The effect of number, severity and loss-aspect of stressful life events on the onset of psychopathology in bipolar offspring

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This study was part of the longitudinal Dutch research project 'Children of Bipolar Parents'

Abstract

<u>Background:</u> Bipolar offspring are genetically at high risk of developing bipolar disorder (BD) and psychopathology in general. From twin –studies we know gene-environment interaction is responsible for this. One possible environmental factor, thought to be involved in the onset of psychopathology, are stressful life events (SLE's). The aim of this research is to study the effect of number, severity and loss-aspect of SLE's on pathogenic onset. <u>Method:</u> Lifetime DSM-IV diagnoses of 129 bipolar offspring were obtained. To assess SLE's the Bedford College Life Events and Difficulty Schedule (LEDS) was used. Binary logistic regression analyses were preformed to calculate odds ratios for the number, severity and loss-aspect of SLE's on pathogenic onset. <u>Results:</u> Number, severity and loss-aspect of SLE's, are all individually significant predictors for the presence of psychopathology. Number of SLE's is the best predictor of the three parameters tested, in both mood disorders and psychopathology in general. <u>Conclusion:</u> In this study we expected that cumulative SLE's, severe events and events with a greater loss-aspect are predictors of psychopathology. These expectations have been met, with the number of SLE's as best predictor. One possible explanation for this association is a kindling effect.

Introduction

Bipolar disorder (BD) is an episodic mood disorder which affects approximately 1 to 2% of the Dutch population (Reichart, Walls & Hillegers, 2007). Two types of BD can be distinguished: bipolar I and bipolar II disorder. The course of a bipolar I disorder is typically hectic and variable. It has been described as 'an unending roller-coaster ride from the peaks of elation to the depths of a despair' (Barlow & Durand, 2005, p. 212). A manic episode might occur only once in bipolar I disorder, or repeatedly, in which BD greatly resembles recurrent

depressive disorders. A bipolar II disorder can be seen as a less severe variant in which major depressive episodes alternate with hypomanic episodes rather than full manic episodes (Barlow & Durand, 2005).

Over the last 30 years twin, adoption and other studies have shown that bipolar offspring are genetically at high risk of developing BD (Bertelsen, Harvald & Hauge, 1977; Kendler et al., 1993; Kendler et al., 1995; Cardno et al, 1999) and psychopathology in general (Chang, Steiner & Ketter, 2000; Chang et al., 2003; Henin et al., 2005). Twin studies compared concordance rates of bipolar disorder between monozygotic (MZ) twins and dizygotic (DZ) twins. MZ twins are genetically identical and DZ twins share on average half of their genes. Because it can be assumed that shared environmental influences of MZ and DZ twins do not differ (the equal environments assumption) the significantly higher concordance rates found in MZ twins reflect the action of genes in BD (Smoller & Finn, 2003). The heritability rates in studies of Bertlsen et al. (1977), Kendler et al. (1993, 1995) and Cardno et al. (1999) range from 59-87%. Although the evidence from adoption studies of bipolar disorder has been limited, the available data are consistent with a role for genetic transmit ion of mood disorders (Smoller & Finn, 2003). In addition, multiple studies since 1997 have reported that about 50% of bipolar offspring meet

criteria for at least one DSM-IV psychiatric disorder (Chang, Steiner & Ketter, 2000). Chang et al. (2003) have reported that bipolar offspring are at a four times higher risk for developing a mood disorder than offspring of parents without DSM-IV diagnosis. Henin et al. (2005) noted that bipolar offspring, compared with offspring of parents without mood disorders, had elevated rates of mood disorders, anxiety and disruptive behavior disorders. Furthermore, since 1988 high incidences of Attention Deficit Hyperactivity Disorder (ADHD) among bipolar offspring have been described, although better diagnostic tools and improvement of treatment may have led to increased diagnosis of ADHD (Duffy et al., 1998; Chang et al., 2003).

