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Research report

Stressful life events and onset of mood disorders in children of bipolar parents during 14-month follow-up

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Abstract

Background: Although multiple studies have examined the association between stressful life events (SLEs) and the development of mood disorders, the exact nature of the association and the degree to which it is independent from familial loading (FL) and gender-specific are still not fully elucidated.
Aims: To study the association between person-independent and -dependent SLEs and first onset or recurrence of a DSM-IV mood disorder episode (MDE) in offspring of bipolar parents. To examine interaction effects of SLEs with familial loading and gender.
Method: Offspring of bipolar parents ($N = 132$) were assessed with the K-LEDS, the FHRDC and the K-SADS. Logistic regression analysis was used to examine main and interaction effects of various operationalizations of SLEs, familial loading and gender.
Results: Dependent SLEs were more likely to occur before onset among the 13 offspring who had a MDE onset during the 14-month follow-up (39%) than in a comparable period among the 67 controls without any lifetime diagnosis (10%). Associations were slightly stronger for first onsets than for recurrences. The association between SLEs and MDE onset/recurrence was independent of socio-demographic characteristics and familial loading, but disappeared when adjusted for baseline anxious/depressive symptoms. Gender and familial loading did not modify the influence of any SLE measure on the development of mood disorders.
Conclusions: In this sample of bipolar offspring dependent stressful SLEs triggered the onset of MDEs, but this association disappeared after adjustment of prior anxious/depressive symptoms, indicating that the association between SLEs and MDE is probably a spurious association. No interaction was found between SLE and FL and gender. Prior anxious/depressive symptoms seem to increase the risk for both occurrence of dependent SLEs and MDE onset or recurrence.
Limitations: Limited statistical power due to small number of MDE onsets.
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Keywords: Life events; Familial loading; Bipolar offspring

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1. Introduction

The impact of environmental factors, especially stressful life events (SLEs), contributing to the development of unipolar and bipolar mood disorders among adults has been the subject of several studies. In a review, Paykel (2003) reported that episodes of unipolar depression in adults are preceded by SLEs at higher rates than in general population or non-depressed patient samples. Kessing et al. (2004) found that first admissions of adults with mania were often preceded by the occurrence of death by suicide in the family or other major SLEs. Petti et al. (2004) found that the depressed offspring of bipolar parents showed higher levels of dependent negative SLEs preceding onset of their disorder than offspring without affective disorders. Studies examining the impact of SLEs on the development of mood disorders among children and adolescents also reported associations between prior SLEs and onset of depressive disorder (e.g. Goodyer et al., 1985, 1987; Williamson et al., 1998).

There is large individual variation in response to SLEs and it is likely that genetic influences are involved in such individual differences (Rutter, 2003). SLEs may have only effects on developing mood disorders in offspring with high genetic risk. Silberg et al. (2001) found no effect of SLEs on depression in 184 same-gender female twin pairs aged 14–17 years in the absence of parental emotional disorder. However, in the presence of parental emotional disorder there was a significant effect of SLEs on the presence of adolescent twins' depression indicating gene–environment interaction. In addition, a number of studies have shown that individuals, through their behavior, shape and select their environments and that this is so for environments that involve substantial risks for psychopathology, indicating gene–environment correlation. For instance, Kendler and Karkowski-Shuman (1997) reported that genetic liability to major depression in a sample of 2164 female twins was associated with a significantly increased risk for six personal SLEs (e.g. assault, serious illness) and one network SLE (trouble getting along with relatives/friends). They concluded that genetic risk factors for major depression increase the probability of experiencing certain SLEs and that genes could impact on the risk for psychiatric illness by causing individuals to select themselves into high-risk environments.

Number of SLEs and its impact on the development of mood disorders may not be equally distributed across gender. Women in adolescence and young adulthood are about twice as likely as men to develop mood disorders (Weissman and Klerman, 1977). A number of studies have explored gender differences in the frequency of reported SLEs or in the sensitivity to the effects of SLEs on mental health (e.g. Nolen-Hoeksema and Girgus, 1994 for a review). For instance, Christensen et al. (2003) reported that, among a sample of bipolar adults, women experienced a significantly higher number of SLEs than men and depressive episodes in women were more often preceded by SLEs than in men.

