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The relationship between stressful life events and Axis I diagnoses among adolescent offspring of probands with bipolar and non-bipolar psychiatric disorders and healthy controls

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Abstract

Background—Previous studies have explored the role of stressful life events in the development of mood disorders. We examined the frequency and nature of stressful life events as measured by the Stressful Life Events Scale (SLES) among three groups of adolescent offspring of probands: with bipolar (BD), with non-BD psychiatric disorders, and healthy control (HC). Furthermore, we examined the relationship between stressful life events and presence of DSM-IV Axis I disorders in these offspring. Stressful life events were characterized as dependent, independent, or uncertain (neither dependent or independent), and positive, negative, and neutral (neither positive or negative).

Method—Offspring of probands with BD aged 13–18 years (N=269), demographically-matched offspring of probands with non-BD Axis I disorders (N=88), and HC probands (N=81) from the Pittsburgh Bipolar Offspring Study were assessed from 2002–2007 with standardized instruments at intake. Probands completed the SLES for their offspring for life events within the prior year. Life events were evaluated with regard to current offspring Axis I diagnoses after adjusting for confounds.

Results—After adjusting for demographic and clinical between-group differences (in probands and offspring), offspring of BD probands had greater independent and neutral life events compared with HC offspring and greater number of more severe stressful life events than HC offspring, but not non-BD offspring. Offspring of BD probands with comorbid substance use disorder reported more independent stressful life events. Greater frequency and severity of stressful life events were associated with current Axis I disorder in offspring of both BD and non-BD affected probands

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regardless of dependency or valence. Greater frequency and severity of stressful life events were associated with greater current Axis I disorder in all offspring.

Conclusions—Offspring of BD probands have greater exposure to independent and neutral life events than HC offspring. Greater frequency and severity of stressful life events was associated with Axis I disorder in offspring of both BD and non-BD affected probands.

Keywords

Stressful life events; adolescents; bipolar offspring

Introduction

Bipolar disorder (BD) affects 2–4% of the population.^{1–2} Adolescent offspring of probands with BD have elevated rates of DSM-IV Axis I disorders compared to the general population, especially BD, major depression and anxiety disorders.^{3–4} Extant literature suggests a role of stressful life events in the development of Axis I disorders. For example, in adults with BD, incidence of negative stressful life events is increased prior to onset and recurrences of depressive and manic episodes.^{5–6} Furthermore, in adolescents with BD, we have described greater exposure to negative, independent, and dependent stressful life events similar to rates described in depressed and anxious youth.⁷ While strong genetic basis of BD is clear,⁸ environmental factors likely further contribute to and moderate the onset of BD and other Axis I disorders in offspring of BD probands.

The biopsychosocial model posits that biological, psychological, and socio-environmental factors all play significant roles in the onset, course, and outcome of psychiatric illness. This model is evidenced by stressful life events preceding onset of Axis I disorders, including BD,⁹ unipolar depression,^{10–14} and anxiety disorders.¹⁴ Specifically, total number of stressful life events during adolescence predicted future depression and anxiety episodes independent of initial symptoms.¹⁵ Understanding the contribution of stressful life events in adolescence is relevant to onset and outcome of Axis I disorders. For example, adolescents who reported ongoing stressors had more persistent depressive symptoms.¹¹ In addition, adults who reported greater exposure to stressful life events in adolescence were shown to have slower response to treatment and slower remission time course in diagnoses of both depression¹⁶ and anxiety disorder.¹⁷

Life events are characterized by valence and dependency. Life events may be stressful even if they have neutral (birth of a sibling) or positive valence (starting a new relationship). In addition, life events may be independent (distinct from personal behavior) or dependent (associated with personal behavior). Individuals with mood disorder more often experience dependent, negative life events, both contributing to and potentially influenced by the chronic nature of mood disorders.¹⁸

It is unclear the extent to which having a parent with BD increases frequency and/or severity of stressful life events. However, there is evidence that the contribution of stressful life events to later psychiatric disorder is significantly influenced by genetic differences.¹⁹ Stressful life events may also have greater impact on offspring with parental emotional

disorder.²⁰ Offspring of BD probands, in particular, have a higher risk profile for sensitivity to stress, demonstrate more risky behavior, and have impaired coping strategies compared to offspring of controls.²¹ Furthermore, individuals with a personal history of BD are more likely to report childhood adversities and recent stressors than individuals without BD.²²

The Pittsburgh Bipolar Offspring Study (BIOS) is the largest study to date of offspring of probands with BD and offspring of community control probands. Prior results from intake assessment demonstrated that offspring of probands with BD had higher rates of anxiety, BD-I and BD-spectrum (BD-I, II or subthreshold BD) disorders as compared to control offspring.^{23–24} In this study, we evaluated adolescent offspring of: probands with BD (OBD), community control probands with other Axis I disorder (offspring of non-BD, ONBD), and healthy control probands who presented with no Axis I disorder (OHC) with regard to their exposure to stressful life events. We evaluated stressful life events in the year preceding intake as reported by offspring and their parents, utilizing the Stressful Life Events Scale (SLES).²⁵ We aim to: 1) describe and quantify stressful life events in OBD compared with ONBD and OHC, 2) explore the association between stressful life events and presence of current Axis I disorder in OBD, ONBD, and OHC at study intake, and 3) examine whether specific categories of stressful life events are differentially associated with current Axis I disorders at intake. We hypothesized that OBD, as compared with ONBD and OHC, would experience a higher number of stressful life events and greater severity of stressful life events in the year preceding intake, independent of demographic characteristics. We further hypothesized that greater severity and frequency of stressful life events would be associated with current Axis I disorder in all three offspring groups. Finally, we hypothesized that negative, dependent and severe life events would have the greatest association with current Axis I diagnosis.

