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Research report

The stress sensitization hypothesis: Understanding the course of bipolar disorder

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Abstract

Background: The influence of psychosocial stress on the course of bipolar disorder has been increasingly recognized. The authors tested hypotheses about both stress and early adversity "sensitization" on the course of bipolar disorder over a one-year period.
Methods: The participants were 58 adults (29 male and 29 female) with a diagnosis of bipolar I disorder. They were evaluated every three months for one year. Stressful life events and the presence of early adversity were assessed by structured interview.
Results: There was no significant interaction between stress and episode number in the prediction of bipolar recurrence. The interaction of early adversity severity and stressful life events significantly predicted recurrence in a manner consistent with the sensitization hypothesis. Participants with early adversity reported lower levels of stress prior to recurrence than those without early adversity. Individuals with early adversity also had a significantly younger age of bipolar onset.
Limitations: The sample size was small and the number of past episodes was determined retrospectively, mainly through self-report.
Conclusions: Severe early adversity may result in a greater effect of stress on bipolar recurrence and earlier onset of bipolar disorder, suggesting the need for further studies of stress mechanisms in bipolar disorder and of treatments designed to intervene early among those at risk.

Keywords: Bipolar disorder; Stress; Kindling; Behavioral sensitization; Stress sensitization

1. Introduction

Etiological research on bipolar disorder has frequently focused on biological variables, often overlooking the role of psychosocial influences such as stress. The growing realization that biological factors cannot entirely account for variability in the course of bipolar disorder has led to an increased focus on the effect of life stress. Psychosocial stress has been shown to affect both the onset and course of bipolar disorder (Johnson and Roberts, 1995), but the specific nature of this relationship has yet to be fully understood. Two proposed pathways for the influence of stress on bipolar disorder involve both proximal and distal effects of stress. Both

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fall under the heading of stress sensitization: kindling/behavioral sensitization and early adversity sensitization.

The kindling/behavioral sensitization hypothesis (Post, 1992) focuses on the effects of proximal stress and integrates both biological and psychosocial influences on the course of bipolar disorder. Post (1992) hypothesized that stressful life events precipitate initial episodes of bipolar disorder, while subsequent episodes become progressively more autonomous from external influence. He based his model on the finding in animal research that repeated administration of a stimulus (e.g. electrical stimulation) precipitates a seizure response that, over time, requires a lower level of stimulus to occur. Post (1992) extended this research to explain recurrence of affective disorders, postulating that over time a progressively lower level of a stimulus (i.e. stress) is needed to precipitate bipolar recurrence.

Post's (1992) kindling/behavioral sensitization model can be distilled into two distinct, albeit related theories. There are ambiguities introduced by failing to account for their different predictions. Both kindling and behavioral sensitization hypotheses propose that repeated stimulus administration elicits a response that, over time, requires a lower level of stimulus to occur; but whether life stress plays a role in recurrence later in the course of the illness is less clear. According to a recent review by Monroe and Harkness (2005), the difference is mostly a function of the definition of "autonomous," whether recurrence becomes autonomous of life events (kindling) or whether less stress is needed to trigger recurrence, so both mild and severe stress still precipitate recurrence (behavioral sensitization). This study focuses on the stress sensitization hypothesis, predicting that both mild and severe stress will precipitate recurrence later in the course of bipolar disorder.

Research indicates that bipolar patients experience stressful life events prior to episode recurrence (Johnson and Roberts, 1995; Hammen and Gitlin, 1997), but the kindling/behavioral sensitization hypothesis has received mixed support. Methodological difficulties, such as the use of life event checklists, lengthy retrospective recall periods, and clinician-based chart reviews are prevalent in older research on this topic (e.g. Dunner et al., 1979). Utilizing improved methodologies, Swendsen et al. (1995) and Hlastala et al. (2000) reported a lack of a statistical relationship between the number of previous episodes and the level of stress prior to recurrence. However, Hammen and Gitlin (1997) reported that patients with a greater number of previous episodes were more likely to relapse following severe life stress. Stress may influence the recurrence of bipolar disorder, but the moderating role of prior episode history in the stress–recurrence relationship has received less support.