There are a number of methodological problems with existing studies, including the reliability of retrospective reporting on SLEs over a relatively long period of time, the methods of measuring SLEs, and the lack of distinguishing between SLEs that were a consequence of the disorder rather than preceding it. To our knowledge, none of the SLE studies has controlled for baseline symptoms. This is important since baseline symptoms could increase the risk for both SLE and MDE onset. In an earlier study we found an association between SLEs and lifetime mood disorders among the adolescent offspring of bipolar parents, which was independent from the impact of familial loading (FL) on lifetime mood disorders in this sample (Hillegers et al., 2004). A problem was that both diagnoses and SLEs were assessed retrospectively over a very long (lifetime) period in the subjects.

The present study explores the association between SLEs and the onset of a mood disorder episode (MDE) in the same cohort, across a 14-month interval. For reasons of brevity "onset of MDE" will include onset of both a first or recurrent episode of a mood disorder. A major advantage of such a relatively short period is that SLEs and symptoms will be recalled more accurately. Since the timing of events as well as the timing of the diagnoses have been established thoroughly within this 14-month follow-up period, it is easier to establish the direction of the possible association between SLEs and onset of MDEs. In line with Brown and Harris (1978, 1989), we differentiated between dependent and independent SLEs, e.g. events that were influenced by respondents own behavior or events that were independent from

respondents own behavior. More specifically, this study is aimed to determine: (1) the association between SLEs and subsequent onset of MDE during a 14-month follow-up, (2) whether this association might be due to prior depressive symptoms, (3) whether SLEs mediate the association between familial loading and MDE onset, (4) whether familial loading moderates the association of SLES with MDE, and (5) whether gender moderates the association of SLEs with MDE.

2. Materials and methods

2.1. Sample

A sample of 140 children (72 boys, 68 girls) aged 12 to 21 years of 86 parents (52 mothers, 34 fathers) with bipolar I or II disorder was initially recruited (T1). Children with a severe physical disease or handicap or with an IQ below 70 were excluded. The mean age of the participating offspring at T1 was 16.1 years (S.D.=2.7; range 12–21). Fourteen months after the first measurement, 132 subjects, aged 13 to 23 years, were reassessed (T2). The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study. After a complete description of the study was given to all participating parents and offspring written informed consent from both parents and their offspring was obtained.

For a more detailed description of the recruitment and demographic characteristics of the sample we refer to Wals et al. (2001).

2.2. Instruments

2.2.1. IDCL
DSM-IV bipolar I or II diagnoses were confirmed by administering the mood disorders section of the International Diagnostic Check List (IDCL, Hiller et al., 1993) in the interview with the bipolar parent. We compared the IDCL-based diagnoses with the DSM-IV diagnoses made by the treating psychiatrist and did not find any discrepancies.

2.2.2. K-SADS-PL
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. If parents and child disagreed on the presence of a symptom, greater weight was typically given to parents' reports of observable behavior and children's' reports of subjective experiences (Kaufman et al., 1997) The K-SADS-PL was conducted by three of the authors (MW, MH and CR), and by five intensively trained interviewers with graduate degrees in psychology.

2.3. Stressful life events (SLEs)

The Bedford College Life Event and Difficulties Schedule (LEDS) (Brown and Harris, 1978, 1989) is a semi-structured interview for assessing SLEs and long-term difficulties in adults. Based on contextual information, the threat for each event is rated through standardized rating procedures. The threat score represents the severity of the event, ranging from mild (1) to severe (4). Contextual threat is conceptualized as: "What most people would be expected to feel about an event in a particular set of circumstances and biography, taking no account of what the respondent says either about his or her reaction or about any psychiatric or physical symptoms that followed it" (Brown and Harris, 1978).