Methods

The methods of BIOS have been described in detail in prior reports.^{23–24} The Institutional Review Board approved the study. Written informed consent and adolescent assent were obtained prior to study procedures. This study explored stressful life events at intake.

Sample

The sample was recruited via the probands between January, 2002 and August, 2007. Probands with BD were recruited via advertisement (53%), other studies (31%) and outpatient clinics (16%). BD probands met DSM-IV criteria for BD-I or BD-II disorders and live within 200 miles of Pittsburgh. Exclusion criteria were lifetime diagnosis of schizophrenia, mental retardation, or mood disorder secondary to medical condition. Community control probands were recruited using random digit dialing, and group matched to BD probands by age, sex, and neighborhood. In addition to exclusion criteria used for BD probands, control probands could not have a parent or sibling with BD and the biological co-parent could not have BD. There were no other diagnostic exclusions for control parent probands. The study included all offspring aged 13 to 18 years, to capture the effect of stressful life events during adolescence, unless the child had mental retardation.

Procedures

Parent probands, participating biological co-probands (31%), and psychiatric history for non-participating biological co-probands (assessed via interview with identified proband) were assessed using the Structured Clinical Interview for DSM-IV (SCID)²⁶ and the ADHD, ODD, CD and separation anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version(KSADS-PL).²⁷ At intake, probands were interviewed (about offspring) and adolescents were interviewed using the KSADS-PL. Symptoms contributing to more than one diagnosis (e.g. distractibility) were not rated as fulfilling criteria for a mood disorder unless there was onset or worsening during a period of abnormal mood. Socioeconomic status was determined using the Hollingshead scale.²⁸ Interviewers had Bachelors or Masters Degrees, intensive training with the diagnostic instruments, and 80% agreement with certified raters. Interviewers who assessed offspring were blind to proband diagnosis. Assessments were presented to child psychiatrists blind to proband diagnosis for confirmation. Diagnostic reliability was assessed using audiotapes of 44 BIOS assessments rated by 2 to 8 BIOS interviewers (mean 5.4). The κ statistic for diagnostic reliability was 0.86 for BD-spectrum disorders, 0.77 for BD-I/II vs. BD-NOS vs. No BPSD, 0.64 for major depressive episode, 0.71 for any depressive episode, 0.86 for ADHD, 0.78 for anxiety disorders, 0.84 for ODD and/or CD, and 1.0 for substance use disorders (SUD).

Life Events Measure—Stressful life event frequency and severity was assessed at intake using the self-report SLES for offspring themselves and for probands about their offspring.²⁵ The SLES is an 80 item scale that directly asks if stressful events occurred in the year prior, and effects are rated using four point Likert severity ratings(1–4) for each event. The SLES is derived from the Bedford Life Events and Difficulties Schedule.^{25,29} The SLES was developed to reduce participant burden and is cost-effective and useful for evaluation of stressful life events in adolescents. Total stressful life events concur well with those assessed by both the Life Events and Difficulties Schedule and the Life Events Checklist.²⁹ Events include those involving education, work, money, housing, crime, health, deaths, romantic relationships, and other relationships.

Independent, dependent, and uncertain (neither independent or dependent on participant behavior)(Supplementary eTable 1) were determined with comparison to independent ("my parents were not home because of work") and dependent ("I was fired from a job") variables on the Life Events Record,¹⁵ the Life Events and Difficulties Schedule,²⁵ and ratings by three independent investigators with consensus. Events were also evaluated as negative ("I was robbed"), positive ("I started dating someone"), or neutral ("My parents had a baby") (Supplementary eTable 2) by three independent investigators with consensus.

Statistical Analyses (Tables 1–4)

Statistical analyses were conducted utilizing SAS v 9.4 (SAS Institute, Inc.). Chi-square tests were used for comparisons involving categorical variables, and analysis of variance (ANOVA) tests were used for those involving continuous variables for adolescent and proband demographic and clinical comparisons. Pairwise comparisons of offspring groups

(OBD, ONBD, OHC) were performed for characteristics with omnibus test p-values less than 0.05.

Analyses involving counts or total effects of stressful life events used generalized linear mixed models (GLMMs) with a random effect for family membership to account for within-family correlation. The total effect of an event type (e.g. independent or negative) is the sum of the event severity ratings over all events of that given type. Multivariate models were used to adjust for possible demographic and clinical confounding variables. FDR correction was applied after multivariate adjustment to control for multiple comparisons.

All associations between event counts/total effects and proband group, except occurrence of the lone positive life event, were modeled using negative binomial GLMMs. A logistic GLMM was used to model occurrence of the positive event. Logistic GLMMs controlling for parent group modeled associations between event counts/total effects and current offspring Axis I diagnoses.

In multivariate analyses, all demographic characteristics and offspring diagnoses that exhibited significant overall between-group differences at the 0.10 level among the three parent groups were considered as candidates for confounding variables. Of the parental diagnosis variables with significant between-group differences at the 0.10 level, we chose SUD and Anxiety since those occurred in at least 20 individuals from the BD parents and non-BD parents. Demographic confounders included whether or not offspring lives with both parents and parental SES. Possible parental lifetime diagnosis confounders included SUD and anxiety, while possible offspring current diagnosis confounders included anxiety, depression, ADHD, and DBD.

