



Stress sensitivity in women with a history of recurrent versus first-episode major depression

Amber K.X. Gan , Brandon E. Gibb ^{*} 

Department of Psychology, Binghamton University (SUNY)

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ABSTRACT

Approximately 50 % of people who recover from an initial episode of major depressive disorder (MDD) experience a recurrence, and the risk for recurrence increases with each additional episode. Consistent with the stress sensitization model, there is evidence that whereas initial MDD onsets are often preceded by major negative life events, recurrences are often triggered by more minor events. However, it is unclear whether this is due to increased frequency of minor life events, increased reactivity to these events, or both. The current study examined these questions in a community sample of 227 adult women with a history of recurrent MDD (rMDD, $n = 77$), first-episode MDD (fMDD, $n = 38$), or no history of MDD ($n = 112$). Women were assessed at baseline and every six months for two years (5 assessments total). Throughout the follow-up, major and minor life events were assessed using contextual threat interviews and depressive symptoms were assessed using a self-report questionnaire. Regarding event frequency, minor events were more common than major events, and the rMDD group experienced more negative events overall (both major and minor) than the never depressed group but not the fMDD group. Regarding stress reactivity, results of linear mixed modeling revealed that whereas all three groups exhibited similar increases in depressive symptoms following major events, only women in the rMDD group experienced significant increases in depressive symptoms following minor events. These findings show that not only are women with rMDD living in more stressful contexts, but they are also more reactive to minor stressors, increasing risk for future depression.

1. Introduction

Major depressive disorder (MDD) is a common mental health disorder that affects approximately 280 million people around the world, with women approximately twice as likely to develop the disorder as men (Salk et al., 2017). MDD is a significant public health concern that has far-reaching personal, social, and economic consequences (Greden, 2001; Greenberg et al., 2021; McLaughlin, 2011). Beyond the impact of the initial MDD episode, data suggest that approximately 50 % of individuals who have recovered from their first episode of MDD are expected to experience a recurrence, with risk for additional episodes increasing with each recurrence (Bulloch et al., 2014; Monroe and Harkness, 2022; Solomon et al., 2000). Even among individuals who are undergoing or have completed treatment for MDD, 25 % to 37 % are expected to experience a recurrence of MDD within approximately two years (Forte et al., 2015; Sim et al., 2015). Clearly then, a greater understanding of factors contributing to MDD recurrence is essential so that more targeted and effective treatments can be developed.

One challenge for prevention and intervention efforts is potential etiological differences in risk for first-episode MDD versus recurrences (Burcusa and Iacono, 2007; Lewinsohn et al., 1999). A key risk factor whose role may change over the course of the disorder is that of acute negative life events. Post (1992) proposed the stress sensitization model according to which individuals become increasingly sensitive to the depressogenic effects of negative life events with each additional episode of MDD. According to this model, a first episode of MDD is more likely to be preceded by major life events than are recurrences. Indeed, studies have shown that major life events have a greater association with first-onset MDD compared to recurrences, and the association between major life events and MDD onset decreases with each additional episode (Farmer et al., 2000; Kendler et al., 2000; Monroe et al., 1999). Expanding this model, Monroe and Harkness (2005, 2011, 2022) highlighted a key aspect of the stress sensitization model. Specifically, they noted that the stronger link observed between major life events and first onset MDD than recurrent MDD is likely not due to individuals with recurrent MDD being less sensitive to major events. Rather, if they are

* Correspondence author at Clearview Hall, Department of Psychology, Binghamton University (SUNY), Binghamton, NY 13902-6000
E-mail address: bgibb@binghamton.edu (B.E. Gibb).