Several studies have supported the reliability (e.g. interrater) and validity (e.g. multiple informant) of the LEDS with adults exhibiting a variety of psychiatric symptoms (Brown and Harris, 1978, 1989). Monck and Dobbs (1985) originally adapted the Bedford College 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 (Monck and Dobbs, 1985). The K-LEDS interviews were conducted by psychologists who had received a K-LEDS training prior to interviewing. All events and difficulties were carefully dated on a monthly basis by using a personal calendar with reference points such as birthdays, holidays, and already dated events. Since the follow-up period was only 14 months and within this period a lot of anchor points could be indicated, we believe that the offspring were accurately able to

date the SLEs that they experienced. The events were rated from written transcriptions of the interview by three independent raters, who had not been involved in the interviews and who were blind to the respondents' mental health status. A panel consisting of the three raters and the two of the authors (MW, MH) reached consensus on the events that raised rating problems. We distinguished the experienced SLEs in events that were dependent from the respondents own behavior (dependent SLEs) versus those who were not (independent SLEs). For independent SLEs we constructed two measures: at least one severe SLE (threat score 3 and 4) and total severity for all SLEs. The same measures were constructed for dependent SLEs.

2.4. Assessment of baseline depressive symptoms

Both affected and non-affected mothers completed the Child Behavior Checklist for ages 4 to 18 (CBCL, Achenbach, 1991) or the Young Adult Behavior Checklist (YABCL, Achenbach, 1997) which is an upward extension of the CBCL for ages 18 years and older, and contains problem items that are completed by parents. The YABCL can be scored on syndrome scales similar to those of the CBCL. For the present study we computed an Anxious/Depressed score from the items that were common to the CBCL and YABCL. The Anxious/Depressed scale consists of the following items: complaints of loneliness, cries a lot, fears he/she might think or do something bad, feels he/she has to be perfect, feels or complaints that no one loves him/her, feels others are out to get him/her, feels worthless or inferior, nervous, high-strung or tense, too fearful or anxious, feels to guilty, self-conscious or easily embarrassed, suspicious, unhappy, sad or depressed and worries. The parents have to circle for each item that is described the 2 if the item is very true or often true of their child, the 1 if the item is somewhat or sometimes true of their child and the 0 if the item is not true of their child.

2.5. Assessment of familial loading

Lifetime prevalence of psychopathology in the parents ($N = 177$) and their non-offspring first-degree relatives ($N = 932$) was assessed with the Family History-Research Diagnostic Criteria (FH-RDC; Andreasen et al., 1977) interview which was administered to both parents. A previously described method of calculating a familial loading score was used, considering family history as an attribute of the individual cases themselves, which might be related to their psychopathological outcome, see Verdoux et al. (1996). This index of familial 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 with the FH-RDC contributed to the index depending on whether the person was affected and on the age at which the person was affected. For the purpose of this study we calculated a familial loading score for unipolar disorder. The FH-RDC was administered by two of the authors (MW, MH), and by five intensively trained interviewers with graduate degrees in psychology. As described by Todd et al. (1993), the completeness of FH-RDC information was rated by the interviewers on a five-point scale (1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = essentially no information). A score of 1 was defined as a diagnosis of unipolar disorder made by a clinician or if the family member fulfilled the criteria of the disorder of e.g. bipolar disorder and was known to be treated with a mood stabilizer. A score of 2 was used when the exact diagnosis was not known but when symptoms were present which indicated the presence of a unipolar depression based on content, duration, and treatment in a treatment setting. Only individuals with scores of 1 or 2 were included. A panel consisting of the five interviewers and three of the authors (MW, CR, MH) reached consensus on the disorders that raised rating problems. We only used the top two categories and therefore applied a relatively high threshold for family members to be diagnosed as mood disordered.

For a more detailed description of the familial loading score we refer to Wals et al. (2003, 2004).

2.6. Socioeconomic status

Socio-economic status (SES) was scored on a 9-point scale of parental occupational level with 1 = lowest and 9 = highest. If both parents worked, the highest score was used.

2.7. Statistical analysis

Because previous studies have shown that the rate of SLEs began to diverge between cases and controls
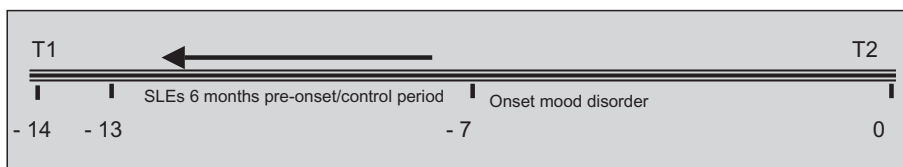
Fig. 1. Index period and control period for affected and non-affected (control) cases.

