Impact of stressful life events, familial loading and their interaction on the onset of mood disorders

Study in a high-risk cohort of adolescent offspring of parents with bipolar disorder

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Background  Stressful life events are established as risk factors for the onset of mood disorders, but few studies have investigated their impact on the development of mood disorders in adolescents.

Aims  To study the effect of life events on the development of mood disorders in the offspring of parents with bipolar disorder, with respect to the possibility of a decay effect and modification by familial loading.

Method  In a high-risk cohort of 140 Dutch adolescent offspring of parents with bipolar disorder, we assessed life events, current and past DSM–IV diagnoses and familial loading. To explore their interaction and impact on mood disorder onset, we constructed four different models and used a multivariate survival analysis with time-dependent covariates.

Results  The relationship between life events and mood disorder was described optimally with a model in which the effects of life events gradually decayed by 25% per year. The effect of life event load was not significantly stronger in the case of high familial loading.

Conclusions  Independent of familial loading, life events increase the liability to mood disorders in children of patients with bipolar disorder but the effects slowly diminish with time.

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The offspring of parents with bipolar disorder have an approximately fourfold increased lifetime risk of developing a mood disorder (Lapalme et al., 1997; Delbello & Geller, 2001). Several studies have established associations between stressful life events and symptoms of depression (Williamson et al., 1998; Goodyer et al., 2000) and other emotional and behavioural disorders (Goodyer et al., 1987; Sandberg et al., 2001). The temporal process of onset of psychiatric disorders following stressful life events remains poorly understood. Surtees & Wainwright (1999) showed clear evidence for the progressive decay in the adverse effects of stressful life events over time. The aim of this study among an adolescent high-risk cohort was to investigate the relationship between stressful life events and the onset of mood disorders, with different models for the degree to which the presumed effects of stressful life events diminish over time. In addition, it was examined whether this relationship was modified by family loading for mood disorders.

METHOD

Design  The study presented here is part of an ongoing prospective high-risk cohort study among adolescent offspring of parents with bipolar disorder in The Netherlands. In this paper we discuss the findings from the first assessment. The study design, study population and prevalence of psychopathology among the offspring have been described by Wals et al. (2001). In brief, 86 parents with bipolar disorder and their spouses and 140 offspring aged 12–21 years were examined between November 1997 and March 1999. In the offspring, 38 (27%) were diagnosed with a lifetime mood disorder according to DSM–IV criteria (American Psychiatric Association, 1994), 23 (16%) had any other lifetime DSM–IV diagnosis and 79 (56%) did not have any DSM–IV diagnosis. We report the results of an analysis of retrospectively collected data from this cohort on the relationship between lifetime life events and subsequent lifetime mood disorder.

Stressful life events

The investigator-based Bedford College Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1978, 1989) is a semi-structured interview for assessing life events and long-term difficulties in adults. The LEDS covers ten domains: education, work, reproduction, money/possessions, housing, crime/legal, health, romantic relationships, other relationships and miscellaneous events (including deaths). It collects detailed information about the event itself, the timing of its occurrence (date) and relevant contextual information for each event. Based on the contextual information, the threat for each event is rated via standardized rating procedures. The threat score represents the severity of the event, ranging from mild (1) to severe (4). Several studies have supported the reliability (e.g. inter-rater) and validity (e.g. multiple informant) of the LEDS with adults exhibiting a variety of psychiatric symptoms (Brown & Harris, 1978, 1989; Ormel et al., 2001).

Monck & Dobbs (1985) originally adapted the LEDS methodology for use with adolescents. They developed a teenage LEDS manual with accompanying event dictionaries based on a study of 67 British female adolescents aged 15–20 years. We modified the Dutch adult LEDS interview and manual and translated the teenage event dictionaries into Dutch: the Kiddie LEDS (K–LEDS). The K–LEDS interviews were conducted by psychologists who had received K–LEDS training prior to interviewing. Because this K–LEDS interview covered the life cycle (childhood and early and late adolescence), all events and difficulties were dated on a yearly basis. In our analysis we used only the life event data because it was possible to date them more accurately than the long-term difficulties. We calculated the percentage fall-off of severe events recalled per annum, which appeared to be 11%. The events were rated from written transcriptions of the interview by three independent raters who had not been involved in the interviews and were masked to the respondents’ mental health status. A panel consisting of the three raters and two of the authors (M.H., M.W.)
reached consensus on the events that raised rating problems.

Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version

All children were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). The K-SADS is an interviewer-oriented diagnostic interview designed to assess current and past DSM-IV symptoms resulting in diagnoses in children and adolescents, by interviewing the parent(s) and child separately. The timing of illness episode onset was determined in cases where the DSM-IV criteria were fully met. If parents and child disagreed on the presence of a symptom, greater weight typically was given to parents' reports of observable behaviour and children's reports of subjective experiences (Kaufman et al., 1997). The K-SADS–PL was conducted by three of the authors (M.H., M.W. and C.R.) and by five intensively trained interviewers with graduate degrees in psychology.

Family History Research Diagnostic Criteria

Parents were interviewed using the Family History Research Diagnostic Criteria (FH–RDC) (Andreasen et al., 1977), which were used to calculate a continuous familial loading score for unipolar mood disorder, bipolar disorder and substance use disorder in first (n = 177) and second-degree relatives (n = 932) of the children. The index of family loading for the bipolar offspring is based on the number and age of the affected first- and second-degree relatives of the adolescent. Every relative examined using the FH–RDC contributed to the index, depending on whether the person was affected and the age at which the person was affected. We arbitrarily divided the continuous familial loading variable into high (> median) and low familial loading (< median). In our analyses we used the familial loading for unipolar mood disorder because all subjects had a first-degree family member with a bipolar disorder, consequently the familial loading for bipolar disorder did not differentiate. For a more detailed description of the calculation of the family loading, see Verdoux et al. (1996) and Wals et al. (2004).

Time-dependent life event load

To study the impact of life events on the onset of mood disorder, a time-dependent (or time-specific) life event load variable was calculated for every year of follow-up. This variable was designed to summarise the exposure load from all adverse events experienced up to a particular point in time, while accounting for number, severity and their lasting effects. The life event load was calculated according to four models. These models reflect different hypotheses concerning the time-related decay of the effect of a life event on the risk of mood disorder. In model I we tested a purely cumulative effect of the impact of life events on the development of mood disorder. Accordingly, the life event load at a particular point in time (year y) was simply calculated as the sum of the threat scores of the life events in year y and all preceding years. In models II, III and IV, the time-dependent life event load was subjected additionally to an exponential decay function. This reflects the hypothesis that the impact of life events principally accumulates but at the same time gradually decays as time goes by. In model II the decay function implied a 25% loss per year. In models III and IV we subjected the life event load to a yearly decay of 50% and 75%, respectively. In view of the retrospective nature of data collection, we included only severe life events (threat score 3 and 4) that had occurred after the age of 4 years. Consequently, follow-up time started at age 5 years. If more than one life event occurred in the same year, the threat scores for these events were summed.