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(also) more sensitive to minor events, recurrences of MDD may be more likely to be triggered by minor events simply because these types of events are more common. Several studies have examined this aspect of the stress sensitization model by comparing the prospective association of major and minor life events between first-episode and recurrent MDD. Indeed, they found that the effect of minor life events is stronger for recurrences, whereas the effect of major life events is stronger for first-episode MDD (Ormel et al., 2001; Stroud et al., 2011). At the outset, it should be noted that the stress sensitization hypothesis is inherently a within-person model of risk in which a person's reactivity to minor events changes across the course of the disorder from first onset through repeated recurrences (see Monroe, Anderson, and Harkness, 2019; Monroe and Harkness, 2022). This said, studies examining between-person differences can be useful in determining which specific differences exist between those with first onset versus recurrent MDD, information that is essential for designing and implementing the types of large-scale longitudinal studies that would be needed to follow individuals from first onset through one or more recurrences of MDD.

Taken together, therefore, studies have provided considerable evidence that individuals with a history of recurrent MDD have increased sensitivity to negative life events and that major life events have a stronger association with first-episode MDD compared to recurrences. However, several important gaps within the literature remain. First, prior studies that examined the stress sensitization model do not clarify whether the increased sensitization observed in individuals with a history of recurrent MDD is due to changes in event frequency, impact, or both (see Stroud et al., 2011, for exception). Monroe and Harkness (2005) highlighted the need to distinguish the role of the frequency versus impact of life stress as these may differ for those with first-onset versus recurrent MDD. Second, our understanding of the stress sensitization model has largely been based on studies of adolescents or young adults (Kendler et al., 2000; Lewinsohn et al., 1999; Monroe et al., 1999; Stroud et al., 2011). Stroud et al. (2008), in a review of studies that examined the stress sensitization model, pointed out that results may differ depending on the sample type, age, and gender of participants.

The present study sought to address these limitations. Using a multi-wave longitudinal design, a community sample of adult women with recurrent MDD (rMDD), first-episode MDD (fMDD), or no history of MDD were assessed for the frequency and severity of negative life events and depressive symptoms every six months for two years. Our focus on depressive symptoms, rather than diagnoses, allowed us to examine symptom fluctuations across the entire two-year follow-up rather than just the onset of a new MDD diagnosis. In assessing negative life events, we considered the impact and frequency of major and minor life events during each follow-up. Consistent with the stress sensitization model, we hypothesized that women with rMDD would be more reactive to the impact of minor life events – that is, exhibit greater depressive symptom increases – than women with a history of fMDD or no MDD history. We also hypothesized that we would observe similar effects for the impact of major life events. However, we predicted that the frequency of minor events during each follow-up interval would be significantly higher than the frequency of major events, which would support Monroe and Harkness's (2005) hypothesis that stress sensitivity is not limited to minor events but rather than minor events are more often seen preceding new onsets because they are much more common. We also examined whether the frequency of major and minor events may differ across the diagnostic groups but did not make explicit hypotheses.

2. Method

2.1. Participants

Participants in this study were 227 women recruited from the community as part of a larger study examining risk for the intergenerational transmission of depression. Of the women, 77 had a history of recurrent MDD (rMDD), 38 had a history of a first episode of MDD (fMDD), and

112 had no lifetime history of any depressive disorder. Recurrent MDD was defined as at least two lifetime episodes of MDD. The number of lifetime MDD episodes within the rMDD group ranged from 2 to 50 ($M = 4.49$, $Median = 2$). The two MDD groups did not differ in the number of months since the most recent MDD episode at baseline, $t(107) = 0.16$, $p = .87$ (fMDD: $M = 54.38$, $SD = 50.54$; rMDD: $M = 52.41$, $SD = 62.38$), indicating that any group differences were not due to differences in the recency of a prior MDD episode between the two MDD groups. Exclusion criteria for all groups included a lifetime history of bipolar disorder or psychosis, or alcohol or substance dependence in the past 6 months. The sample ranged in age from 24 to 55 ($M = 40.38$, $SD = 6.80$) with 86.34 % non-Hispanic White, 4.41 % Black or African American, 3.52 % multiracial, 1.32 % Asian, and the remainder from other racial/ethnic groups.

2.2. Measures

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 2002) was administered at the baseline assessment to determine women's lifetime histories DSM-IV Axis I disorders. To assess interrater reliability, a subset of 20 SCID-I interviews from this project were coded by a second interviewer, and inter-rater reliability for diagnoses of MDD was excellent ($\kappa = 1.00$).