Summarized, bipolar offspring has large potential in revealing important aspects of the development of psychopathology. However, MZ concordance rates and heritability estimates are less than 100%, demonstrating that environmental influences also are involved in the onset of psychopathology (Smoller & Finn, 2003). One possible environmental factor thought to be involved is stress, caused by stressful life events (hereafter: SLE's). As Goodyer (1996) described in his study on the influence of SLE's on subsequent psychopathology, SLE's may carry a potential threat by altering an individual's present state of mental or physical well-being and may trigger psychopathology through their

impact on affective cognitive processes. Already in the late 1960s researchers found associations between SLE's and psychopathology (Paykel et al., 1969) and more studies followed (Kendler et al., 1995; Goodyer, 1996; Brilman & Ormel, 2001; Paykel, 2001; Paykel, 2003; Duffy et al., 2007;).

In the literature SLE's are classified according to a number of different criteria. For example, psychiatrist Adolf Meyer stated that life events need not to be very unusual or catastrophic to be pathogenic. The most important feature responsible for the onset of psycho-pathology he assumed was life change rather than the unpleasantness of the event (Goodyer, 1996). Duffy et al. (2007), however, noted that typically undesirable life events are related to the onset of psychopathology among bipolar offspring and that this relation may only exist through its association with emotionality. Brilman and Ormel (2001) found that severe events show the largest relative risk factor for onset of a depressive episode in old age and that this association tends to be stronger in first than recurrent episodes. Likewise, though in contrast to Meyer, Paykel (2003) found that when life events are classified in broad terms such as 'undesirable' the strongest associations between events and affective disorders appear. On the other hand, instead of taking severity, life change or pleasantness as a matter of classification,

Kendler and colleagues (1995) found that adults at genetic risk for depression experienced *more* SLE's and thereby they also are more sensitive to these events. Furthermore, research demonstrated that single life events do not exert much risk for subsequent disorders but that cumulative life stress increases the risk of psychopathology onset (Goodyer, 1996). One possible explanation for this kindling effect is that an accumulation of stress results in long-lasting changes in the brain's biology by crossing a certain threshold. When this threshold has been reached, it makes people more vulnerable of undergoing psycho-pathology (Grossman et al., 2003; Sadock & Sadock, 2007).

Another way of classifying SLE's is according to their loss-aspect. Loss could be either real loss, as caused by death of a loved one, or perceived loss such as the loss of a belief or conviction. Studies have found relations between on the one hand 'loss' events such as (interpersonal) separations, bereavements, loss of self esteem and on the other hand psychopathology onset in high risk offspring (Goodyer, 1996; Kendler et al; 2003 & Paykel, 2001). The impact of other aspects of life events, without underestimating their impact, are beyond the scope of this article.

Although various associations between certain aspects of SLE's and pathogenic onset emerged in literature, still a lot of questions concerning these associations remain unanswered, spec-

ifically with regard to the development of psychopathology in bipolar offspring. The current study investigates three aspects of SLE's: the number, severity and perceived loss-aspect of SLE's and their association with psychopathology onset in bipolar offspring. Based on previous research the expectation is that cumulative SLE's, severe events and events with a greater loss-aspect are predictors of psychogenic onset. Using these aspects we attempt to define the features of SLE's most likely to lead to psychopathology in children of bipolar parents. To investigate associations between these features of SLE's and psychopathology, we compare three dichotomous groups of bipolar offspring in this study. The first group consists of bipolar offspring with any psychological disorder versus children with no psychological disorder. The second group consists of offspring diagnosed with any mood disorder versus no psychological disorder and the last group consists of offspring diagnosed with bipolar I versus bipolar II disorder. By conducting this research, we might ultimately be able to improve prevention and intervention methods for alleviating psychopathology among bipolar offspring.

Method

Participants

This study was part of the longitudinal study 'Children of Bipolar Parents' ('Kinderen van Bipolaire Ouders', KBO) in the Netherlands. All subjects were enrolled between 1997 and 1999. Children with one parent diagnosed with a bipolar I or II disorder were recruited. A family was only included if all adolescents of the family aged 12 to 21 years agreed to participate. Those with a severe physical disease, a severe handicap or with an IQ less than 70 were excluded from the study. To recruit the children a survey was sent to 1961 members of the Dutch Association for Manic-Depressives and Relatives (Nederlandse Vereniging voor Manisch-Depressieven en Betrokkenen, VMDB). Of these, 712 members returned the survey and 110 of these reported that they had one or more children who met the inclusion criteria. Sixty-two of these 110 members agreed to participate with a total of 102 children. Additionally, nine psychiatric hospitals with a clinic for outpatients with bipolar disorder were approached with the same procedure. 24 bipolar patients with a total of 38 children were identified and agreed to participate. All parents with a bipolar disorder were treated in outpatient clinics during recruitment. In total, 140 children were participating at the first measurement of the study. During the second measurement 14 months later, 132 children were still included. At the third measurement, 41 months after the second measurement, 129 children were still participating. Characteristics of the children and their parents at the third measurement are shown in Table 1.