For multivariate analyses of associations between counts/total effects of life events and parent group (Table 3), covariates were cumulatively selected from demographic confounders, then parent lifetime diagnosis confounders, and finally offspring current diagnosis confounders. For each group of covariates, variables were selected for the final multivariate model by backward selection until all covariates are significant at the 0.10 level. The same procedure minus the adjustment for offspring current diagnosis confounders was used for multivariate analyses of associations between counts/total effects of life events and offspring current diagnoses (Table 4).

Results

Participants

The sample included 438 offspring: 269 OBD, 88 ONBD and 81 OHC. Offspring did not differ in age, gender, race, or proband socioeconomic status. OBD were less likely to live in intact families (Table 1–2).

Offspring Current Diagnoses at Assessment

In keeping with prior reports from this sample,^{8,23–24,30} OBD as compared with ONBD ($p<0.002$) and OHC ($p<0.0001$) had significantly higher rates of any current Axis I disorder. OBD had greater rates of bipolar spectrum illness than ONBD ($p=0.002$) and OHC ($p=0.03$).

OBD had greater rates of anxiety ($p=0.003$), depression ($p=0.002$), ADHD ($p<0.02$), and disruptive behavior disorders (DBD) ($p<0.02$) than OHC.

Frequency of Stressful Life Events

Offspring groups did not differ significantly in total number of stressful life events reported. Offspring did differ in number of stressful life events rated severity 3 or 4 (affected the participant "somewhat" or "a lot") ($p=0.02$). Pairwise comparisons revealed that OBD reported greater frequency of stressful life events and greater number of stressful life events with severity 3 than OHC ($p=0.003$, 0.01) (Table 3).

Categorization of Stressful Life Events

Groups differed significantly in number of independent stressful life events ($X^2=11.96$, $p<0.04$, Supplementary eTable 1) and neutral stressful life events ($X^2=17.99$, $p<0.003$). Increased independent and neutral life events, but not dependent events, compared with OHC were associated with OBD status ($p<0.01$, 0.003). ONBD and OHC did not differ significantly with regard to type of stressful life event.

A multiple regression GLMM model revealed that OBD had greater frequency of independent stressful life events if the proband had comorbid SUD ($p=0.024$). In addition, OBD with personal diagnosis of DBD experienced more stressful life events ($p=0.044$). OBD with a personal diagnosis of MDD or BD had more independent life events than OBD with different Axis I diagnoses ($p=0.028$).

Severity of Categorized Stressful Life Events

Severity was determined by maximum effect scoring on the SLES Likert Scale, as above. Groups differed significantly only with regard to effect of neutral stressful life events scored 3 or 4 ($X^2=17.2$, $p<0.01$). The effect was significantly greater in OBD than OHC ($p<0.01$, Table 3).

Relationship of Stressful Life Events to Current Axis I Diagnosis (Table 4)

Total number, severity, and all categories of life events except positive and neutral events were associated with greater odds of any current Axis I Disorder, adjusted for demographic group differences, and corrected for multiple comparisons (Table 4). The interaction between stressful life events and group (OBD or ONBD) was not significant. Total number, severity, and all categories of life events except positive events were associated with DBDs in offspring. Total number and severity of total life events, dependent, and negative life events were associated with greater rates of depression. Total number and severity of total life events, dependent, uncertain, and negative life events were associated with SUD. Total number of life events and negative life events were associated with ADHD. Only severity of life events (Likert scale 3) was associated with anxiety disorder.

Multivariate Analyses

Multivariate analyses were completed utilizing parent and offspring responses, demographic confounders, parent lifetime diagnosis confounders, and finally offspring current diagnosis confounders. In multivariate analyses, the offspring responses to the SLES showed no

significant effect for parent group after FDR correction (Table 5). When utilizing parental reports of the offspring stressful life events, the parent group effect was significant for stressful life event frequency, severity and all SLE categories for parent responses except positive and neutral after FDR correction ($p < 0.001$, Table 6).

Discussion

To our knowledge, this is the largest study to examine stressful life events and their relationship to current Axis I diagnoses in OBD. The relationship between stressful life events and Axis I disorder in OBD is important in that it may provide information about modifiable environmental contributions to the heritability of mood disorder. We hypothesized that OBD, as compared with ONBD and OHC, would exhibit a higher number of stressful life events in the year preceding intake, independent of demographic characteristics.

Contrary to our hypothesis, after adjusting for the presence of confounders (e.g., demographics and between group parental and offspring psychopathology for the affected groups), OBD and ONBD did not differ in total number of stressful life events or maximum effect of these stressful life events. However, OBD reported greater number of stressful life events affecting them "somewhat" or "a lot" (Likert scale 3) compared with OHC. OBD also reported being exposed to increased independent and neutral life events than OHC, while ONBD affected probands did not. Greater exposure to independent life events in OBD indicates that they were more likely to be exposed to stressors in which they did not have a direct role. This finding is in agreement with previous studies indicating greater conferred risk in adolescents with a parent with BD and with less family cohesion,^{31–33} and may indicate need for early intervention to assist parents with BD in reducing environmental stressors for their offspring. The relationship between greater frequency of independent stressful life events and proband comorbid SUD for OBD is also worth noting. Our findings highlight a population for whom family interventions may greatly benefit both parent and child. Such intervention may reduce potential familial contributors to Axis I disorder in OBD. This is supported by findings that participants with bipolar spectrum disorders in family-focused treatment had less severe manic symptoms in the following year than participants in family psychoeducation alone.³⁴ It is interesting to note that SES was not associated with the number or severity of stressful life events. This null finding may be related to the period of time assessed (one year) or the greater contribution of proband psychopathology to assessed stressful life events may confound the role of SES in this population.