Women's symptoms of depression were assessed at each time point using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), which is a 21-item self-report measure. The BDI-II has been shown to have high reliability and validity (Beck et al., 1996), and exhibited good internal consistency in our study ($\alpha = 0.92$ – 0.94 across time points).

To assess acute, episodic life events occurring during the follow-up, we used the UCLA Life Stress Interview (Hammen, 1991), which is a semi-structured interview modeled after contextual threat interviews (Brown and Harris, 1978). The interview was administered at each follow-up assessment and focused on events that happened since the last assessment. For each event reported, interviewers recorded objective information regarding the timing, duration, and context of the event. This information, devoid of any subjective information, was then presented to a team of four to seven independent coders who rated the objective impact of the event on a 1–5 scale (1=No impact, 2=Mild impact, 3=Moderate, 4=Severe, 5=Very severe). Events were categorized as "major" if they received an objective impact score of 3 or higher, and they were categorized as "minor" if they received an objective impact score of <3. This categorization of major and minor life events is consistent with prior studies (e.g., Feurer et al., 2016; Uliaszek et al., 2012). Before conducting any analyses, objective impact scores that were initially rated on a 1–5 scale were re-coded to a 0–4 scale to avoid inflation of stress scores by excluding events rated as having no impact. Impact scores were calculated by summing the objective impact of all events reported as having occurred within that follow-up interval. Frequency scores were calculated by summing the number of events reported. Scores were calculated separately for Major events and Minor events.

2.3. Procedure

Potential participants were recruited from the community through a variety of means (e.g., newspaper and bus ads, flyers). Women responding to the recruitment advertisements were initially screened over the phone to determine potential eligibility. Upon arrival at the laboratory for the baseline assessment, and after providing informed consent, participants were administered the SCID-I and BDI-II. Following the baseline assessment, participants completed follow-up assessments approximately every six months for two years (five assessments total) during which they completed the BDI-II and the UCLA Life Stress Interview. In practice, the average duration between follow-ups was 6.11 months ($SD = 0.45$). Participants were compensated monetarily for their time. The study was approved by the university's

Institutional Review Board.

2.4. Analysis plan

A repeated measures ANOVA was used to test for potential differences in the frequency of major versus minor events across the three groups. The dependent variable for these analyses was the average number of each event type (major or minor) reported at each follow-up assessment. Event type (major, minor) was included as a within-subject predictor and MDD group (Never Depressed, fMDD, rMDD) was included as a between-subjects predictor. We also examined the MDD group \times Event type interaction.

Next, to test our stress sensitivity hypotheses, we used linear mixed models in SPSS (version 29). In these analyses, BDI-II score at a given time point (time T) was used as the dependent variable and BDI-II score at time T-1 was included as a within-subject (Level 1) predictor, which allowed us to examine changes in depressive symptom levels from time T-1 to time T. Level of negative events reported for each follow-up interval (from time T-1 to time T) was also included as a within-subject predictor and MDD group (rMDD, fMDD, Never Depressed) was included as a between-subjects (Level 2) predictor. The key effect of interest was the MDD group \times Events interaction, allowing us to determine whether the impact of negative life events on depressive symptom changes differed across MDD groups. Level 1 predictors were person centered so that the dependent variable reflected each person's average level of depressive symptoms during the follow-up at their own average level of stress and Event scores reflected fluctuations (increases or decreases) in negative life events at each assessment relative to each person's average level of stress. All models initially included a random intercept and random slopes for Events and BDI-II_{T-1} scores, with nonsignificant effects omitted from the final models. Separate analyses were conducted for major life events and minor life events.