The study was approved by the Human Ethics Committee of the University Medical Center Utrecht. After full description of the study to the parents and children, written informed consent was obtained.

Table 1
Parent characteristics at the recruitment (N=86) and participant characteristics at the third measurement of the study (N=129)

	N	%	Age(SD)
Bipolar fathers	32	40	
Bipolar mothers	48	60	
Bipolar I	59	74	
Bipolar II	21	26	
Married	57	71	
Divorced	23	29	
Male bipolar offspring	69	53	20.52 (2.81)
Female bipolar offspring	60	47	21.14 (2.47)

Instruments

Bipolar offspring were evaluated by a battery of structured interviews and questionnaires. In this section only the interviews as used for this study will be discussed in further detail.

The International Diagnostic Checklist (IDCL).

The mood disorders section of the IDCL (Hiller, 1993) was used to check the parents' DSM-IV bipolar I or II diagnoses during the recruitment phase. No discrepancies were found between the diagnoses made by treating psychiatrists and the IDCL based diagnoses.

Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version(K-SADS-PL).

During the first and second measurement the K-SADS-PL (Kaufman et al., 1997) was used to asses current and lifetime DSM-IV diagnoses in children and adolescents. The K-SADS-PL is a semi-structured interview which inquires symptoms of psychopathology. Both parent(s) and child were interviewed separately. If there was disagreement about the presence of a symptom, greater weight was given to the parents' report of observable behaviour rather than the children's report of subjective experiences.

Inter-rater reliability of the K-SADS-PL is supported and test-retest reliability coefficients were 'excellent' (κ=.77 to 1.00) for present and/or lifetime diagnoses of major depression

and any bipolar, generalized anxiety, conduct, or oppositional defiant disorder and 'good' (κ=.63 to 67) for present diagnoses of posttraumatic stress disorder and attention-deficit hyper-activity disorder. Rating scale data support the concurrent validity of screens and K-SADS-PL diagnoses (Kaufman et al., 1997).

Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I).

Because of age, the K-SADS-PL was replaced by the SCID-I (First et al., 1997). This semi-structured interview inquires axis I disorders and is designed for adults. An example of a question derived from the SCID-I is: 'Have you ever had a panic attack?' Because not all DSM-IV diagnoses are included in this clinical interview, some parts of questionnaires originating from the K-SADS were added as a supplement to the SCID-I. Among these were question-naires for attention-deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder and tic disorders. Multiple studies have supported the reliability and validity of the SCID-I (Basco et al., 2000, Kranzler, et al., 1996, Zanarini, & Frankenburg, 2001).

Bedford College Life-Events and Difficulty Schedule (LEDS).

To measure SLE's, the teenage version of the LEDS as developed by Monk and Dobbs (1985) and based on the adult version of Brown and Harris (1978) was used. The LEDS is a 90-minute semi-

structured face to face interview, administered by intensively trained interviewers. The interview contains standardized questions to obtain detailed information on different domains of the participant's life such as education, work, reproduction, housing, money/ possessions, crime/legal, health, marital/ partner, other relationships and miscallaneous/death. An example of a question derived from the LEDS is: 'Has anyone of your closest ties passed away in the last 12 months?' The LEDS with its standardized questions was used to minimize the participants reporting bias and forgetfulness while reporting life events. In addition, at the beginning of the interview, the interviewer and the participant filled out a timeline in order to aid the subject's memory. Anchor points like the subject's birthday and other significant events were inserted in this calendar to create an overview. Empirical research confirms that this procedure reduces problems with identifying the date and duration of an event (McQuaid et al., 1992; Sobell, Toneatto, Sobell, Schuller, & Maxwell, 1990). Also, the older subjects were asked to bring their curriculum vitae. In this study, life events from five years old until the first measurement and respectively 14 and 41 months later were assessed. The personal context in which events took place was taken into account. For example, a pregnancy will have different implications for a 15-year-old compared with a 30-year-old.