There was an association between stressful life events and presence of Axis I disorder in offspring of all affected probands, after adjusting for confounders, which may have implications with regard to long-term resilience, coping strategies, and outcome, though the interaction between stressful life events and group (OBD and ONBD) was not significant. Greater total number of life events was associated with DBDs, greater rates of depression, SUD, and ADHD in offspring. Greater overall severity of life events was associated with DBDs, depression, SUD, and anxiety in offspring. Except positive events, all categories of life events were associated with DBDs in offspring. Dependent and negative life events were

associated with greater rates of depression. Dependent, uncertain, and negative life events were associated with SUD. Negative life events were associated with ADHD. The broad impact of stressful life events and their relationship to Axis I disorder indicates potentially modifiable contributors to risk, and suggests a need for early intervention in OBD and ONBD.

Multivariate analyses controlling for parent group and incorporating parental responses as well as demographic, parent lifetime diagnosis, and offspring current diagnosis confounders indicated that parental group had a significant effect when utilizing parental responses, but not when considering offspring responses. This was an unexpected finding, and may indicate an interaction between parental diagnosis and reporting of number and severity of stressful life events described by parents about their offspring. In contrast, it may be that offspring of bipolar parents evaluate and report stressful life events differently. In other words, it may be that parents with BD are more sensitive to stressful life events with higher likelihood of reporting, or it may be that offspring of bipolar parents are desensitized to stressful life events and/or underreport their frequency or severity.

There were limitations of the study. This report focused on adolescents aged 13–18 only; future studies should include younger children. This study was cross-sectional, making it impossible to know whether life events for both proband or offspring preceded or followed the onset of psychopathology. Therefore, we report only an association. There is extensive literature supporting an association between life events and psychopathology, as well as the observation that families with a mood-disordered parent experience increased levels of stress. Proband and offspring disorder may have contributed to ratings of frequency and severity of stressful life events, and there is evidence that psychopathology may influence self-reported stressful life event severity.³⁵ However, ratings between offspring and probands were similar. The observation that probands reported more frequent and more severe stressful life events than their parents did may reflect a greater knowledge of personal life events especially because the sample only include adolescents, minimization of stressful life events by parents, or a contribution of proband or offspring psychopathology. An additional limitation was that stressful life events were measured utilizing a self report checklist rather than a semi-structured interview with consensus. Although interview methods may provide greater detail and therefore greater certainty regarding the classification and severity of life events, the SLES provides a reliable estimate of the overall stress level, and is feasible to use in large samples.²⁵ Stressful life events were measured only in the year prior to assessment. While this reduced the likelihood that events would be forgotten or under-reported, we may have missed significant earlier events.

In univariate analyses, OBD were exposed to significantly more independent and neutral stressful life events than OHC. Explanations for higher rates of independent and neutral stressful life events in OBD may include limited social support or less cohesive family environments,^{7,36–37} with contribution of impairment attributable to BD in the probands. Impaired family function and lower cohesion negatively impact outcome in youth BD, in particular.^{33,38} Previous studies also have indicated greater risk for mood disorder in offspring exposed to parental BD, and a role for intervention in families with a bipolar parent.³⁹ In particular, comorbid SUD in BD probands was associated with a greater number

of independent stressful life events for offspring. This finding is consistent with previous reports in of poorer outcomes in offspring of BD probands with SUD.^{32,40} This strongly suggests a need for early intervention with parents with BD and SUD, and suggests that treatment interventions for parents with this comorbidity is an important part of treating their offspring who are presenting with Axis I disorders as well. Finally, OBD with comorbid Axis I diagnoses who had personal diagnosis of MDD or BD also reported more frequent independent stressful life events. Familial treatment and individual treatment to address symptoms in adolescent OBD is indicated, and has previously been shown to improve mood symptoms in these offspring at risk.³⁴

In summary, these findings indicate that, while risk for any Axis I disorder in OBD is highly heritable in comparison with community samples, there are contributions to risk for onset of Axis I disorder from stressful life events. OBD may experience greater severity of effect of stressful life events than HC. OBD, in particular, report exposure to an increased number of independent and neutral life events. Greater frequency and severity of stressful life events was associated with current Axis I disorder in offspring of both BD and non-BD affected probands, suggesting a role for early intervention in offspring of patients with Axis I disorders, but particularly in offspring of BD probands.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points

1. Offspring of bipolar parents have high heritability of Axis I disorder compared to community samples.
2. Stressful life events may contribute to the heritability of Axis I disorder in offspring of both parents with bipolar disorder and non-bipolar affected parents, suggesting a role for early intervention.

Demographic variables for offspring of probands with bipolar disorder (OBD), offspring of probands with non-bipolar disorder (ONBD) and offspring of healthy controls (OHC)

