., 2006; Hammen et al., 2000; La Rocque et al., 2014; Rudolph & Flynn, 2007) or by taking the average threat rating (e.g., Harkness et al., 2006; Slavich et al., 2011). Thus, although we have evidence that individuals with a history of early adversity develop psychopathology in the face of lower *cumulative* and *average* levels of stress (as compared to those without this history), we know little about whether those with a history of early adversity develop psychopathology in the face of exclusively *minor* stressful life events (for an exception, see McLaughlin, Conron, et al., 2010). Future research investigating whether individuals with early adversity develop psychopathology in the face of even minor events (accounting for the presence of major events; S. M. Monroe, personal communication, March 17, 2017) would complement existing evidence for stress sensitization.

In addition, as noted by others (e.g., Harkness et al., 2006), with few exceptions, the literature demonstrating that individuals with early adversity develop psychopathology in the face of lower levels of stress (as compared to individuals without such history) cannot ascertain whether the findings reflect stress sensitization or stress autonomy processes (for an exception, see Harkness et al., 2006). That is, it could be the case that individuals with early adversity develop depression in the face of lower levels of stress (consistent with the stress sensitization model) or in the absence of stress (consistent with the stress autonomy model; Harkness et al., 2006). Thus, one challenging next step is to investigate whether the findings which appear to suggest that those with early adversity develop

psychopathology in the face of lower levels of stress indeed reflects a stress sensitization process.

Neurobiological and Psychosocial Mechanisms Underlying Stress Sensitization Effects

Surprisingly, relatively little is known about the underlying mechanisms of stress sensitization. Existing research and theory have focused on (a) neuroendocrine reactivity and other neurobiological mechanisms (e.g., neural structure and function, genetics) and (b) cognitive and other psychological mechanisms (e.g., personality, rumination). Importantly, however, although research and theory have implicated mechanisms in an array of domains, prior work has not explicitly tested whether such mechanisms *mediate* stress sensitization effects. That is, although prior episodes and early adversity have each been shown to be related to several potential mechanisms, it is not known whether such mechanisms are in turn related to a decrease in the threshold of stress needed to trigger episode onset (i.e., stress sensitization). In addition, most work has focused on depression, and thus, research is needed to evaluate the mechanisms underlying stress sensitization in the context of other forms of psychopathology. In this section, potential mechanisms underlying the sensitizing effects of prior episodes and early adversity will be reviewed separately, but given overlap in the proposed mechanisms for each type of sensitization, an important question for future research is to investigate the extent to which the underlying mechanisms are shared versus distinct.

Mechanisms Underlying the Sensitizing Effect of Prior Episodes

One potential neurobiological mechanism of stress sensitization is alterations in hypothalamic-pituitary-adrenal (HPA) axis regulation. Although HPA dysregulation has not been directly examined as an underlying mechanism, several studies support its potential role. First, currently depressed individuals with a history of two or more prior episodes of recurrence show greater cortisol reactivity to pharmacological challenges than depressed individuals experiencing fewer episodes (e.g., Gervasoni et al., 2004). Second, HPA axis responses to laboratory-based stressor tasks, such as the Trier Social Stress Task (TSST), appear to vary as a function of depression history. For example, in one study of young adults, greater cortisol reactivity predicted increases in depressive symptoms more strongly among those with more prior episodes of depression (Morris, Rao, & Garber, 2012). Notably, results from this study also suggested that the HPA axis might become increasingly sensitized to low levels of stress with successive episodes. Specifically, higher levels of cortisol in the anticipatory period prior to the beginning of

TSST predicted increases in subsequent depressive symptoms, with a stronger link observed among those with more prior episodes. Moreover, individuals with high levels of cortisol in the anticipatory period and more prior episodes had the greatest risk for recurrence during the follow-up. This suggests that cortisol reactivity in response to relatively low levels of acute stress (i.e., anticipating an upcoming stressor) may be a mechanism through which individuals become sensitized to stress with repeated episodes (Morris et al., 2012). Interestingly, other evidence suggests that changes in the HPA axis response to stress as a function of depression history may only occur among individuals who experience a stressful life event prior to depressive episode onset. Mazurka and colleagues (2015) showed that among youth experiencing their first depressive episode, those who experienced a life event (of any severity) prior to episode onset exhibited blunted cortisol reactivity in response to the TSST (in comparison to youth without a history of depression), whereas youth experiencing a recurrent episode who experienced a prior life event exhibited steeper cortisol recovery (in comparison to youth without a history of depression or youth experiencing a first onset). In contrast, among those without precipitating life events, there were no differences in cortisol reactivity or recovery as a function of depression history. This suggests the neuroendocrine mechanisms underlying stress sensitization may vary according to depression history, and whether (or not) episodes are precipitated by life events.