After the interview an extensive report of the events reported by the subject was written. Subsequently, the reports were blindly and independently rated by at least two independent researchers. To increase the reliability of these ratings, the LEDS manual of events was used which provided numerous examples of events and rating guidelines. Therefore, it was possible to rate events objectively (blind to the participants' subjective feelings and interpretations of events) from 1=mild; 2=moderately severe; 3=severe of 4=very severe on a contextual long-term threat scale. Only the most severe events, those rated with a 3=severe and 4=very severe, were analysed in further detail by also rating aspects like the degree of loss (on a scale from 1 to 4). The panel consisting of at least two raters and two supervisors reached consensus on the items that raised rating problems.

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; Brown & Harris, 1989). Because the LEDS has significant higher reliability and validity than self-report measures, it is the instrument of choice for this study (Brown & Harris, 1987; Brown & Harris, 1989; Gorman, 1993).

Variable construction

In this study, three independent variables are used: the number of SLE's, severity of SLE's and the loss-aspect of SLE's. To measure the overall number of SLE's experienced per subject, SLE's of all three measurements of the KBO-study are summed up. Also, to create *one* severity score derived from the three measurements in the longitudinal KBO-study, severity scores (ranging from 1=mild to 4=very severe) of SLE's are derived by calculating the product of the number of SLE's summed up for all three measurements *and* their severity scores summed up for all three measurements. Hereby taking into account the pathogenic effect of cumulative life stress as opposed by Goodyer (1996). The loss- aspect is calculated in the same way, except only events rated with a 3=severe or a 4=very severe were included. This is because only those events are judged on their loss-aspect (Brown & Harris, 1987). To clarify, see Appendix table 1.

The dependent variables are sorted into three dichotomous groups; respectively any psychological disorder (yes/no), any mood disorder (yes/no*)

and bipolar mood disorders (unipolar /bipolar).

Statistical analyses

All of the statistical analyses are conducted on data derived from the first, second and third measurement of the KBO-project. To explore complex mo-dels, multivariate binary logistic re-gression analyses were performed by analysing three models consisting of either psychopathology, mood disorders or uni-/bipolar disorders on the one hand and the number of SLE's, their severity and loss on the other hand. To detect collinearity, Variance Inflation Factors (VIF) were determined using linear regression analyses. Based on the assumptions of Miles & Shevlin (2007), in this study a VIF equal to four is used as an arbitrary cut-off to determine if collinearity has become too serious. Because of the explorative nature of this research, also univariate binary logistic regression analyses were preformed when multivariate testing did not detect significant results. Odds ratios per variable; respectively SLE's, severity of SLE's and perceived loss of SLE's were calculated to predict pathogenic onset in general and mood disorders.

*Note: in this dichotomous group ´no mood disorder´ represents a group of participants not only without mood disorders but those without *any* psychological disorder

Results

The offspring cohort consisted of 60 males and 69 females, mean age of 20.8 years (SD=2.7) within a range of 16-26 years. The number of lifetime DSM-IV diagnosis and variable statistics are presented in table 2.

Table 2
Number of bipolar offspring (N=129) with lifetime DSM-IV diagnosis, mean (standard deviation), minimum and maximum per independent variable respectively number of SLE's, severity of SLE's and perceived loss-aspect of SLE's.

	N	M(SD)	Min	Max
Stressful life events # (SLE's)				
No psychopathology	53	33.30(9.82)	17.00	54.00
Bipolar disorder	13	42.08(10.40)	18.00	54.00
Unipolar disorder	38	39.05(9.12)	23.00	56.00
Other disorder[a]	25	38.24(9.12)	20.00	54.00
Severity SLE[aa]				
No psychopathology	53	21.88(12.21)	5.44	52.92
Bipolar disorder	13	36.29(16.54)	6.30	61.56
Unipolar disorder	38	30.48(14.71)	9.89	67.20
Other disorder[a]	25	28.49(12.80)	8.00	57.24
Perceived loss SLE[aa]				
No psychopathology	53	1.55(1.29)	0.06	5.74
Bipolar disorder	13	3.87(4.00)	0.40	14.30
Unipolar disorder	38	2.89(2.79)	0.40	12.20
Other disorder[a]	25	2.31(1.63)	0.12	6.80