Table 1

	OBD	ONBD		OHC		Pairwise Comparisons				Pairwise Comparisons (FDR)			
		N=269	N=88	N=81	count; %	Chi-sq stat	p-value	p-value (FDR)	p-value	OBD vs. ONBD	OBD vs. OHC	OBD vs. ONBD	OBD vs. OHC
		count; %	count; %	count; %						p-value	p-value	p-value	p-value
gender (F)		134 49.81%	45 51.14%	42 51.85%		0.12	0.94	1	0.83	0.75	0.93	1	1
Live w/ both parents		112 41.64%	48 54.55%	61 75.31%		28.97	<0.0001	0.0001	0.03	<0.0001	0.01	0.30	<0.0001
race (white)		220 81.78%	68 77.27%	67 82.72%		1.06	0.59	1	0.35	0.85	0.38	1	1
		mean (sd)	mean (sd)	mean (sd)		F-stat	p-value						
age at 1st SLES		14.93 (1.31)	14.95 (1.35)	14.79 (1.25)		0.39	0.68	1	0.9	0.41	0.44	1	1
	OBD	ONBD		OHC		Pairwise Comparisons				Pairwise Comparisons (FDR)			
		N=269	N=88	N=81	count; %	Chi-sq stat	p-value	p-value (FDR)	p-value	OBD vs. ONBD	OBD vs. OHC	OBD vs. ONBD	OBD vs. OHC
		count; %	count; %	count; %						p-value	p-value	p-value	p-value
BP spectrum		41 (15.24%)	1 (1.14%)	2 (2.47%)		Fisher	0.0001	0.003	0.0001	0.001	0.61	0.003	0.02
Anxiety		84 (31.23%)	17 (19.32%)	11 (13.6%)		12.45	0.002	0.03	0.03	0.002	0.32	0.30	0.03
Depression		86 (31.97%)	18 (20.45%)	3 (3.7%)		Fisher	0.0001	0.003	0.04	0.0001	0.001	0.37	0.003
SUD		19 (7.06%)	4 (4.55%)	2 (2.47%)		Fisher	0.32	1	0.4	0.18	0.68	1	1
OCD		10 (3.72%)	1 (1.14%)	0 (0%)		Fisher	0.15	1	0.31	0.12	1	1	1
MDE		63 (23.42%)	11 (12.5%)	2 (2.47%)		Fisher	0.0001	0.003	0.03	0.0001	0.02	0.30	0.003
ADHD		78 (29%)	18 (20.45%)	9 (11.11%)		11.67	0.003	0.04	0.12	0.001	0.1	0.99	0.02
DBD		68 (25.28%)	13 (14.77%)	7 (8.64%)		12.67	0.002	0.03	0.04	0.001	0.22	0.37	0.02
Any Axis 1		180 (66.91%)	47 (53.41%)	30 (37.04%)		24.18	<0.0001	0.0003	0.02	<0.0001	0.03	0.23	0.0001

Table 2

Proband Demographics

	BD		Non-BD		Healthy Control		F stat	p-value	p-value (FDR)
	N=173	Mean (sd)	N=61	Mean (sd)	N=53	Mean (sd)			
SES		34.72 (14.15)		36.56 (13.46)		39.40 (12.43)	2.43	0.09	0.81
Age at offspring 1st SLES		40.28 (7.26)		42.45 (6.83)		41.49 (6.76)	2.29	0.1	0.85
	Count (%)		Count (%)		Count (%)		Chi-sq stat	p-value	p-value (FDR)
gender (F)	138 (79.77%)		45 (73.77%)		39 (73.58%)		1.45	0.48	1
race (white)	152 (87.86%)		49 (80.33%)		44 (83.02%)		2.34	0.31	1
DBD *	50 (28.9%)		5 (8.2%)		N/A		10.75	0.001	0.02
SUD *	114 (65.9%)		30 (49.18%)		N/A		5.32	0.02	0.23
Anxiety *	128 (73.99%)		24 (39.34%)		N/A		23.78	<0.0001	0.0001
ADHD *	35 (20.23%)		3 (4.92%)		N/A		Fisher	0.004	0.05
Psychotic *	5 (2.89%)		1 (1.64%)		N/A		Fisher	1	1
OCD *	25 (14.45%)		1 (1.64%)		N/A		Fisher	0.004	0.05
Any Axis I *	173 (100%)		60 (98.36%)		N/A		Fisher	0.26	1

* Based on comparing BP and non-BP parents.

Table 3

Stressful Life Events in Offspring

OBDD	ONBD	OHC	Neg-Bin GLMM			Pairwise Comparisons		Pairwise Comparisons (FDR)	
			Chi-sq	p-value	p-value (FDR)	OBD vs. ONBD	OBD vs. OHC	OBD vs. ONBD	OBD vs. OHC
	N=269 m (se) *	N=88 m (se) *	N=81 m (se) *						
Total # of events	13.89 (0.05)	12.91 (0.07)	10.22 (0.08)	9.97	0.01	0.41	0.001	1	0.02
# of events with effect = 4	3.78 (0.07)	2.75 (0.14)	1.92 (0.16)	15.75	0.0004	0.05	0.0001	0.40	0.003
# of events with effect = 3	7.45 (0.06)	6.35 (0.09)	4.62 (0.11)	13.95	0.001	0.12	0.0002	0.84	0.01
Severe	1.13 (0.09)	0.96 (0.18)	0.66 (0.16)	9.69	0.01	0.42	0.003	1	0.05
Independent	7.08 (0.05)	6.55 (0.08)	4.97 (0.08)	11.96	0.003	0.43	0.0003	1	0.01
I/D	2.44 (0.05)	2.45 (0.07)	1.87 (0.10)	6.27	0.04	0.94	0.02	1	0.21
Dependent	4.36 (0.06)	3.92 (0.09)	3.39 (0.11)	4.36	0.11	0.30	0.05	1	0.41
Negative	11.41 (0.05)	11.03 (0.07)	8.82 (0.08)	7.25	0.03	0.70	0.01	1	0.10
P/N	2 (0.07)	1.47 (0.12)	1.02 (0.16)	17.99	0.0001	0.02	0.0001	0.21	0.003
Event Count	**Positive Count(%)								
Severity	127 (47.21%)	37 (42.05%)	32 (39.51%)	1.82	0.4	1			
Independent	3.15 (0.09)	2.63 (0.19)	1.92 (0.17)	7.28	0.03	0.26	0.01	1	0.13
I/D	18.86 (0.06)	16.92 (0.08)	13.41 (0.09)	9.48	0.01	0.11	0.002	1	0.03
Dependent	6.32 (0.05)	6.11 (0.08)	5.14 (0.10)	3.34	0.19	1	0.08	1	0.59
Negative	11.57 (0.06)	9.74 (0.09)	8.67 (0.12)	5.81	0.05	0.44	0.03	0.84	0.28
P/N	30.19 (0.05)	28.21 (0.08)	23.47 (0.09)	6.1	0.05	0.40	0.01	1	0.15
Total Effect	5.13 (0.07)	3.46 (0.13)	2.70 (0.16)	17.2	0.0002	0.01	0.0003	0.11	0.01
Positive	1.44 (0.07)	1.10 (0.14)	1.05 (0.17)	5.09	0.08	0.10	0.08	0.71	0.64