Finally, there is evidence that heightened cortisol reactivity to low stress may be associated with increases in depressive symptoms over time, regardless of depression history. Morris and colleagues (2012) showed that accounting for depression history, young adults who exhibited higher cortisol reactivity to a low stress control TSST (which involved performing the task without being evaluated) experienced increases in depressive symptoms over the 6-month follow-up, whereas cortisol reactivity in the high-stress TSST (which contained a social evaluative component) was not associated with subsequent depressive symptoms. In accord with the stress sensitization model, these intriguing findings suggest that heightened cortisol reactivity to minor stress may be a mechanism through which low levels of stress contribute to depression.

Given their role in regulation of behavioral and neuroendocrine responses to stress, and their potential to be damaged by stress exposure (via high levels of glucocorticoids; e.g., McEwen, 2007), structural abnormalities in the medial prefrontal cortex (mPFC) and the hippocampus have also been proposed as potential mechanisms of stress sensitization. Indeed, research indicates that the volume of the hippocampus is smaller in recurrently depressed patients, as compared to both never-depressed individuals (MacQueen et al., 2003; Sheline, Sanghavi, Mintun, & Gado, 1999) and individuals experiencing a first onset (e.g., MacQueen et al., 2003). Interestingly, hippocampal volume is negatively correlated with total time depressed, but not age, suggesting that hippocampal volume loss may occur as a function of depression, rather than increasing age (Sheline et al., 1999). Importantly, some research suggests progressive changes in these regions with successive episodes. For example, in a cross-sectional study of currently depressed and never-depressed adults, reduced volume in the hippocampus, and in particular the dentate gyrus, as well as cortical thinning of the left mPFC, were related to a greater

number of past depressive episodes (Treadway et al., 2015). Future longitudinal research is needed to examine whether progressive changes in these areas over the course of depression mediate increasing sensitivity to stress with successive episodes, or whether individual differences in hippocampal volume and cortical thickness in the mPFC represent biological markers of risk for recurrent depression, present prior to first onsets (e.g., Treadway et al., 2015).

Cognitive mechanisms have also been identified. For example, Segal and colleagues (1996) proposed a model in which stress and depressive episodes lead to changes in information processing, thereby reducing the level of stress needed to trigger a recurrence. Specifically, the model posits that stress and depressive episodes strengthen the connections between the nodes of a depressogenic associative network, containing events, emotions, and memories that have been linked with depression. As a result, the accessibility of elements in the network (i.e., depressogenic patterns of thinking and information processing) progressively increases, and the threshold for activating the patterns progressively decreases, such that an increasingly minor level of dysphoria and stress develop the capacity to trigger recurrences. Consistent with the notion that the link between negative cognitions and depressive symptoms increases with successive episodes, findings from a recent study revealed that high levels of dysfunctional attitudes predicted increases in depressive symptoms among individuals with a history of depression, but not among never-depressed individuals (Morris, Kouros, Fox, Rao, & Garber, 2014). An important question to address in future work is whether changes in the accessibility of depressogenic patterns of information processing, and in the activation threshold of such patterns, contribute to stress sensitization effects.