[a] *Attention deficit hyperactivity disorder (ADHD), disruptive behavior disorder, anxiety disorders, substance abuse, enuresis, encopresis, pervasive developmental disorder (PDD), tic- and eating disorders.*
[aa] *∗100*

By performing multivariate logistic regression analyses we found that a model including all three independent variables (number of SLE's, severity and loss) could not significantly distinguish between the presence of psychopathology or no psychopathology (X^2=16.07, df=3, N=129, p>0.05), mood disorders or no psychopathology (X^2=13.12, df=3, n=106 $p>0.05$) or uni- and bipolar disorders (X^2=1.85, df=3, n=51 $p>0.05$) among bipolar offspring due to collinearity (Appendix table 2). However, because of the explorative nature of this study we still performed univariate analyses. The results of these analyses are described below.

Presence of psychopathology in general versus no psychopathology
By performing univariate logistic regression analyses we found that the number of SLE's was a significant predictor for lifetime psychopathology, when comparing the number of SLE's among bipolar offspring with and without psychopathology. Also, severity and loss are significant predictors of lifetime

psychopathology (table 3). Table 4 shows that the number of SLE's generally best predicts psychopathology among this cohort of bipolar offspring; 81% of the participants with psycho-pathology were successfully predicted. However, only 45.3% of the predictions for the participants without psycho-pathology were accurate. Overall 66.7% of predictions were accurate. The severity of SLE's predicted 76.3% of par-ticipants with psychopathology correctly and 49.1% of participants without psychopathology were accurate. Overall 65.1% of predictions based on severity were accurate. Perceived loss success-fully predicted 76.3% of the participants with psychopathology accurately and 52.8% of predictions for participants without psychopathology were correct. Overall 66.7% of predictions based on the 'loss' variable were accurate.

Table 3
B(SE) and Odds Ratios (95% confidence interval) to predict the presence of psycho-pathology versus no psychopathology among bipolar offspring.

	B(SE)	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
Constant	-2.028(.744)			
SLE's*	.066(.020)	1.027	1.068	1.111
Constant	-.968(.422)			
Severity of SLE's**	.001(.000)	1.000	1.001	1.001
Constant	-.415(.299)			
Perceived loss of SLE's***	.004(.001)	1.001	1.004	1.006

*$Note:$R²=.088 (Cox & Snell), .119 (Nagelkerke). Model χ²(1)=11.894, $p<.01$
**$Note:$R²=.098 (Cox & Snell), .133 (Nagelkerke). Model χ²(1)=13.357, $p<.01$
*** $Note:$R²=.094 (Cox & Snell), .126(Nagelkerke). Model χ²(1)=12.692, $p<.01$

Table 4
Correctly % predicted (absence of) psychopathology among bipolar offspring for SLE's, severity of SLE's and perceived loss aspect of SLE's.

	Correctly % predicted		
	Psychopathology n=76	No Psychopathology n=53	Overall n=129
SLE's	81.0	45.3	66.7
Severity of SLE's	76.3	49.1	65.1
Perceived loss of SLE's	76.3	52.8	66.7

Presence of mood disorders versus no psychopathology

By performing univariate logistic re-gression analyses we also found that the number of SLE's is a significant predictor for the onset of mood disorders. Also, severity and loss are significant pre-dictors of mood disorders (table 5).

Table 6 shows that 'loss' overall best predicts (absence of) mood disorders with 59.1%. In addition, all three predictors were better at predicting absence than presence of mood disorders among bipolar offspring (for 'number' and 'severity' respectively; 58.5% and '59.1% predictions were correct). For participants without a mood disorder the number of SLE's predicted 61.8% correctly, severity of SLE's predicted 69.1% accurate and perceived loss of SLE's predicted 74.5% of participants without a mood disorder successfully. However, only 54.9% of predictions for participants with mood disorders were accurate when predicted by the number of SLE's. 'Severity' and 'loss' predicted even less participants with a mood disorder accurate, respectively; 45.1% and 43.1%.

All three predictors could not significantly differentiate between the presence of a uni- or bipolar disorder (n=51) among bipolar offspring with a mood disorder (respectively; $X_2=1.03$, df=1, $p>0.05$; $X_2=1.42$, df=1, $p>0.05$; $X_2=0.90$, df=1, $p>0.05$).