* Standard errors are in log scale.

** Occurrence of positive event was modeled differently.

P/N indicates neutral valence and I/D indicates unclear dependency.

Table 4

Stressful life events and Axis I disorders

	Current Any Axis I				Current MDE				Current ADHD			
	Odds Ratio	t stat	p-value	p-value (FDR)	Odds Ratio	t stat	p-value	p-value (FDR)	Odds Ratio	t stat	p-value	p-value (FDR)
total # of events	1.05	4.14	0.002	0.003	1.05	2.94	0.004	0.05	1.04	3.19	0.002	0.03
# of events with effect = 4	1.14	4.21	<0.0001	0.002	1.18	4.37	<0.0001	0.002	1.03	1.12	0.26	1
# of events with effect >= 3	1.08	4.17	0.001	0.003	1.11	3.92	0.0001	0.003	1.03	1.67	0.1	0.73
Independent	1.07	3.09	0.002	0.03	1.08	2.27	0.02	0.21	1.07	2.79	0.006	0.09
I/D	1.27	3.94	0.0001	0.003	1.26	2.28	0.02	0.21	1.22	2.89	0.005	0.07
Dependent	1.15	4.51	<0.0001	0.002	1.18	3.47	0.001	0.02	1.11	3.07	0.003	0.05
Negative	1.06	4.2	<0.0001	0.002	1.07	2.97	0.003	0.05	1.05	3.31	0.001	0.02
P/N	1.18	2.71	0.008	0.10	1.2	2	0.05	0.42	1.15	2.15	0.03	0.28
Positive	1.28	1.17	0.24	1	2.09	1.6	0.11	0.78	0.98	-0.06	0.95	1
Independent	1.03	3.32	0.001	0.02	1.04	3	0.003	0.05	1.02	2.13	0.03	0.28
I/D	1.09	3.73	0.0003	0.01	1.1	2.57	0.01	0.12	1.05	2.04	0.04	0.36
Dependent	1.05	4.35	<0.0001	0.002	1.07	3.88	0.0001	0.003	1.02	1.9	0.06	0.48
Negative	1.02	4.27	<0.0001	0.002	1.03	3.59	0.0004	0.01	1.01	2.34	0.02	0.21
P/N	1.06	2.53	0.01	0.12	1.08	2.47	0.01	0.12	1.04	1.54	0.13	0.88
Positive	1.12	1.69	0.09	0.67	1.33	2.18	0.03	0.28	0.99	-0.09	0.93	1
Total Effect												

	Current DBD				Current SUD				Current Anxiety			
	Odds Ratio	t stat	p-value	p-value (FDR)	Odds Ratio	t stat	p-value	p-value (FDR)	Odds Ratio	t stat	p-value	p-value (FDR)
total # of events	1.08*	5.26	<0.0001	0.0001	1.08	3.86	0.0002	0.01	1.03	1.99	0.05	0.41
# of events with effect = 4	1.12	3.69	0.0003	0.01	1.13	2.9	0.004	0.06	1.14	4.24	<0.0001	0.002
# of events with effect >= 3	1.07	3.52	0.001	0.01	1.11	3.5	0.001	0.01	1.07	3.18	0.002	0.03
Independent	1.13	4.81	<0.0001	0.0001	1.1	2.73	0.01	0.10	1.05	2.12	0.04	0.32
I/D	1.44*	4.82	<0.0001	0.0004	1.64	4.16	<0.0001	0.002	1.12	1.54	0.13	0.86
Dependent	1.19*	4.86	<0.0001	0.0004	1.27*	4.35	<0.0001	0.002	1.05	1.45	0.15	1
Negative	1.09*	5.44	<0.0001	0.0001	1.1	3.9	0.0001	0.003	1.03	1.95	0.05	0.43

	Current DBD				Current SUD				Current Anxiety			
	Odds Ratio	t stat	p-value	p-value (FDR)	Odds Ratio	t stat	p-value	p-value (FDR)	Odds Ratio	t stat	p-value	p-value (FDR)
P/N	1.23 *	3.17	0.002	0.03	1.29	2.51	0.01	0.15	1.13	1.84	0.07	0.52
Positive	1.57	1.62	0.11	0.78	4.47	2.59	0.01	0.12	0.92	-0.31	0.76	1
Independent	1.04	4.42	<0.0001	0.002	1.04	3.03	0.003	0.05	1.02	2.67	0.01	0.11
I/D	1.11	3.79	0.0002	0.01	1.17	3.75	0.0003	0.01	1.06	2.4	0.02	0.19
Dependent	1.05	3.79	0.0002	0.01	1.09 *	4.33	<0.0001	0.002	1.02	1.95	0.05	0.43
Negative	1.03	4.71	<0.0001	0.001	1.04	4.03	0.001	0.003	1.02	2.7	0.01	0.10
P/N	1.06 *	2.45	0.01	0.16	1.09	2.23	0.03	0.27	1.05	1.87	0.06	0.49
Total Effect Positive	1.11	1.23	0.22	1	1.47	2.57	0.01	0.13	1.02	0.2	0.84	1

* Model includes no random effect for family membership.