Early adversity sensitization is another form of stress sensitization involving distal stress as the initial stimulus. Early adverse events may permanently alter the stress response system, sensitizing individuals to later stress, and leading to early onset and severe course of clinical disorders including bipolar disorder (Post et al., 2001). Research involving depressed populations has supported early adversity sensitization (Hammen et al., 2000). However, a few studies have investigated the role of early adversity sensitization in bipolar disorder. Leverich et al. (2002) found that bipolar patients who experienced sexual and physical abuse during childhood reported earlier onset of bipolar illness, faster cycling, increased suicidality, more Axis I and II comorbidity, more time ill, and greater psychosocial stress prior to the first and most recent episodes. However, they used a retrospective stress checklist and did not differentiate between severe and mild stressors. Other studies have confirmed the association between early adversity and greater severity of illness features, but did not include measures of recent stressors (e.g. Garno et al., 2005).

The present study focuses on how kindling/behavioral sensitization and early adversity sensitization affect recurrence in bipolar I disorder over the course of one year. We hypothesized that bipolar patients with a greater number of prior episodes would relapse under conditions of both mild and severe stress (stress sensitization), whereas individuals with a fewer number of episodes would relapse following severe stress only. Also, bipolar individuals with severe childhood adversity were predicted to relapse following mild stress regardless of the number of episodes. Finally, we hypothesized that bipolar patients with early adversity would have an earlier age of onset, due mainly to the influence of sexual and physical adversity.

2. Methods

2.1. Participants

Participants were 64 adults (32 men, 32 women; mean age 41.5+/−12.4 years) with confirmed bipolar I disorder. Participants were recruited in Los Angeles from outpatient clinics (32.8%), university-based projects (32.8%), advertising at the University of California, Los Angeles in classes (18.7%), and support groups (15.7%). Individuals were admitted to the study if they had achieved remission (defined as at least 2 months

with less than two symptoms of mania, major depression, or hypomania based on retrospective assessment; $n=47$) or their best clinical state (defined as stable low-level symptoms for at least the past 6 months; $n=17$) (Ellicott et al., 1990). Individuals not in treatment with a psychiatrist and receiving medication were excluded, as were those with diagnosis of schizoaffective or bipolar II disorder. Six participants (3 men, 3 women) did not complete the full year of the investigation, and therefore analyses were conducted on 58 individuals (29 men, 29 women).

The sample was primarily Caucasian (74%; 12.5% African American; 7.8% Latino; 3.1% Asian American; 3.1% Other). Current comorbidity with other Axis I disorders including substance abuse and dependence was relatively low (18.75%). The participants' illness characteristics are summarized in Table 1. Several participants ($n=10$) reported their number of episodes as "too many to count" and were assigned a value of the upper end of the distribution of valid scores (50) plus one standard deviation (10.6), resulting in a score of 61.

2.2. Procedure

An initial direct interview included written informed consent, assessment of diagnostic criteria, chronic stress, medication compliance, and childhood adversity as detailed below. Four follow-up interviews assessing clinical status and medication compliance were conducted by telephone at three-month intervals. The 6- and 12-month follow-up interviews also included an assessment of chronic and episodic stress over the past 6 months.

Table 1
Participant illness characteristics and recurrence

Characteristic	Mean	SD	Range
Duration of bipolar illness	21.3	11.7	2–55
Age of onset	20.2	8.69	8–54
Age at first diagnosis	26.2	10.6	12–54
Lifetime depressive episodes	9.48	11.1	0–31
Lifetime of manic episodes	8.43	9.27	0–31
Number of hospitalizations	3.41	3.38	0–17
Number of stressful life events during one year	0.95	1.24	0–6

	Recurrence over 12 months ($N=37$)	
	N	%
Mania	10	27
Major depressive episode	18	49
Mixed	1	3
Hypomania	3	8
Minor depression	5	13

2.3. Measures

2.3.1. Current and lifetime Axis I symptomatology

The well-validated Structured Clinical Interview for DSM-IV (First et al., 1996) was administered at the initial interview to assess both remission state and Axis I diagnoses; participants' physicians were consulted to confirm bipolar I diagnosis. The age of onset of bipolar disorder was operationalized as the first appearance of a manic or depressive episode meeting full DSM-IV diagnostic criteria.