In a recently developed cognitive model, the two-factor sensitization model, Farb and colleagues (2015) posited that sensitization occurs because dysphoric attention (i.e., fixation on negative life events) and dysphoric elaboration (i.e., via rumination) become increasingly “coupled” with each episode, such that minor stress develops the capacity to trigger dysphoric elaborations, thereby increasing risk for relapse/recurrence. In this model, fixation on the negative aspects of stressful events leads to dysphoric elaboration, a process driven by rumination; through rumination the negative aspects of events are integrated into negative schema. With each episode of depression, fixation leads to increases in rumination, further solidifying global negative schema. Increases in rumination, in turn, serve to enhance fixation, reinforce negative schema, and amplify the perceived implications of increasingly more minor stressful life events. Though not designed to explicitly test this model, results from a recent study provided support for rumination as a mechanism of stress sensitization (Ruscio et al., 2015). Specifically, rumination in response to daily stressful life events mediated the link between perceived stressfulness and symptoms of anxiety and depression. Interestingly, this meditational pathway was stronger among those diagnosed with major depression and generalized anxiety disorder (GAD), as compared to healthy controls, and most events were minor. This suggests that increased rumination following even minor events may increase

vulnerability to depressive and anxiety symptoms, particularly in those experiencing major depression and GAD. Future research is needed to evaluate whether this link strengthens with successive episodes and whether fixation plays a role in this process, in accord with the central thesis of the two-factor model.

Personality changes, which occur as a result of depressive episodes, may also lead to stress sensitization. Specifically, progressive increases in neuroticism (with successive episodes) are theorized to render individuals increasingly sensitive to lower and lower levels of stress, thereby increasing risk for recurrences (e.g., Ormel et al., 2001). Supporting this, results of one study indicated that neuroticism and minor stressful life events were each more strongly associated with recurrences than first onsets (Ormel et al., 2001). In addition, Kendler and colleagues (1993) demonstrated that even after accounting for levels of neuroticism prior to first onsets, at the 1-year follow-up, neuroticism was higher among those who had experienced an episode of depression during the follow-up period, as compared to those who did not. Thus, depressive episodes may lead to increases in neuroticism, which in turn may increase daily stress reactivity (Bolger & Zuckerman, 1995). The next step is to examine whether increases in neuroticism with successive episodes serves a pathway through which individuals become progressively sensitized to stress.

Mechanisms Underlying the Sensitizing Effect of Early Adversity

Substantial evidence indicates that early adversity leads to lasting alterations in stress-responsive physiological and neuroendocrine systems among children, adolescents, and adults (e.g., Cicchetti & Rogosch, 2012; Tarullo & Gunnar, 2006); in turn, such disruptions result in the inability of such systems to adaptively respond to subsequent stress, permitting lower levels of stress to trigger episode onsets (i.e., stress sensitization; e.g., Heim & Nemeroff, 2001; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Consistent with this, prior work has shown that early adversity leads to disruptions in HPA axis regulation, with individuals who experienced early adversity exhibiting different patterns of HPA axis functioning, including both hyper- and hypocortisolism (e.g., Cicchetti & Rogosch, 2012; Tarullo & Gunnar, 2006). For instance, one study of adults found that those with a history of moderate to severe childhood maltreatment exhibited diminished cortisol reactivity to a laboratory-based stressor task, as compared to those without such history (Carpenter et al., 2007).

The second line of research that supports alterations in stress response systems as a mechanism of stress sensitization is abundant evidence indicating that such alterations are concurrently and longitudinally associated with internalizing psychopathology among children, adolescents, and adults (e.g., Cicchetti & Rogosch, 2001; Lopez-Duran, Kovacs, & George, 2009). Stronger evidence, however, comes from a limited number of

prospective studies showing that alterations in stress response systems mediate the prospective relation between early adversity and internalizing psychopathology. For example, findings from one study demonstrated that greater early adversity within the family environment (e.g., low levels of family cohesion, poor parent relationship quality) and low socioeconomic status each predicted greater stress reactivity (assessed via apprehension to venipuncture and ear puncture) in young adulthood, which in turn predicted the subsequent onsets of major depression and anxiety disorders (McLaughlin, Kubzansky, et al., 2010). Given this initial support for disruptions in stress response systems as a mechanism of stress sensitization, a critical next step will be to examine whether such disruptions engender increased sensitivity to low levels of stress among those with a history of early adversity.