Table 5
B(SE) and Odds Ratios (95% confidence interval) to predict the presence of mood disorders versus no psychopathology among bipolar offspring

| | B(SE) | 95% CI for Odds Ratio | | |
		Lower	Odds Ratio	Upper
Constant	-2.477(.818)			
SLE's*	.065(.022)	1.023	1.068	1.114
Constant	-1.399(.457)			
Severity of SLE's**	.000(.000)	1.000	1.000	1.001
Constant	-1.763(.309)			
Perceived loss of SLE's***	.003(.001)	1.001	1.003	1.005

*Note:R^2=.092 (Cox & Snell), .123 (Nagelkerke). Model $\chi^2(1)$=10.266, $p<.01$
**Note:R^2=.105(Cox & Snell), .140 (Nagelkerke). Model $\chi^2(1)$=11.747, $p<.01$
*** Note:R^2=.092 (Cox & Snell), .123(Nagelkerke). Model $\chi^2(1)$=10.239, $p<.01$

Table 6
Correctly predicted (absence of) mood disorders among bipolar offspring after the third measurement for SLE's, severity of SLE's and perceived loss aspect of SLE's.

| | Correctly % predicted | | |
	Mood disorders n=51	No mood disorders n=55	Overall n=106
SLE's	54.9	61.8	58.5
Severity SLE's	45.1	69.1	57.5
Perceived loss of SLE's	43.1	74.5	59.1

Discussion

The aim of this study was to examine the association between the number of SLE's, the severity of these events and perceived loss-aspect of SLE's on the one hand and the presence of lifetime psychopathology among bipolar offspring on the other hand. When using multivariate analyses, the models consisting of all three predictor variables could not significantly predict psychopathology or mood disorders. Because of the explorative nature of this study, univariate analyses were also performed on the data. The results of these analyses indicate that all three variables prove to be significant predictors for pathogenic onset in general and mood disorders more specifically. The number of SLE's best predicts the presence of psychopathology.

This finding is in line with previous findings concerning the kindling effect (Grossman et al., 2003; Sadock & Sadock, 2007). Cumulative life stress could increase the risk of pathogenic onset in two ways. First, cumulative life stress could deregulate the hypothalamic-pituitary-adrenal axis (HPA-axis) which controls reactions to stress and regulates many body processes including mood and emotions. Therefore, a lasting deregulation of this axis through cumulative life stress may cause psychopathology (Monroe & Harkness, 2005). A second way to explain the association between the number of SLE's and the onset of psychopathology is from a cognitive perspective. Repeated stressors could cause changes in information processing thereby altering cognitive schemes about the self, others and the surrounding world. The implication that these negative belief structures could cause psychopathology forms the core of Beck's cognitive theory on the onset of psychopathology, more specifically depression (1976). An interesting question concerning these two hypotheses on pathogenic onset caused by accumulation of SLE's, is whether they differ. It could be possible that neurobiological changes also mediate cognitive scheme consolidation over time (Monroe & Harkness, 2005). Alternatively, cognitive schemata might mediate neurobiological changes. This implicates interesting further research questions.

Although severity and the perceived loss-aspect of SLE's also have proven to be significant predictors of psychopathology (and mood disorders), their impact is tremendously small in this study. A possible explanation for this effect, as well as a limitation of this study is hidden in the way the variables are constructed, in particular the variable that measures the loss-aspect of SLE's. Only events rated as 'severe' or 'very severe' are taken into account due to scoring procedures, thereby excluding mild SLE's resulting in loss of information. In addition, events that are categorized as severe can also be events affiliated with a great amount of loss thereby obscuring distinction between

these two variables. Future research should construct more strict and more differing variables. In this way it therewith allows to counter collinearity, a problem in this research whereby all three variables cannot be placed in one explanatory model due to their rather small distinguishing qualities (Miles & Shevlin, 2007).

Another limitation in this study must be recognized. Causality cannot be inferred because of the cross-sectional set-up of this current study (despite the fact that it is derived from the longitudinal KBO-study) and the use of lifetime DSM-IV diagnoses. Given this research, it could be the case that life events cause psychopathology, although psychopathology could result in SLE's as well (I.e. dismissal can lead to a depression though a depression could likewise lead to dismissal). In addition, it is possible that the lifetime prevalence of psychopathology among participants in this study will further increase because the current mean age of the participants is relatively low (20 years) to reveal pathogenic onset. Research has shown that the median age of onset among people with anxiety and impulse control disorders is 11 years. However, for substance abuse and mood disorders this is respectively 20 and 30 years of age (Kessler et al., 2005). Furthermore, in this study participants who met DSM-IV criteria for depression could, especially given their age and genetic make-up, still develop BD. Future research should

take these considerations into account by carrying out longitudinal research, using a broad age range among those who participate in the study.