2.3.2. Ongoing symptom assessment

The participants' current and past symptoms since the last follow-up were assessed at each interview using the SCID (see Table 1). Recurrence was defined as an episode of hypomania, mania, major depression or a mixed episode that met SCID-based DSM-IV diagnostic criteria and that occurred following at least two months of syndromal remission. In cases where a participant experienced more than one recurrence, the first was chosen for analyses.

2.3.3. Stressful life events

The life stress interview was based on the contextual threat assessment methods of Brown and Harris (1978) and has been utilized extensively by Hammen and colleagues (1991; 1997; 2000). The interviewer obtained the dates, context, duration, expectation of, consequences of, and resources for, the event. A blind rating team scored each event for objective threat based on a 5-point scale ranging from 1 (no negative impact) to 5 (extremely severe negative impact). Reliability of severity ratings yielded an intraclass correlation of .90 for objective impact. This interview was used to generate the total objective stress variable used in analyses by adding the objective impact ratings for all events (excluding those rated not at all stressful) in the three-month interval. A random period of three months was selected for obtaining the total objective stress variable for those who did not have a recurrence, a method used by Hammen et al. (2000).

2.3.4. Chronic stress

The chronic stress interview (Hammen, 1991) assessed the level of chronic stress across several domains over the past 6 months: work, school, finances, romantic relationships, best friendships, social circle, family relationships, and health (self and family). Chronic stress was rated from 1 (exceptionally good) to 5 (extremely stressful and maladaptive), based on objective information. Intraclass correlations for

reliability ranged from .73 to .95 with a mean intraclass correlation of .88. Average chronic stress over the one year period was controlled statistically to rule out its potentially confounding effects on clinical course.

2.3.5. Medication compliance

Participants listed all prescribed psychotropic medications and reported their compliance with the prescribed regimen (e.g. frequency of missed dosages, changes made due to side effects) during each assessment. Confirmation that the participants were currently maintained on medication was obtained through contact with the treating psychiatrist. The interviewers rated medication compliance on a 5-point scale ranging from 1 (ceased completely) to 5 (perfect compliance). An average compliance rating across the 12 months of the study was generated and compliance was controlled statistically. Reliability based on independent raters resulted in an intraclass correlation of .94.

2.3.6. Childhood adversity interview

The instrument designed for the present study attempted to facilitate accurate event recall through the use of specific recognition cues and the encouragement of elaborated responses. The interview is semi-structured, and involved assessment of adverse events which occurred up to the age of 13 (12 and under). Age 12 was selected as the cutoff to focus on events that occurred before the period of increased risk for onset of mood disorders, and because trauma before age 12 has been shown to be more predictive of behavioral disturbances than adolescent events (Van der Kolk et al., 1991). Interviewer-rated severity of adverse events was rated on a 5-point scale for each of the following: separation and loss involving the primary caretaker(s), physical neglect, emotional abuse or assault, physical abuse or assault, witnessing violence, sexual abuse or assault, and peer victimization, and was scored on a 5-point scale ranging from 1 (no adversity) to 5 (extreme impact). Intraclass correlations for the severity ratings ranged from .63 to 1.00, mean correlation of .86.

2.4. Statistical analyses

Logistic regression analyses were conducted to predict recurrence status. The first analysis examined the stress sensitization hypothesis, that prior episode history moderates the depressive response to stressors. Episode history was operationalized as the number of past episodes. The second analysis was similar, but tested the role of early adversity severity as a moderator of the effects of stressors on recurrence. In both analyses, potentially confounding variables were controlled: age of onset, Axis I comorbidity, average chronic stress and medication compliance. The variables of total objective stress, number of episodes, and early adversity severity were dichotomized to correct a skewed distribution. Dichotomization was also employed to replicate past research which involved the assessment of the effects of mild vs. severe stress (Hlastala et al., 2000). Analyses were also conducted without the ten participants who reported their number of episodes as "too many to count," because their inclusion may have resulted in violations of the assumptions of normality.