Cognitive vulnerabilities have also been proposed. Segal and colleagues (1999) posited that exposure to early adversity strengthens the connections between a network of thoughts, events, and emotions associated with depression, which serves to increase the accessibility of depressogenic patterns of thinking, and lower the threshold for activating such patterns, resulting in stress sensitization. Cognitive models also implicate early adversity in the development and consolidation of cognitive vulnerabilities (e.g., schema, cognitive styles, dysfunctional beliefs), which are posited to shape the interpretation of subsequent stressors, thereby increasing vulnerability in the face of stress (e.g., Beck, 1967; Rose & Abramson, 1992). Indeed, considerable evidence has shown that early adversity (particularly childhood maltreatment) contributes to the development of negative cognitive schemas and dysfunctional attitudes (for reviews, see Alloy, Abramson, Smith, Gibb, & Neeren, 2006; Gibb, 2002). Furthermore, cross-sectional as well as a handful of prospective longitudinal studies show that cognitive vulnerabilities mediate the relation between early adversity and the development of depression (for a review, see Alloy et al., 2006). Interestingly, there is some evidence that certain types of childhood maltreatment, such as childhood emotional abuse, may be more strongly related to negative cognitive vulnerabilities (Gibb et al., 2002), perhaps because the negative cognitions are directly provided to the child by the perpetrator (Rose & Abramson, 1992). Notably, this aligns with some prior work indicating that childhood emotional abuse, but not other types of maltreatment, leads to stress sensitization (e.g., La Rocque et al., 2014). These promising findings, as well as the substantial research and theory linking early adversity, cognitive vulnerabilities, and depression, underscore the need to directly examine whether cognitive vulnerabilities act as a pathway through which early adversity contributes to stress sensitization.

Notably, Harkness and Lumley (2008) developed an integrated psychobiological developmental model, which theorizes that early adversity (specifically childhood maltreatment) contributes to stress sensitization via increasing cognitive schema consolidation and by altering the HPA axis response to stress. The model posits that these two processes interact during adolescence, particularly in the context of high levels of ongoing chronic stress, and stabilize as a result of neurobiological, cognitive, and emotional development. Consequently, the depressogenic schema and HPA axis are “kindled” to respond to subsequent stress, rendering those with a history of early

adversity more vulnerable to depression in the face of stress (as compared to those without such history). Future longitudinal research that simultaneously investigates multiple mechanisms (e.g., Harkness et al., 2006), such as those proposed in this model, will shed light on the ways in which early adversity influences stress sensitization on multiple levels of analysis.

Genetic variation in susceptibility to depression may also be a mechanism (e.g., Harkness et al., 2006). Specifically, it has been suggested that individuals with a history of early adversity may have a genetic susceptibility to depression that renders them more sensitive to stress (e.g., Harkness et al., 2006). Supporting this, one prior investigation showed that shared genetic factors contributed to both risk for major depression and increased likelihood of experiencing proximal stressful life events, suggesting that genetic factors may increase risk for depression via increasing exposure to environmental adversities (Kendler & Karkowski-Shuman, 1997). Moreover, research indicates that women with the highest genetic risk for major depression may be “prekindled” (or presensitized) prior to the first onset of depression, suggesting that genetic variation may contribute to stress sensitization (or stress autonomy) prior to the first episode of depression (Kendler et al., 2001). The findings underscore the need for future research investigating whether genetic variation is a mechanism of stress sensitization.

Future Directions of Research

Providing Robust Support for Stress Sensitization

In brief, additional evidence providing *unequivocal* support for the stress sensitization model in the context of prior episodes, as well as early adversity, is clearly needed. Indeed, in line with earlier reviews (Bender & Alloy, 2011; Hlastala et al., 2000; Monroe & Harkness, 2005), much of the literature remains ambiguous regarding whether the findings support the stress sensitization or stress autonomy models. Relatedly, even when the stress sensitization model is supported, few studies have addressed whether the observed effects reflect changes in the impact or frequency of stress, or both (Monroe & Harkness, 2005). To provide robust support for stress sensitization, prospective longitudinal studies that (a) recruit individuals experiencing first onsets and follow them across recurrences; (b) include individuals with and without a history of early adversity; and (c) investigate within-person changes in the impact and frequency of different forms of stressful life events across successive episodes are needed (e.g., Bender & Alloy, 2011; Hammen, 2005; Monroe & Harkness, 2005). Moreover, such investigations should examine how the role of chronic stress changes with successive episodes and as a function of early adversity—a critical question that has been rarely pursued in the literature (e.g., Monroe & Harkness, 2005). This work could further advance the field by

elucidating how the stress sensitization process unfolds across development (e.g., La Rocque et al., 2014; Rudolph & Flynn, 2007), as well as by identifying additional factors that moderate stress sensitization effects (e.g., Hammen, 2015).