3–4 months before onset (Brilman and Ormel, 2001), only SLEs occurring in the 6 months preceding the onset of the disorder were used for the present analyses. For the unaffected control cases, SLEs occurring within the 6 months prior to the mean number of months that diagnosis in the affected cases appeared before T2 were used for analysis (see Fig. 1). As shown in Fig. 1, on average, onset of mood disorder occurred 7 months before T2 (S.D.=5). So, for the control (unaffected) cases the LEDS reference period was between 7 and 13 months before the interview.

The SLEs occurring in the reference periods were analyzed by means of logistic regression analysis, with onset of MDE (first episode or recurrence) between T1 and T2 among subjects with MDE ($N=13$) versus a contrast group of subjects without any lifetime diagnosis ($N=67$) as the outcome variable. Odds ratios (ORs) were used to express the strength of the association between predictors and onset of depression.

First, unadjusted associations between dependent and independent SLEs with MDE onset were calculated. Then, these analyses were adjusted for gender, age and SES. We chose gender, age and SES as covariates since these variables may be associated with both the predictor variable (SLEs) and the outcomes (mood and no disorders in the offspring). Next, the associations between SLEs and MDE onset were adjusted for baseline depressive symptoms.

In order to examine the possibility that number of SLEs acted as a mediator for the association between familial loading and mood disorder onset (gene–environment correlation), we adjusted the associations between familial loading and MDE onset for SLEs. In addition, interactions between SLEs and familial loading and between SLEs and gender were calculated. The level of significance (alpha) in all analyses was 0.05 (two-sided), except for the interactions for which the alpha was set at 0.01.

3. Results

At T2, 43 (33%) of the participating offspring ($N=132$) were diagnosed with a lifetime mood disorder (Reichart et al., 2004). Sixty-seven (51%) never had any lifetime diagnosis ($N=67$, 32 females, 35 males, mean age=17.0 years). Of the total sample 13 (10%, 8 females, 5 males, mean age=15.9 years) had developed a first onset mood disorder ($N=8$) or a recurrence of a mood disorder ($N=5$) during the 14-month follow-up. One of the offspring developed bipolar disorder during follow-up and 4 already had developed a bipolar disorder at first measurement. For a more detailed description of the prevalence of psychopathology in our sample we refer to our previous publications (Reichart et al., 2004; Wals et al., 2001).

Table 1
Frequencies of SLEs for offspring with a MDE onset during 14-month follow-up versus no lifetime disorder

Stressful life events	Contrast group[a]					Subjects with MDE onset				
	Total ($N=67$)	FL+[b] ($N=27$)	FL−[b] ($N=40$)	Males ($N=35$)	Females ($N=32$)	Total ($N=13$)	FL+[b] ($N=7$)	FL−[b] ($N=6$)	Males ($N=5$)	Females ($N=8$)
≥1 any severe	22 (33%)	9 (33%)	13 (33%)	8 (23%)	14 (44%)	7 (54%)	4 (57%)	3 (50%)	2 (40%)	5 (63%)
≥1 severe independent	16 (24%)	6 (22%)	10 (25%)	2 (6%)	10 (31%)	6 (46%)	3 (43%)	3 (50%)	2 (40%)	3 (38%)
≥1 severe dependent	7 (10%)	3 (11%)	4 (10%)	6 (17%)	14 (44%)	5 (39%)	3 (43%)	2 (33%)	2 (40%)	4 (50%)

[a] Subjects without any life time DSM-IV diagnosis.
[b] FL+, familial loading score above median of the whole sample ($N=80$); FL−, familial loading score below median.