Another interesting question concerning the influence of SLE's on pathogenic onset, is to what extent children of parents with no DSM-IV diagnosis who experience SLE's develop psychopathology. Unfortunately, in this study there was no control group available.

Despite these limitations, the strengths of this study should not be underestimated. Because of the large sample size of this study the standard error is reduced and therefore optimizing opportunities of finding significant associations (Miles & Shevlin, 2007). In addition, the fact that the number of SLE's is a predictor of psychopathology among bipolar offspring can contribute to prevention and intervention methods. It could be interesting to look for protective factors, such as coping styles. It is well known that active problem solving (e.g. seeking help/information, internal reflection or accepting social support) is more functional than long-term avoidant coping or withdrawal (Seiffke-Krenke, 2000). Researchers found relations between these maladaptive coping styles and the development of psychopathology (Gazzaniga & Heatherton, 2005). To learn how to develop more functional coping styles might be a first step to reduce psychogenic onset among those who are vulnerable (Seiffke-Krenke,

2000).

In conclusion, the number of SLE's best predicts the onset of psychopathology among bipolar offspring although severity and the loss-aspect are related to pathogenic onset as well. Future research is necessary to further clarify these findings and to detect, develop and test suited intervention and prevention methods.

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Appendix

Table 1
Example of independent variable constructions of the number of SLE's (#), severity and loss-aspect given participant 'X'

Measurement KBO-study	Description SLE's	Severity Score	Loss Score
First measurement (T1)	*Death of biological mother at age 10*	*4= very severe*	*4= marked*
	Suicidal thoughts of a friend	*3= severe*	*2 = some*
	Start of high school	*1= mild*	*-*
	Car accident involving father, no permanent injuries	*2 = moderate*	*-*
Total T1	**# SLE's: 4**	**Severity: 10**	**Loss: 6**
Second measurement (T2)	*Starting first job*	*1= mild*	*-*
	Start of first relationship	*1= mild*	*-*
	First sexual intercourse	*1= mild*	*-*
	Knowing father has got a drug addiction	*3= severe*	*2= some*
	Friend commits suicide	*4= very severe*	*4= marked*
Total T2	**# SLE's: 5**	**Severity: 10**	**Loss: 6**
Third measurement (T3)	*Graduating from high school*	*1= mild*	*-*
	Death of grandfather	*2= moderate*	*-*
	Start therapy for depression	*3= severe*	*3= moderate*
	Girlfriend ends relationship after three years	*3= severe*	*3= moderate*
Total T3	**# SLE's: 4**	**Severity: 9**	**Loss: 6**

Variable construction *SLE's*: SLE's T1+SLE's T2+ SLE's T3   *Example Participant X: 4+5+4= 13*
Variable construction *Severity*: (SLE's T1+SLE's T2+ SLE's T3) x (Total severity score T1+ Total severity score T2+ Total severity score T3)   *Example Participant X: (4+5+4) x (10+10+9)=377*
Variable construction *Loss*: (Total severity score T1+ Total severity score T2+ Total severity score T3) x (Total loss score T1+ Total loss score T2 + Total loss score T3)   *Example Participant X: (10+10+9) x (6+6+6)= 522*

Table 2
Variance Inflation Factors (VIF) for the relation between number of SLE's, severity and loss on the one hand and (no) psychopathology, (no) mood disorder or (uni-) bipolar disorder on the other hand

	Variance Inflation Factors (VIF)		
	(No) Psychopathology N=129	(No)Mood disorder n=106	(Uni-)Bipolar disorder n=51
SLE's	22.23[a]	29.51[a]	32.96[a]
Severity of SLE's	29.74[a]	40.05[a]	46.45[a]
Perceived loss SLE's	3.04	4.46[a]	4.46[a]

[a]*Note:* VIF > 4 indicates collinearity problems (Miles & Shevlin, 2007)