Investigating Mechanisms of Stress Sensitization

Although many promising mechanisms have been identified (e.g., alterations in HPA axis regulation), research has not yet tested whether these mechanisms *mediate* stress sensitization effects in the context of prior episodes and early adversity, representing a critical direction for future research (e.g., Hammen, 2015; Harkness et al., 2015). Moreover, as highlighted by others (e.g., Harkness et al., 2006), multivariate models should be used to examine multiple mechanisms simultaneously (Hammen, 2015; Harkness et al., 2015), given theoretical models suggest that the underlying mechanisms may complement one another and/or interact throughout development (e.g., Farb et al., 2015; Harkness & Lumley, 2008; Post, 1992; Segal et al., 1996). Additional mechanisms should also be evaluated in future work. For instance, there are hints that inflammatory activation (e.g., Smid et al., 2015), emotion regulation difficulties (Heleniak, Jenness, Van der Stoep, McCauley, & McLaughlin, 2016), and insecure attachment (Rudolph & Flynn, 2007) might be potential mechanisms of the sensitizing effect of early adversity. In addition, an interesting question to explore in future work will be whether the mechanisms are disorder-specific or apply transdiagnostically (e.g., Hammen, 2015; Harkness et al., 2015). Finally, research has not yet evaluated whether the mechanisms underlying stress sensitization effects vary according to other factors, such as gender, developmental stage, event type, and genetic variation. For example, genetic variation in each CRHR1 and 5-HTTPLR (both of which have connections to stress-responsive systems, including the HPA axis; Heim & Nemeroff, 2001) may moderate the mechanisms (e.g., alterations in HPA axis regulation) underlying the sensitizing effect of early adversity (Starr et al., 2014). Pursuing research that strives to elucidate the underlying mechanisms is critical given the potential that such mechanisms could be targeted by intervention and prevention efforts (e.g., Hammen, 2015).

Testing and Refining the Conceptualization of Different Forms of Stress

A priority for future research will be to test and refine different methods of conceptualizing both recent and early stress (e.g., Hammen, 2015; Monroe & Harkness, 2005). One challenge will be to reliably measure even more minor levels of stress, such as daily hassles, to determine whether those who appear to succumb to psychopathology in the absence of stress (perhaps reflecting stress autonomy) might actually be developing psychopathology in the face of even lower levels of stress (reflecting stress sensitization; e.g., Harkness et al., 2006; Monroe & Harkness, 2005). A second interesting question is how to define recent stress. Curiously, studies examining stress sensitization as a function of successive episodes have largely operationalized stress as the presence (versus absence) of events, whereas studies examining stress sensitization as a function of early adversity have largely operationalized stress as total or mean level. It will be important to consider the rationale for, and implications of, each operationalization for the stress sensitization model. Research examining the role of recent chronic stress (e.g., Monroe & Harkness, 2005) and continued exploration of the facets of different types of stress that influence stress sensitization effects are additional areas to pursue. For research examining early adversity, it will be critical to examine whether sensitization effects, as well as the mechanisms underlying those effects, vary according to type (e.g., childhood maltreatment, parental divorce; e.g. La Rocque et al., 2014), severity, duration, and timing of the early adversity (e.g., early childhood versus adolescence; e.g., Rudolph & Flynn, 2007), and the timing of the early adversity relative to disorder onset (e.g., Harkness et al., 2006; La Rocque et al., 2014).

Investigating Different Ways of Conceptualizing Psychopathology

Given research indicating that transdiagnostic factors underlie the major psychiatric disorders (e.g., Krueger, 1999) as well as evidence that the effect of childhood maltreatment on psychiatric disorder onset is fully explained by underlying vulnerabilities to experience internalizing and externalizing psychopathology (versus risk for developing specific disorders; Keyes, Eaton, et al., 2012), future research should consider the implications of adopting transdiagnostic models (e.g., Hammen, 2015). Indeed, such an approach would also permit the evaluation of mechanisms and moderators of stress sensitization that cut across various disorders, which may be particularly informative for intervention and prevention efforts. Another compelling question is whether sensitization processes have similar implications and mechanisms depending on whether the development of symptoms (e.g., Shapero et al., 2014) or diagnosable disorders (e.g., Harkness et al., 2006) is explored. This too would be informative for prevention efforts: If indeed the model applies to symptoms (as some research suggests), then the underlying mechanisms could be targeted even prior to the development of diagnosable disorders.