Table 2
Pearson correlations between SLEs, gender, age, baseline symptoms and familial loading (FL) of unipolar disorder and onset of mood disorder episode (MDE) during 14-month follow-up

	≥ 1 severe independent SLE	≥ 1 severe dependent SLE	Total severity independent SLEs	Total severity dependent SLEs	Gender	Age	SES	FL	Baseline symptoms	MDE
≥ 1 severe independent SLE	–									
≥ 1 severe dependent SLE	0.055	–								
Total severity independent SLEs	0.532**	− 0.011	–							
Total severity dependent SLEs	0.172	0.408**	0.319**	–						
Gender	0.168	0.140	0.170	0.164	–					
Age	− 0.233*	− 0.199	− 0.042	− 0.027	0.076	–				
SES	− 0.304**	− 0.023	− 0.276*	− 0.259*	− 0.110	0.123	–			
FL	0.001	− 0.010	0.089	− 0.008	0.144	− 0.052	0.141	–		
Baseline symptoms	0.260*	0.260*	0.110	0.391**	0.110	0.002	− 0.056	0.026	–	
MDE onset	0.184	0.289**	0.041	0.241*	0.102	0.142	− 0.151	− 0.102	0.612**	–

* $P<0.05$.
** $P<0.01$.

Table 1 shows the frequencies of offspring with any or at least one severe SLE and the total severity of SLEs for offspring with a MDE onset versus those who never had any lifetime diagnosis. As shown in the table, dependent SLEs were more likely to occur before onset among the 13 offspring who had a MDE onset during the 14-month follow-up (39%) than in the control period among the 67 controls without any lifetime diagnosis (10%).

Pearson correlations between SLEs, gender, age, SES, familial loading, and CBCL/YABCL Anxious/Depressed scores with MDE onset are shown in Table 2. We will only discuss the significant associations. Dependent SLEs (both SLE measures) were correlated with MDE onset. SES was negatively correlated with independent SLEs (both SLE measures) and with at least one severe dependent SLE, indicating that the lower the SES, the higher the severity level of SLEs and the higher the number of offspring experiencing at least one severe SLE. Age at initial assessment was negatively correlated with at least one severe independent SLE.

Table 3 shows associations, based on logistic regression analyses, between the two SLE measures for dependent and independent SLEs with MDE onset during follow-up. Both measures for dependent SLEs were significantly associated with onset of MDE. Independent SLEs were not significantly associated with onset of MDE. The total number of offspring with at least one severe dependent SLE remained significantly associated with MDE onset after adjustment for gender, age and SES. Total severity for dependent SLEs was not significantly associated with MDE onset anymore after adjustment for gender, age and SES, but the OR only slightly decreased and the confidence intervals remained the same.

In Table 4, the associations between SLEs, adjusted for familial loading, and MDE onset and interac-

Table 3
Logistic regression analysis: impact of pre-onset stressful life events (SLEs) on MDE onset during 14-month follow-up[a]

	Unadjusted SLEs			SLEs adjusted for gender, age and SES			SLEs adjusted for baseline symptoms		
	OR	CI	P	OR	CI	P	OR	CI	P
Total severity independent SLEs	1.0	0.9–1.2	0.718	1.0	0.8–1.2	0.837	0.9	0.7–1.2	0.560
Total severity dependent SLEs	1.3	1.0–1.6	0.044	1.2	1.0–1.6	0.100	0.9	0.6–1.4	0.722
≥ 1 severe independent SLE	2.7	0.8–9.3	0.108	3.1	0.7–14.0	0.134	1.1	0.2–6.0	0.933
≥ 1 severe dependent SLE	5.4	1.4–21.0	0.016	11.1	2.0–61.7	0.006	2.2	0.3–14.4	0.395

[a] Subjects with MDE onset ($N=13$) compared with a contrast group without any lifetime diagnosis ($N=67$).