3. Results

Of the 227 women who completed the baseline session, 211, 197, 170, and 174 completed the 6-, 12-, 18-, and 24-month follow-up assessments, respectively, and 82.5 % completed at least 3 of the 5 assessments. To examine the pattern of missing data, we used Little's missing completely at random test (Little and Rubin, 1987), for which the null hypothesis is that the data are missing at random. This test was

nonsignificant, $\chi^2(599) = 634.53, p = .15$, supporting the estimation of missing values. Given this, we used the expectation maximization approach in SPSS to generate maximum likelihood estimates of missing data, which were then used for all analyses.

3.1. Frequency of life events

Focusing first on potential differences in the frequency of major versus minor life events, the repeated measures ANOVA revealed a significant main effect of event type, $F(1, 224) = 93.62, p < .001, \eta^2_{\text{partial}} = 0.30$, with participants, on average, experiencing more minor life events ($M = 0.99, SE = 0.05$) than major life events ($M = 0.46, SE = 0.03$) during each follow-up interval. Furthermore, there was a significant main effect of MDD group, $F(2, 224) = 10.54, p < .001, \eta^2_{\text{partial}} = 0.09$, with the rMDD group ($M = 0.88, SE = 0.05$) experiencing significantly more life events (averaged across the number of major and minor events in each follow-up interval) than the never depressed group ($M = 0.57, SE = 0.04, p < .001$). However, the fMDD group ($M = 0.73, SE = 0.07$) did not differ significantly from either the rMDD ($p = .11$) or never depressed ($p = .06$) group. The interaction between event type and MDD group was nonsignificant, $F(2, 224) = 0.59, p = .56, \eta^2_{\text{partial}} = 0.01$. These results are presented in Fig. 1.

3.2. Impact of life events

Next, we examined the impact of major life events, focusing on the total objective impact of major events within each follow-up interval. Results of the linear mixed model analyses revealed a main effect of MDD group, $F(2, 223.10) = 51.47, p < .001$, with the rMDD group reporting higher levels of depressive symptoms across the study ($M = 11.55, SE = 0.65$) than the fMDD group ($M = 8.25, SE = 0.93, p = .004$) who, in turn, had higher average depressive symptom levels than the never depressed group ($M = 3.08, SE = 0.54, p < .001$). There was also a main effect of major life events on depressive symptom change, $F(1, 661.05) = 8.46, p = .004$, with increases in major life events within a given follow-up interval, compared to the person's own average level of major events, predicting increases in depressive symptoms. However, the MDD group \times major life events interaction was not significant, $F(2, 660.91) = 2.69, p = .07$, suggesting that the impact of major events on depressive symptom change did not differ significantly across the three groups.

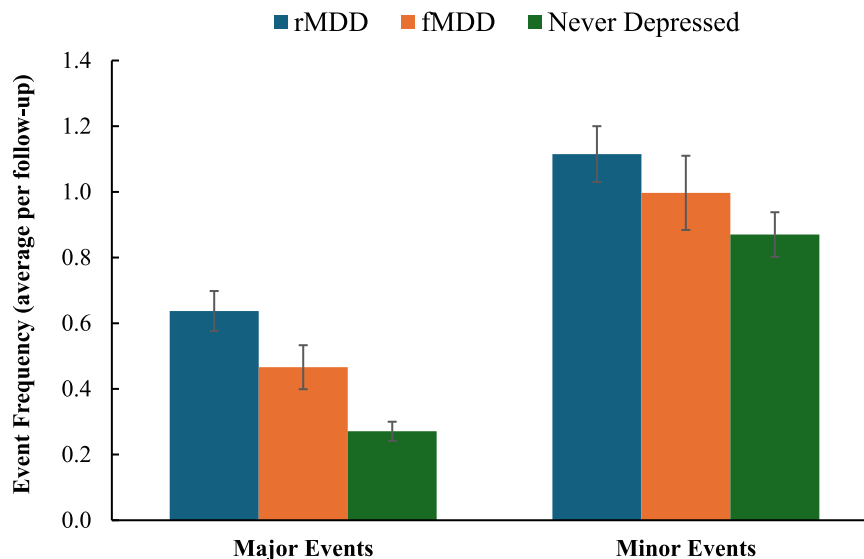


Fig. 1. Frequency of Major and Minor Life Events by History of MDD.