Data analysis

The relationship between life events and the occurrence of mood disorder was studied using a statistical model relating determinants whose statuses change over time to survival-type (censored) outcome data, i.e. Cox regression with time-varying covariates (Cox, 1972). Because the 140 children originated from 86 families, data must be considered correlated through family. Therefore, we used a ‘frailty’ model, i.e. a Cox model with a cluster variable indicating family. Time-varying influence of life events was permitted by including the time-dependent life event load as a continuous time-varying covariate in the model. In this model the dependent variable was time from age 5 years to first mood disorder or, if no mood disorder occurred, time from age 5 years to interview. The results are expressed as hazard ratios indicating the instant relative risk of mood disorder per unit life event load, thus representing the strength of the association. Hazard ratios were presented with 95% confidence intervals (95% CIs). To find out which of the four life event load (decay) functions is optimally in agreement with the observed data, we compared Akaïke's information criterion \((-2 \times \text{maximised log-likelihood} + 3 \times \text{number of parameters})\) between the four regression models (Akaïke, 1973). This index can be interpreted only in a relative sense, i.e. lower values indicate better agreement. We included familial loading and gender as fixed covariates in the regression models to examine whether they confounded the association between life event load and onset of mood disorder. Confounding was considered present if inclusion of these variables substantially (by at least 10%) changed the hazard ratios for life event load. To investigate whether the relationship between life event load and mood disorder depended on familial loading (i.e. multiplicative interaction or effect modification), we included an interaction term of familial loading variable \(\times\) life event load variable as a covariate in the model, and tested its statistical significance. Interaction was explored further by presenting separately the life event hazard ratios for children with familial loading above and below the median. The analyses of interaction were performed for the model showing optimal agreement with the observed data only. The level of significance in all analyses was \(P < 0.05\) (two-sided).

RESULTS

The general characteristics of our study population are shown in Table 1. Thirty-eight (27%) of the children developed a mood disorder during follow-up at a median (range) age of 14 (7–20) years. Of these, four had bipolar disorder, eight had major depressive disorder, eight had dysthymic disorder, two had cyclothymic disorder, fifteen had depressive disorder not otherwise specified, one had adjustment disorder with depressed mood and two had mood disorder not otherwise specified. Because one individual could receive more than one lifetime diagnosis, there are 40 diagnoses among 38 individuals. The median of the familial loading scores for unipolar
mood disorder and the median of the number of severe life events are also shown in Table 1.

The life event load in 5-year age categories is displayed in Table 2, demonstrating the net effect of the summation (model I) and decay functions (models II, III, and IV) on the life event load in these age groups for all individuals during the entire follow-up period. As a consequence, life events that had occurred after the onset of a mood disorder also contributed to the life event load. (In the analyses examining the association between life events and mood disorders, only events preceding the onset of the first mood disorder were taken into account.) In models I and II a monotonous increase was found, but in the models with the strong decay functions superimposed an inverse U-shape of the mean life event load with age was observed.

The relation between life event load and mood disorder is depicted in Table 3. Irrespective of the model employed, the life event load was significantly associated with an approximately 10% increased risk (hazard ratio = 1.1) of mood disorder per unit life event load. Although high familial loading (> median) itself was strongly related to mood disorder, with hazard ratios of 3.05 (95% CI 1.49–6.25), 2.61 (95% CI 1.29–5.30), 2.53 (95% CI 1.25–5.10) and 2.54 (95% CI 1.27–5.11) for models I–IV, respectively, adjustment for this variable hardly had an effect on the life event load–mood disorder association. This indicates that familial loading was no confounder. Adjustment for gender did not change the life event hazard ratios either. According to Akaike’s information criterion, model II was most in agreement with the observed data.

Figure 1 illustrates the relationship between life event load and mood disorder. It shows that in the majority of follow-up years the life event load was considerably higher for those who developed a mood disorder than for those who did not. Above and below the median of the familial loading variable the hazard ratios in model II for the relation between life event load and mood disorder were similar: 1.090 (95% CI 0.928–1.280) and 1.110 (95% CI 1.059–1.163), respectively. In line with this, the interaction term was not statistically significant (P = 0.73), indicating no modification of the relationship between life event load and mood disorder by familial loading.

**DISCUSSION**

In the present study a strong relationship between life events and the risk of mood disorder in the offspring of patients with bipolar mood disorder was demonstrated. The relationship was best described using model II, in which the effects of life events steadily decay by 25% per year. Both Delbello & Geller (2001) and Lapalme et al. (1997) found that offspring of parents with bipolar disorder are at increased risk of developing mood disorders and other psychopathology. Familial loading of unipolar disorder was significantly associated with the lifetime prevalence of mood disorders in our sample of adolescent offspring of parents with bipolar disorder (Wals et al., 2004). However, familial loading did not confound or modify the relation between life events and mood disorder in this study. Both had independent effects on risk of mood disorders.