The hypothesis that bipolar individuals with early adversity would have a younger age of onset was tested using a two-tailed *t*-test. Because the hypothesis supposes that adversity may be a risk factor for the earlier onset of bipolar disorder, 8 participants with bipolar onset prior to age 12 were excluded from this analysis. Exploratory analyses were conducted to compare the adversity present/absent groups (two-tailed *t*-test) on each type of early adversity.

3. Results

Descriptive data involving participant clinical history characteristics, recurrence, and life event information are presented in Table 1. There was no significant difference between the groups with and without recurrence on medication compliance, past number of manic and depressive episodes, number of hospitalizations, and age of bipolar onset.

The stress sensitization hypothesis was tested using a logistic regression analysis to predict recurrence, with controls for chronic stress, age, and presence of comorbid diagnoses entered in the first step (non-significant effects). The second step of the model included the two dichotomized predictor variables of total stress and past number of episodes, yielding significant effects ($\chi^2 = 6.34$, $df = 2$, $p = 0.042$). The final model, testing the interaction of number of past episodes and total stress failed to predict episode recurrence, $\chi^2 = 0.33$, OR 2.14 (CI 0.16–29.3) contrary to hypothesis.

Similar analyses were conducted to test the early adversity sensitization hypothesis. The third step of the regression, which evaluated the interaction term (early adversity by stressors), was statistically significant ($\chi^2 = 4.63$, OR 0.05 (CI 0.01–0.91), $p = 0.042$). The direction of the relationship supported the early adversity sensitization hypothesis: individuals with relatively severe early adversity had a higher likelihood

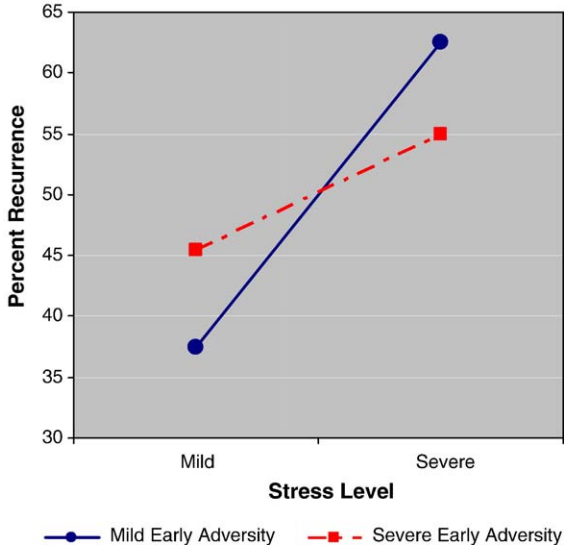

Fig. 1. The distribution of percent recurrence across early adversity severity and stress level.

of recurrence under conditions of mild stress than individuals with mild or no early adversity. The distribution of percent recurrence illustrating this interaction is presented in Fig. 1.

As predicted, the group that had experienced early adversity had a significantly lower age of onset than the group without early adversity, $t(55)=3.30$, $p=0.036$. The mean age of onset for the early adversity group was 18.8 (SD=7.0) compared to the adversity-absent group 28.4 (SD=12.2). Analyses were also conducted with the 8 participants that were excluded due to early age of onset and the results were unchanged. Exploratory analyses were conducted for each of the seven types of early adversity. Although there was a trend for the mean age of onset of bipolar disorder to be lower for the present-adversity group for each type of adversity, only the groups that reported sexual adversity, $t(52)=3.24$, $p=0.002$, and neglect, $t(55)=2.09$, $p=0.043$ had significantly earlier ages of onset. The mean age of onset of bipolar disorder was 15.94 (SD=4.75; $n=16$) for the sexual adversity-present group and 22.22 (SD=9.80; $n=41$) for the sexual adversity-absent group. The mean age of onset was 17.17 (SD=7.35; $n=18$) for the neglect-present group and 21.97 (SD=9.50; $n=39$) for the neglect-absent group.