Exploring Complementary and Alternative Theoretical Models

One important question for future work will be to explore theoretical models that may complement the stress sensitization model. For example, stress generation (Hammen, 1991) and stress sensitization may reciprocally influence one another, progressively increasing the rate of recurrences (Monroe & Harkness, 2005). That is, individuals with a history of depression may not only be more likely to generate stress, but also may be more sensitive to that stress when it occurs, setting up a vicious cycle wherein stress and depression continue to reciprocally influence one another over time (see also Monroe et al., 2007). Moreover, early adversity has been identified as a predictor of both stress generation (e.g., Liu, Choi, Boland, Mastin, & Alloy, 2013) and stress sensitization (e.g., Harkness et al., 2006), raising the possibility that individuals with a history of early adversity not only tend to generate higher levels of stress but, in turn, are also more vulnerable to that stress when it occurs, further increasing risk of first onsets and recurrences. In the context of bipolar disorder, Bender and Alloy (2011) have recently explored the possibility that the behavioral approach system (BAS) dysregulation theory and the social rhythm disruption theory might complement and inform research investigating the stress sensitization model in bipolar spectrum disorders.

Alternative theoretical models should also be tested and developed. For example, in depression research, distinctions have been made between the stress sensitization and stress amplification models (e.g., Morris et al., 2010; Oldehinkel, Ormel, Verhulst, & Nederhof, 2014; Rudolph & Flynn, 2007), the latter of which predicts that early adversity and prior episodes of depression amplify depressive reactions to severe, but not nonsevere, stress. In the context of early adversity, an intriguing model for future pursuit is the stress inoculation model (also called the steeling effect), which proposes that exposure to moderate levels of early adversity protects individuals from risk for psychopathology in the face of subsequent stress (for a review, see Liu, 2015; e.g., Oldehinkel et al., 2014; Rudolph & Flynn, 2007). In this model, individuals with a history of *low* levels of early adversity would be expected to be *more* vulnerable to subsequent stress, as compared to those exposed to *moderate* levels of early adversity. Finally, recent critiques have called into question research supporting stress sensitization as a function of prior episodes (Anderson, Monroe, Rohde, & Lewinsohn, 2016), arguing that the association between major stress and successive episodes only seems to weaken as a result of Slater’s fallacy—highly recurrent individuals with lower levels of stress needed to trigger recurrences become a larger portion of the sample with each recurrence. In other words, rather than reflecting within-person changes in the stress-depression association over time as proposed by the stress sensitization model, the weakening association observed in prior work reflects between-person differences: As compared to less recurrent individuals, highly recurrent individuals would be expected to develop depression in the face of lower levels of stress even prior to the first onset (Anderson et al., 2016).

Thus, a challenge for future research will be to conduct research (a) investigating the integration of multiple models, with the goal of understanding how such models might complement and refine the theory of stress sensitization; (b) test alternative approaches for understanding how early adversity and disorder history shape the relationship between stress and psychopathology; and (c) continue to develop new explanations for how this relation changes.

Conclusion

The importance of pursuing research to enhance our understanding of the relation between stress and psychopathology is inherent in the stress sensitization model: Stress becomes even more etiologically important as people become more vulnerable. Consequently, this suggests that prevention efforts must equip those with a history of psychopathology and/or early adversity with strategies for increasing their resiliency in the face of stress, consistent with evidence-based interventions that incorporate strategies designed to manage stress (e.g., cognitive-behavioral therapy, interpersonal psychotherapy). As I hope is evident, we need to design studies that will provide robust evidence for the stress sensitization model, determine how the role of stress changes, elucidate the underlying mechanisms and moderators, and advance theory and measurement. This work will refine our intervention efforts, by, for example, helping individuals develop coping strategies for specific types of events, targeting those individuals who are most likely to be sensitized to stress, and focusing on the mechanisms underlying sensitization effects. In doing so, our intervention and prevention efforts will become more effective in promoting resiliency in those most vulnerable to stress.

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