Note. rMDD = history of recurrent major depressive disorder. fMDD = history of only a first episode of major depressive disorder. Never depressed = no lifetime history of any depressive disorder. Error bars reflect ± 1 standard error of the mean.

Turning next to minor life events, we again found a significant main effect of MDD group, $F(2, 223.65) = 51.82, p < .001$, with the rMDD group reporting higher average levels of depressive symptoms ($M = 11.56, SE = 0.65$) than the fMDD group ($M = 8.25, SE = 0.93, p = .004$) who, in turn, had higher average depressive symptom levels than the never depressed group ($M = 3.07, SE = 0.54, p < .001$). In addition, although the main effect of minor life events on depressive symptom change was not significant, $F(1, 659.41) = 2.33, p = .13$, there was a significant MDD group \times minor life events interaction, $F(2, 659.56) = 4.29, p = .01$. Examining the form of this interaction, we found that within-person increases in minor life events during a given follow-up interval predicted increases in depressive symptoms for the rMDD group, $t(224.18) = 2.15, p = .03$, but not the fMDD group, $t(97.63) = 0.77, p = .44$, or the never depressed group, $t(312.74) = -1.07, p = .28$. These results are depicted in Fig. 2.

4. Discussion

The goal of this study was to evaluate the role of life stress in depression risk to determine whether the increased sensitization to stress observed in individuals with a history of recurrent MDD is due to increased frequency of minor life events, increased reactivity to these events, or both. Focusing first on the frequency of major and minor life events, we found that women with a history of recurrent MDD reported more events overall than never depressed women. Although the precise reasons for this finding are not clear, it is possible that women with recurrent MDD live in contexts characterized by higher stress than never depressed women. Importantly, though, there were no differences in the overall frequency of events between women with a history of recurrent versus first-episode MDD.

In terms of the impact of negative life events, the role of major life events was similar across all three groups. Specifically, all three groups reported significant increases in depressive symptoms following increases in major life stress and the strength of this effect did not differ across the groups. This contradicts our hypotheses based on the stress sensitization model that the impact of both major and minor events would increase as individuals experience greater number of depressive episodes and therefore be stronger among women with a history of recurrent MDD. However, our current findings are consistent with prior research finding no differences in the impact of major life events for first

onsets versus recurrences (Stroud et al., 2011). In contrast, and consistent with our hypothesis, women with a history of recurrent MDD, but not women with only a single prior episode of MDD or women with no history of MDD, reported significant increases in depressive symptoms following an increase in minor life stress. This finding extends those from prior studies, which found that recurrences of MDD are more strongly related to the presence of minor life events than with major life events (Monroe et al., 1999; Ormel et al., 2001; Post, 1992; Stroud et al., 2011) and suggests that this is due to increased sensitivity to more minor stressors in women with a history of recurrent MDD. Because minor events are more common than major events, this increased stress sensitivity could be an important predictor of future risk in individuals with a history of recurrent MDD.

What remains unclear is what mechanisms account for this increased sensitivity to minor events (sometimes referred to as hassles) and how these mechanisms change across the progression of MDD episodes. One potential mechanism, based on neurobiological research, is that experiences of stress lead to dysregulation of stress-related neural pathways such as the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. As a result, there is enhanced responsiveness to stress levels below the initial threshold, allowing stress levels in the lower threshold to acquire the capacity to trigger increases in depression (Belda et al., 2015). Another mechanism, proposed by Farb et al. (2015), is that the coupling of dysphoric attention and elaboration in response to stress is strengthened with each additional MDD episode, such that there is increased fixation to and increased rumination about the negative aspects of life events. This cognitive vulnerability may amplify the impact of more minor stressful life events, contributing to stress sensitization. Future research is needed to better understand the specific mechanisms underlying increases in stress sensitivity so that they can be incorporated into more targeted interventions designed to reduce risk of MDD recurrence.