Table 4

Logistic regression analysis: impact of pre-onset stressful life events (SLEs) on MDE onset during 14-month follow-up: adjusted for familial loading (FL)[a] and interactions between SLEs by FL and SLEs by gender [b]

	Odds ratio	CI	P
Total severity independent SLE	1.0	0.9–1.2	0.655
FL dep	0.7	0.3–1.5	0.348
Total severity SLEs × FL dep	1.0	0.9–1.2	0.747
Total severity SLEs × gender	0.8	0.6–1.1	0.211
Sum severity dependent SLE	1.3	1.0–1.6	0.047
FL dep	0.7	0.3–1.6	0.380
Total severity SLEs × FL dep	1.5	1.0–2.2	0.110
Total severity SLEs × gender	1.0	0.6–1.7	0.877
≥1 severe independent SLE	2.8	0.8–9.5	0.107
FL dep	0.7	0.3–1.6	0.357
≥1 severe independent SLE × FL dep	0.7	0.1–2.9	0.688
≥1 severe independent SLE × gender	0.7	0.1–5.8	0.768
≥1 severe dependent SLE	5.5	1.4–22.1	0.015
FL dep	0.6	0.3–1.6	0.338
≥1 severe dependent SLE × FL dep	1.2	0.2–6.5	0.847
≥1 severe dependent SLE × gender	0.3	0.0–3.3	0.403

[a] Subjects with MDE onset ($N = 13$) are compared with a contrast group of subjects without any lifetime diagnosis ($N = 67$).
[b] For interactions a confidence interval of 90% was used.

tions between SLEs and familial loading and gender are presented. The associations between both measures for dependent SLEs remained significant after adjustment for familial loading.

The association between familial loading and MDE onset did not decrease after adjustment for SLE, indicating that SLEs did not mediate the association between familial loading and MDE onset.

To examine whether the association between dependent SLEs and MDE was due to baseline anxious/depressive symptoms, we repeated the logistic regression analyses between SLEs and MDE onset while adjusting for baseline anxious/depressive symptoms as assessed with T1 CBCL/YABCL Anxious/Depressed scale scores. After adjustment, none of the initially significant associations between dependent SLEs and MDE was significant anymore. The association between dependent SLEs and MDE onset decreased from 5.4 (CI = 1.4–21.0) to 2.2 (CI = 0.3–14.4) for at least one severe dependent SLE and from 1.3 (CI = 1.0–1.6) to 0.9 (CI = 0.6–1.4) for total severity of dependent SLEs. The as-

sociation between CBCL/YABCL Anxious/Depressed scores and MDE did not decrease after adjustment for dependent SLEs, indicating that dependent SLEs did not mediate the association between CBCL/YABCL Anxious/Depressed scores and MDE onset.

There were no significant interactions between both measures for dependent or independent SLEs and familial loading on MDE onset. In addition, no significant interactions were found for SLEs and gender. This indicates that the association between SLEs with MDE onset is neither weakened nor strengthened by the presence or absence of familial loading of unipolar disorder or by the gender of the offspring. However, because the logistic regression model is multiplicative (the predictor variables are additively associated with the logit of the probability of onset, but multiplicatively linked to the probability itself), the question whether familial loading or gender influenced the risk of MDE onset associated with SLEs could not be answered in a straightforward matter (i.e. by testing the interaction terms, see Ormel et al., 2001). Therefore, we decided to divide our sample into two subgroups with high or low familial loading, i.e. scoring above or below the median of the familial loading score, respectively. In the logistic regression analysis for these two subgroups we did not find a significant association between any SLE measure and onset of MDE in the high or in the low familial loading subgroup. In addition, we divided our sample in female and male offspring and ran the logistic regression analyses again. We did not find a significant association between any SLE measure and onset of MDE for females and for males separately, with the exception that males showed a significant association between at least one dependent SLE and MDE onset, but this association disappeared when adjusted CBCL/YABCL Anxious/Depressed scores.

In order to examine whether our familial loading score is predominantly genetic of origin or confers predominantly an environmental risk, we partitioned risk according to relatives living with the offspring versus those who are not. After excluding the first-degree relatives from the familial loading score all significant associations remained significant, but again these associations disappeared when adjusted for CBCL/YABCL Anxious/Depressed scores.