**Comparison with other studies**

Few high-risk studies report the influence of stressful life events as a risk factor for the development of bipolar disorder. Johnson et al. (2000) concluded that patients with bipolar disorder and with high constitutional vulnerability had an earlier age of onset and needed fewer stress factors (early parental separation and life events) to become ill compared with patients with unipolar illness. The Cardiff Depression Study (Farmer et al., 2002) investigated the suggested co-familiality of depression and life events and whether there might be a common familial factor influencing vulnerability to depression and the experience of life events. Using a sib-pair design, they reported no evidence for a common factor influencing both depression and life events. Kendler & Karkowski-Shuman (1997) showed that, in adults, negative life events were most likely to lead to the onset of major depressive disorder in individuals inferred to have a genetic liability to depression, and also that the genetic liability to depression overlaps with the genetic liability to experience stressful life events. So, through their behaviour, people can to some extent shape and select their environments.

Our findings are in line with the work of Wainwright & Surtees (2002), who developed sophisticated analytical approaches to study adversity–disorder relationships. Their study, like ours,

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**Table 1** General characteristics of study population (n = 140)

| Characteristic                  |  
|--------------------------------|--------------------------------|
| Male (n, %)                     | 72 (51%)                      |
| Female (n, %)                   | 68 (49%)                      |
| Any mood disorder (n, %)        | 38 (27%)                      |
| Any non-mood disorder (n, %)    | 23 (16%)                      |
| No disorder (n, %)              | 75 (56%)                      |
| Age (mean, s.d.)                | 16 (2.7)                      |
| Life events (median, range)     | 4.0 (1–16)                    |
| Familial loading (median, range)| -0.38                         |

1. Adolescents with a lifetime DSM–IV diagnosis.
2. This category consisted of anxiety, attention-deficit hyperactivity disorder, disruptive behaviour, substance abuse, enuresis, encopresis, pervasive developmental disorder, tic, obsessive–compulsive disorder and eating disorders.

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**Table 2** Life event load according to age category and model

<table>
<thead>
<tr>
<th>Model</th>
<th>Age category (years)</th>
<th>5–10</th>
<th>11–15</th>
<th>16–20</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (cumulative)</td>
<td>1.7 (2.3)</td>
<td>6.6 (5.2)</td>
<td>11.9 (6.1)</td>
<td></td>
</tr>
<tr>
<td>II (25% decay)</td>
<td>1.3 (1.6)</td>
<td>3.4 (2.7)</td>
<td>4.0 (3.0)</td>
<td></td>
</tr>
<tr>
<td>III (50% decay)</td>
<td>1.0 (1.2)</td>
<td>2.1 (1.7)</td>
<td>2.0 (2.2)</td>
<td></td>
</tr>
<tr>
<td>IV (75% decay)</td>
<td>0.8 (0.9)</td>
<td>1.5 (1.2)</td>
<td>1.3 (1.6)</td>
<td></td>
</tr>
</tbody>
</table>

1. Values are means, with standard deviations in parentheses.

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**Table 3** Relative risk of a mood disorder using four models of events effect decay

<table>
<thead>
<tr>
<th>Model</th>
<th>Life event load</th>
<th>Life event load (FL adjusted)</th>
<th>−2 log-likelihood +3</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (cumulative)</td>
<td>1.069 (1.033–1.106)</td>
<td>1.073 (1.041–1.106)</td>
<td>327.2</td>
</tr>
<tr>
<td>II (25% decay)</td>
<td>1.100 (1.064–1.137)</td>
<td>1.091 (1.053–1.130)</td>
<td>324.8</td>
</tr>
<tr>
<td>III (50% decay)</td>
<td>1.114 (1.072–1.157)</td>
<td>1.101 (1.057–1.148)</td>
<td>325.6</td>
</tr>
<tr>
<td>IV (75% decay)</td>
<td>1.115 (1.069–1.162)</td>
<td>1.102 (1.053–1.153)</td>
<td>328.2</td>
</tr>
</tbody>
</table>