4. Discussion

The present study investigated the role of stress sensitization in the recurrence of bipolar I disorder consistent with the kindling/behavioral sensitization and early adversity models. The early adversity sensitization hypothesis was supported. Individuals with severe early adversity relapsed following lower levels of stress than those with mild or no early adversity. This result is in keeping with similar studies investigating the stress–relapse relationship for unipolar depressed individuals (Hammen et al., 2000). Significant early adversity may be a risk factor for a more severe course of bipolar disorder (Post et al., 2001) and therefore, interventions may be especially important for individuals who have experienced severe early adversity.

Individuals who experienced early adversity also reported a younger age of onset of bipolar disorder than those who did not. This finding is in agreement with the results of Leverich et al. (2002) and also supports the early adversity sensitization hypothesis. Both sexual adversity and neglect were associated with a significantly earlier age of onset. Leverich et al. (2002) reported that sexual adversity and physical adversity, rather than neglect, were related to an earlier age of onset of bipolar disorder. The lack of significance for physical adversity may be due to methodological differences (questionnaire vs. interview), to different criteria for physical abuse, or to small sample size in the present study. Earlier age of onset of bipolar disorder for individuals who experienced early adversity has potentially significant consequences, given the associations between early onset of bipolar disorder and adverse social, educational and occupational functioning, worse course, and lack of response to treatment for these individuals (Post et al., 2001).

The behavioral sensitization hypothesis was not upheld because the number of episodes failed to moderate the association between stress and recurrence. This finding replicated the results of several past studies that also failed to support the behavioral sensitization hypothesis (Swendsen et al., 1995; Hlastala et al., 2000). There are several possible reasons for this lack of support. The current study involved between-group analyses, whereas a prospective within-subjects design would be more accurate and sensitive to changes in the association among stress, the number of prior episodes, and recurrence (Kendler et al., 2000). The number of past episodes was dichotomized and it is possible that a different cutoff point may have resulted in a significant interaction effect. Kendler et al. (2000) reported that the association between life stress and recurrence in unipolar major depression differed following nine

episodes. Finally, a third factor such as age may be involved in the sensitization effect (Hlastala et al., 2000).

An ideal test of the stress sensitization hypothesis would involve a prospective, longitudinal investigation of individuals at high genetic risk for bipolar disorder where the effects of stress on the very early episodes might be directly assessed. The influence of childhood adversity on the role of stress early in the course of the disorder could be determined in such a design. Early adversity (especially sexual abuse) may also be a consequence of the symptoms of bipolar disorder which may call the early adversity sensitization results into question. Geller and Luby (1997) reported that childhood onset bipolar disorder is characterized by hypersexuality which may influence the incidence of sexual abuse in childhood. To account for this limitation, participants with bipolar onset prior to age 12 (the cutoff for early adversity) were eliminated from the analysis involving sexual adversity. Additionally, in the current study, key clinical variables, including the number of prior episodes and age at onset, were determined based on retrospective self-report and are consequently vulnerable to problems in recall. The small number of participants in this study may reduce the statistical power needed to detect significant interaction effects. Another possible limitation is the lack of assessment of the influence of genetic risk for bipolar disorder. However, past research on kindling in bipolar illness has investigated the influence of stress and episode number on recurrence apart from possible genetic influence (Ghaemi et al., 1999). The calculation of the "too many to count" number of total episodes is another possible limitation although the analyses were also conducted without these participants and the results did not change significantly.

The key implication of this study is that childhood adversity may be related to a more challenging presentation of bipolar disorder, with an earlier age at onset and greater vulnerability to experiencing recurrences of mood episodes in the face of even mild stress. Earlier onset and a more difficult course of bipolar disorder may have serious consequences for both the efficacy of treatment of bipolar disorder and for the functioning of bipolar individuals. Post et al. (2001) reported that there is commonly a five to ten year lag between the onset of bipolar illness and the initiation of treatment, and that earlier onset in addition to the lack of treatment may lead to lack of response to lithium and more comorbid diagnoses. If childhood adversity is a trigger of earlier onset and sensitizes individuals to stress, preventing stress exposure in high risk families, or promoting coping capabilities in such youngsters might have positive consequences on the course of illness.

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