P/N indicates neutral valence and I/D indicates unclear dependency

Table 5

a: Association between SLES and parent group, offspring responses																		
	BP	Non-BP		Healthy Control	Neg-Bin GLMM		Pairwise Comparisons p-values											
	N=269	N=88	N=81	Chi-sq	p-value ^c	BP vs. Non-BP	BP vs. HC	non-BP vs. HC										
	m (se) ^a	m (se) ^a	m (se) ^a															
Total # of events	13.89 (0.05)	12.91 (0.07)	10.22 (0.08)		9.97	0.0068	0.41	0.001	0.03									
# of events with effect = 4	3.78 (0.07)	2.75 (0.14)	1.92 (0.16)		15.75	0.0004	0.05	0.0001	0.09									
# of events with effect >= 3	7.45 (0.06)	6.35 (0.09)	4.62 (0.11)		13.95	0.0009	0.12	0.0002	0.03									
Severity	1.13 (0.09)	0.96 (0.18)	0.66 (0.16)		9.69	0.008	0.42	0.003	0.11									
Independent	7.08 (0.05)	6.55 (0.08)	4.97 (0.08)		11.96	0.0025	0.43	0.0003	0.02									
Uncertain	2.44 (0.05)	2.45 (0.07)	1.87 (0.10)		6.27	0.0435	0.94	0.02	0.03									
Dependent	4.36 (0.06)	3.92 (0.09)	3.39 (0.11)		4.36	0.1131												
Negative	11.41 (0.05)	11.03 (0.07)	8.82 (0.08)		7.25	0.0267	0.70	0.01	0.04									
Neutral	2 (0.07)	1.47 (0.12)	1.02 (0.16)		17.99	0.0001	0.02	0.0001	0.06									
Event Count	127 (47.21%)	37 (42.05%)	32 (39.51%)	chisq = 1.82	p-value = 0.40													
Severe	3.15 (0.09)	2.63 (0.19)	1.92 (0.17)	7.28	0.0262	0.40	0.01	0.22										
Independent	18.86 (0.06)	16.92 (0.08)	13.41 (0.09)	9.48	0.0087	0.28	0.002	0.06										
Uncertain	6.32 (0.05)	6.11 (0.08)	5.14 (0.10)	3.34	0.1879													
Dependent	11.57 (0.06)	9.74 (0.09)	8.67 (0.12)	5.81	0.0547													
Negative	30.19 (0.05)	28.21 (0.08)	23.47 (0.09)	6.1	0.0473	0.48	0.01	0.12										
Neutral	5.13 (0.07)	3.46 (0.13)	2.70 (0.16)	17.2	0.0002	0.01	0.0003	0.24										
Total Effect	1.44 (0.07)	1.10 (0.14)	1.05 (0.17)	5.09	0.0786													
b: Association between SLES and current pathology, offspring responses																		
	Current Any Axis I			Current MDE		Current ADHD		Current DBD		Current SUD		Current Anxiety						
	Odds Ratio*	t stat	p-value ^a	Odds Ratio*	t stat	p-value	Odds Ratio ^a	t stat	p-value	Odds Ratio*	t stat	p-value	Odds Ratio*					
total # of events	1.06	4.6	<0.0001 [*]	1.05	2.94	0.0035 [*]	1.05	3.75	0.0003 ^{**}	1.08	5.77	<0.0001 [*]	1.08	3.86	0.0002 [*]	1.03	2.54	0.0123