3.1. First ever onsets versus recurrent episodes

Since previous studies reported that the association between SLEs and major depression was stronger for people experiencing a first as opposed to a recurrent episode (e.g. Perris, 1984; Ezquiaga et al., 1987; Ghaziuddin et al., 1990), we investigated whether the impact of SLEs in our sample was stronger in first onsets as compared to recurrences of mood disorders. We therefore ran the logistic analyses for offspring with a first onset (N=8) and for offspring with a recurrent onset (N=5) versus those without any lifetime diagnosis (N=67) separately. The results of these analyses showed that only for offspring with first onsets of mood disorders the association between at least one dependent SLE and MDE was significant (OR=8.6, CI=1.7–42.1, P=0.008). However, when adjusted for CBCL/YABCL Anxious/Depressed scores it was not significant anymore. For offspring with recurrences the association between dependent SLEs and MDE was not significant (OR=2.1, CI=0.2–21.9, P=0.521). Thus, it seemed that dependent SLEs were more strongly associated with a first MDE as compared to a recurrent MDE, but again when we adjusted for baseline symptoms this association disappeared.

4. Discussion

To our knowledge this is the first study that examined the association between SLEs and subsequent onset of a first or recurrent mood disorder episode (MDE) in adolescent and young adult offspring of bipolar parents, while controlling for familial loading, gender, age and SES. The methodology facilitated a more accurate recall and timing of SLEs and symptoms than in studies covering longer time intervals and using less accurate measures. This enabled us to focus on SLEs preceding the onset of the disorder and to adjust for baseline symptoms.

The first aim of our study was to determine the association between SLEs and subsequent MDE onset. In line with a number of other studies, we found that dependent (e.g. Silberg et al., 2001; Kendler and Karkowski-Shuman, 1997; Kendler et al., 1995) SLEs preceding onset were significantly associated with MDE onset. Unlike in a number of other studies (e.g. Goodyer et al., 1985; Kendler and Kar-

kowski-Shuman, 1997; Kendler et al., 1995), however, in the present study independent SLEs were not associated with MDE onset. Furthermore, in line with other studies is the finding that first ever MDE onsets were more often preceded by SLEs than recurrences (e.g. Perris, 1984; Ezquiaga et al., 1987; Ghaziuddin et al., 1990). This phenomenon has been called the kindling phenomenon (Post, 1992). It is important to note that almost half (46%) of the offspring who developed a mood disorder or recurrence during follow-up did not experience a severe negative SLE in the 6 months prior to onset.

The second aim of our study was to determine whether the association between SLEs and MDE onset might be due to prior anxious/depressive symptoms. This study showed that the association between both dependent SLEs and MDE onset decreased to non-significance after adjustment for prior affective problems. These results suggest that the association between dependent SLEs and MDE could be accounted for by prior parent reported Anxious/Depressed scores. Hankin and Abramson (2001) state that the stress–depression relationship is not a static, unidirectional process, but rather a transactional process in which increases in depressive symptoms can contribute to further SLEs as depressed individuals seek reassurance excessively and are rejected by others. Thus, depressive symptoms can lead to the occurrence of a full episode of a mood disorder via the occurrence of dependent SLEs. However, in our study, SLEs were not significantly associated with MDE onset anymore after adjustment for baseline anxious/depressive symptoms. This shows that baseline anxious/depressive symptoms fully accounted for the association between SLEs and MDE onset. In addition, baseline symptoms were significantly associated with MDE onset, and remained so after adjustment for dependent or independent SLEs. This shows that SLEs did not mediate the association between baseline symptoms and MDE onset. Thus, baseline symptoms accounted for both MDE onset and the occurrence of SLEs. Since we used offspring's self-reports to assess SLEs and parent reports to assess baseline anxious/depressive symptoms we may conclude that a rater bias accounting for these findings is unlikely. The finding that baseline anxious/depressive symptoms predicted MDE onset during follow-up is reminiscent of the findings from Clayton et al. (1994)