The current study has several strengths, including the use of longitudinal design to assess within-person effects of life events on depressive symptom changes as well as the use of semi-structured interviews and independent coders to identify the frequency and impact of major versus minor events. However, there are limitations that warrant discussion. First, although we were able to document between-subject differences in the frequency and impact of negative life events, we could not formally evaluate within-person changes in reactivity to minor life event

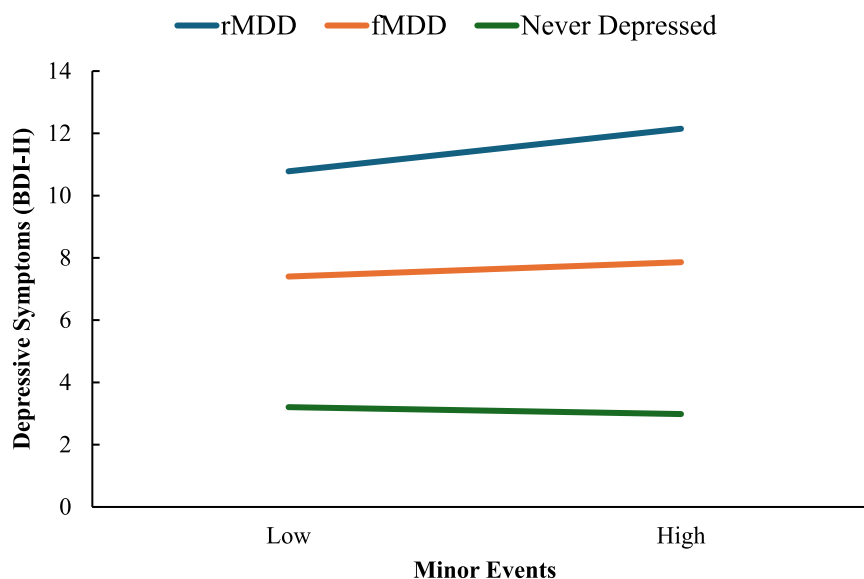


Fig. 2. Impact of Minor Life Events on Prospective Changes in Depressive Symptoms by History of MDD.

Note. rMDD = history of recurrent major depressive disorder. fMDD = history of only a first episode of major depressive disorder. Never depressed = no lifetime history of any depressive disorder.

predicted in stress sensitization models (Monroe and Harkness, 2022). Because of this, we cannot determine whether individuals become increasingly sensitized to more minor stress with successive episodes of MDD or whether differences in stress reactivity may have existed prior to the first onset of MDD that put women in our rMDD group at risk for recurrent episodes of MDD. Although it is almost certainly not feasible to evaluate life stress and depression within the context of a multi-wave longitudinal studies using gold-standard assessments in a population prior to first onset of MDD, future research should seek to follow individuals presenting with their first MDD episode to determine how reactivity to minor (and major) life stress may change over time, specifically following a second episode of MDD. A third limitation is that we only followed participants for a maximum of two years and it is likely that at least some of the individuals in the fMDD group will go on to develop additional MDD episodes. Fourth, as with other studies examining the stress sensitization model, we focused on episodic stress. However, there is also evidence that reactions to chronic stress may differ depending on one's history of depression and could potentially interact with episodic stress to contribute to depression (Daley et al., 2000; Hammen, 2005; Monroe et al., 2007). Future research should explore the extent to which chronic stress and episodic stress contributes to stress sensitization.

5. Conclusion

In summary, the current results support a key hypothesis of the stress sensitization model in showing that women with a history of recurrent MDD are more sensitive to the impact of minor life events than women with a history of first-episode MDD or no history of MDD. Specifically, only women in the recurrent MDD group, but not women in the other groups, exhibited significant increases in depressive symptoms following increases minor life stress. Future studies are needed to clarify the specific mechanisms underlying the increased stress reactivity in those with recurrent MDD and whether these mechanisms may change across consecutive episodes. This line of research may help to identify key targets for intervention that can be used to reduce the risk of depression in vulnerable individuals.

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Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRedit authorship contribution statement

Amber K.X. Gan: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Brandon E. Gibb:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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