1. Values are hazard ratios for mood disorder per unit life event load, with 95% confidence intervals in parentheses. FL, familial loading (dichotomised at median).
showed that the simplest model involving a single time-dependent covariate was inappropriate because it failed to capture the decay in the event effects and that an exponential decay of the adverse effects of life events over time had to be modelled. In studying the effects of negative life events on the onset of mood disorders in a high-risk group of adolescents, Silberg et al. (2001) found that there was no effect of independent life events on the adolescents' depression in the absence of parental emotional disorder but there was a significant effect in its presence. In our sample all subjects had a parent with bipolar disorder. As described, high familial loading was based on the number and age of unipolar affected first- and second-degree relatives of the adolescents.

**Strengths and limitations**

A major limitation of this study is that all data were collected at a particular point in time. Within a cross-sectional design we employed a longitudinal approach by dating the onset of episodes of mood disorders and the occurrence of life events. This approach brings a number of limitations in its wake. First, subjects with a mood disorder could have been more inclined to remember life events than those without this condition, which would result in recall bias; therefore, we restricted our analyses to severe life events and omitted the first 5 years of life. Also, the events were rated from written transcripts of the interview by three independent raters who had not been involved in the interviews and were masked to the respondents' mental health status. To explore the possibility of recall bias we divided the subjects with a mood disorder into current cases (i.e., at the time of the interview) and past cases, and compared the life events reported in the preceding 2 years. If recall bias played an important role, it would probably influence the current cases more than the past cases. The results of this analysis, however, showed that the mean threat scores were similar (.42 and 4.0, respectively).

Second, one could question the validity of the LEDS used retrospectively to collect the life event data. Most of the studies concerning the validity of retrospective reports collected by the LEDS were restricted to a 12-month period. There have also been studies using the LEDS to test the validity of life events reported over a 10-year period. The 'fall-off in terms of the length of time from the date of the reported event or difficulty to the point of interview was checked and found to be surprisingly low for all events; 4.8% per year (Neislon et al., 1989). In our sample, as mentioned before, we calculated the percentage fall-off of severe events recalled per annum, which appeared to be 11%. Retrospective reporting of life events using checklist inventories typically declines at a rate of 5% or more each month (Funch & Marshall, 1984). This suggests that in an aetiological enquiry it might well be possible to use the LEDS to cover a whole decade.

A further limitation might be that the sample is not population based. Only patients with children aged 12–21 years who were willing to participate were included. A control group of adolescents without a parent with bipolar disorder would have given more data to study the impact of stressful life events on the onset of mood disorders. Because the LEDS interview alone takes about 3h and the rating takes another hour, financially this was not an option. Another limitation is that the group of adolescents with a mood disorder is relatively small in our sample. Consequently, the statistical power to demonstrate an interaction between life event load and familial loading was limited.

According to our study the impact of stressful life events principally accumulates but at the same time gradually decays (25% per year) as time goes by. This suggests that the effects of stressful life events do not simply add up or rapidly extinguish but, in a gradually fading fashion carry over into the future risk of an episode of mood disorder. What drives the decay is not known, it might result from coping strategies or the effect of neutralising life events. Although high familial loading for unipolar depression was strongly related to risk of mood disorder, familial loading did not confound the relationship between life event load and mood disorder. There was also no evidence suggesting that familial loading modified the relationship between life event load and mood disorder.

**Future directions**

Improvements in the specification of stress modelling procedures might facilitate the integration of ideas from competing aetiological models of the onset and subsequent course of mood disorders. There are still many aspects of the stressful life illness relationship that should be considered in future studies: the underlying assumption of an additive effect of multiple life events, the possible dose–response effect of adverse life events and the existence of threshold effects. Other interesting topics for further research are the influence of life events on the duration and course of the mood disorders and the effects of comorbidity, temperament and specific coping skills. Goodyer (2002) referred also to limbic–cortical neural networks in his framework for future research on this topic.

**REFERENCES**


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