who found high scores on a neurotic subscale, which consisted of mainly depressive and anxiety symptoms, to predict depression in Swiss army recruits at age 18; and from Roza et al. (2003) who found, among a Dutch general population sample of 1580 subjects, that at 14-year follow-up mood disorders were significantly predicted by high scores on the Anxious/Depressed scale and on the internalizing composite (withdrawn, somatic complaints, and Anxious/Depressed) of the CBCL. The predictions based on problem behavior remained stable during the 14-year period across adolescence and young adulthood. Our sample of bipolar offspring comprised 5 offspring who had developed bipolar disorder at second measurement. Previous studies have shown that depression is often the first pole of bipolar disorder. It is therefore likely that a major proportion of the depressive offspring in our sample will continue to develop bipolar disorder. For instance, Angst et al. (2005), who followed up 406 patients with major mood disorders, reported that more than half of their severe mood disorder cases developed bipolar disorder. Likewise, Geller et al. (1994) reported a switch to mania among 31.7% ($N = 25$) of 79 6- to 12-year-old prepubertal subjects with DSM-III major depressive disorder (MDD) who were followed for a 2- to 5-year period. Loaded FH and multigenerational FH were significantly associated with bipolar I.

Familial loading for mood disorders was not associated with MDE onset or SLEs and did not modify the association of SLEs and MDE onset. The associations between dependent SLEs (both severity and number of severe SLEs) remained significant after adjustment for familial loading. This suggests that there was no evidence of gene–environment correlation and interaction as far as it concerns familial loading and SLEs. So, there is no spurious association between SLEs and MDE as far as it concerns familial loading. Familial loading is not associated with both SLE and MDE, which was the case with baseline anxious/depressive symptoms.

Women did not show a greater sensitivity to the depressogenic effects of SLEs, as we did not find a significant interaction effect between gender and SLEs with regard to MDE onset. This is consistent with Kendler et al. (2001) who concluded in their study among female–female, male–male and male–female twin pairs that the gender difference in depression was neither due to more frequent exposure to SLEs nor to differential sensitivity to their depressogenic effect. But it is inconsistent with a number of other studies reporting gender differences in the frequency of SLEs and/or in the sensitivity to their effects (Cyranowski et al., 2000; Nolen-Hoeksema and Girgus, 1994).

The major conclusion to be drawn is that SLEs are the consequence of prior anxious/depressive symptoms rather than causing depression across the 1.2 year interval.

5. Limitations

The major limitation of our study is the small number of MDE onsets during the 14-month interval resulting in low statistical power to demonstrate significant interactions with gender and familial loading on MDE onset. Another limitation is that the sample was not population-based. Only bipolar patients with spouses and offspring aged 12–21 years at initial assessment, who were all willing to participate, were included. Therefore, the findings may not be generalized to the total offspring of bipolar parents, nor to other children without parents with a bipolar or other mood disorder. In addition, we did not examine the possible impact of long-term difficulties on the onset of MDE, whereas these may also have played a role in the development of mood disorders in our sample. For instance Hammen et al. (1990) found chronic interpersonal difficulties to be more predictive of depressive symptoms in offspring of depressed women, while recent stressful SLEs predicted depression in offspring of never-depressed women in a community sample of 812 fifteen-year-old children of depressed and non-depressed women.

Finally, the FH-RDC is relatively insensitive for the diagnosis of mood disorders when compared to the family study method (Andreasen et al., 1977). We therefore may have missed diagnoses. In addition, direct interview of a relative is well known to be more accurate than a family history report. However, in a study by Zimmerman et al. (1988), the test–retest interrater reliability of the FH-RDC was good to excellent for specific FH-RDC diagnoses. In addition, in this study a higher diagnostic threshold was associated with greater reliability, especially for the diag-

nosis of depression. As described above, FH-RDC information was rated by the interviewers as to completeness on a five-point scale (1 = very good to 5 = essentially no information). We only used the top two categories and therefore applied a relatively high threshold for family members to be diagnosed as mood disordered, but it increases type II error.

6. Implications

To our knowledge, this is the first study that assessed the impact of SLEs on the onset of MDE among a sample of children of bipolar parents, while controlling for familial loading, gender, age, SES and baseline depressive symptoms. This study shows that the relationship between SLEs occurring prior to onset and MDE onset is a spurious association since it disappeared after adjustment for baseline anxious/depressive symptoms. Thus, baseline symptoms, or factors responsible for baseline symptoms, were entirely responsible for the association between SLEs and MDE onset.

A major implication of our findings for clinicians is that residual or antecedent anxious/depressive symptoms in a high risk population predict new onsets or recurrences of mood disorder episodes and significant stressful life events.

Acknowledgments

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