b: Association between SLES and current pathology, offspring responses

b: Association between SLES and current pathology, offspring responses																													
	Current Any Axis I					Current MDE					Current ADHD					Current DBD					Current SUD					Current Anxiety			
	Odds Ratio [*]	t stat	p-value ^a	Odds Ratio [*]	t stat	p-value	Odds Ratio ^a	t stat	p-value	Odds Ratio ^a	t stat	p-value	Odds Ratio ^a	t stat	p-value	Odds Ratio [*]	t stat	p-value	Odds Ratio [*]	t stat	p-value	Odds Ratio [*]	t stat	p-value					
# of events with effect = 4	1.15	4.59	<0.0001 [*]	1.18	4.37	<0.0001 [*]	1.05	1.7	0.0911	1.13	4.32	<0.0001 [*]	1.13	2.9	0.0043 [*]	1.17	5.15	<0.0001 [*]											
# of events with effect >= 3	1.09	4.57	<0.0001 [*]	1.11	3.92	0.0001 [*]	1.04	2.24	0.0265	1.08	4.14	<0.0001 [*]	1.11	3.5	0.0006 [*]	1.08	4.19	<0.0001 [*]											
Independent	1.08	3.58	0.0005 [*]	1.08	2.26	0.0244	1.08	3.32	0.0011	1.14	5.3	<0.0001 [*]	1.10	2.73	0.0071	1.06	2.68	0.0082											
Uncertain	1.31	4.42	<0.0001 [*]	1.26	2.28	0.0232	1.27	3.45	0.0008**	1.49	5.35	<0.0001 [*]	1.64	4.16	<0.0001 [*]	1.12	1.67	0.0973											
Dependent	1.16	4.89	<0.0001 [*]	1.18	3.47	0.0006 [*]	1.12	3.53	0.0006**	1.20	5.32	<0.0001 [*]	1.27	4.35	<0.0001 [*]	1.07	2.06	0.0416											
Negative	1.07	4.6	<0.0001 [*]	1.07	2.97	0.0032 [*]	1.06	3.78	0.0002**	1.10	5.87	<0.0001 [*]	1.10	3.9	0.0001 [*]	1.03	2.37	0.0193											
Neutral	1.22	3.41	0.0009	1.20	2	0.0463	1.21	2.94	0.0039	1.29	3.99	<0.0001 [*]	1.29	2.51	0.0133	1.19	2.77	0.0064											
Count	1.36	1.47	0.1444	2.09	1.6	0.1104	1.07	0.26	0.7928	1.71	1.96	0.0506	4.47	2.59	0.0105	1.07	0.25	0.8047											
Independent	1.03	3.82	0.0002 [*]	1.04	3	0.0029 [*]	1.02	2.75	0.0067	1.04	5.04	<0.0001 [*]	1.04	3.03	0.0029 [*]	1.03	3.47	0.0007 [*]											
Uncertain	1.10	4.22	<0.0001 [*]	1.10	2.57	0.0104	1.07	2.65	0.009	1.12	4.41	<0.0001 [*]	1.17	3.75	0.0003 [*]	1.07	2.75	0.0067											
Dependent	1.05	4.7	<0.0001 [*]	1.07	3.88	0.0001 [*]	1.03	2.34	0.0205	1.05	4.24	<0.0001 [*]	1.09	4.33	<0.0001 [*]	1.03	2.8	0.0059											
Negative	1.02	4.69	<0.0001 [*]	1.03	3.59	0.0004 [*]	1.02	2.9	0.0044	1.03	5.27	<0.0001 [*]	1.04	4.03	<0.0001 [*]	1.02	3.4	0.0009 [*]											
Neutral	1.07	3.16	0.0019	1.08	2.47	0.0139	1.05	2.26	0.0253	1.08	3.21	0.0014	1.09	2.23	0.0276	1.07	2.91	0.0042 [*]											
Total Effect	1.13	1.92	0.0574	1.33	2.18	0.0295	1.01	0.18	0.861	1.13	1.52	0.1291	1.47	2.57	0.0112	1.07	0.87	0.387											

^dStandard errors are in log scale.

^bOccurrence of positive event was modeled differently.

^cNone of these effects were significant after multivariate adjustment and FDR correction

^dControlling for parent group

^{*}Significant at 0.05 level after multivariate adjustment and FDR correction

Table 6

a.: Association between SLES and parent group, parent responses												
Event Count	Positive Count(%) ^b	BP		Non-BP		Healthy Control		Neg-Bin GLMM		Pairwise Comparisons p-values		
		N=269 m (se) ^a	N=88 m (se) ^a	N=81 m (se) ^a	Chi-sq	p-value	BP vs. Non-BP	BP vs. HC	non-BP vs. HC			
Total # of events		11.39 (0.04)	9.80 (0.07)	6.52 (0.08)	36.82	<0.0001 [*]	0.0795	<0.0001	0.0002			
# of events with effect = 4		3.45 (0.09)	2.32 (0.16)	1.33 (0.17)	25.4	<0.0001 [*]	0.0261	<0.0001	0.0184			
# of events with effect >= 3		6.64 (0.06)	5.49 (0.11)	2.81 (0.13)	37.45	<0.0001 [*]	0.1394	<0.0001	<0.0001			
Severity		0.68 (0.10)	0.51 (0.18)	0.25 (0.25)	14.23	0.0008 [*]	0.1618	0.0003	0.0255			
Independent		6.11 (0.05)	5.16 (0.08)	3.32 (0.09)	37.1	<0.0001 [*]	0.0633	<0.0001	0.0002			
Uncertain		1.92 (0.06)	1.93 (0.10)	1.10 (0.13)	16.13	0.0003 [*]	0.975	0.0001	0.0009			
Dependent		3.29 (0.06)	2.64 (0.11)	2.05 (0.12)	13.3	0.0013	0.0791	0.0005	0.1198			
Negative		9.32 (0.05)	8.08 (0.08)	5.57 (0.08)	29.04	<0.0001 [*]	0.1097	<0.0001	0.0012			
Neutral		1.64 (0.07)	1.40 (0.12)	0.72 (0.16)	23.07	<0.0001 [*]	0.2516	<0.0001	0.001			
					chisq = 5.77	p-value = 0.06						
Severe		2.30 (0.13)	1.82 (0.22)	0.74 (0.25)	15.66	0.0004	0.3661	<0.0001	0.0084			
Independent		16.50 (0.05)	13.42 (0.09)	7.54 (0.10)	48.37	<0.0001 [*]	0.0544	<0.0001	<0.0001			
Uncertain		5.68 (0.07)	5.42 (0.12)	3.04 (0.13)	18.09	0.0001 [*]	0.7313	<0.0001	0.0012			
Dependent		9.48 (0.08)	6.88 (0.13)	5.30 (0.14)	15.32	0.0005	0.0325	0.0002	0.168			
Negative		26.11 (0.05)	21.80 (0.09)	13.81 (0.09)	34.58	<0.0001 [*]	0.0822	<0.0001	0.0005			
Neutral		4.59 (0.08)	3.71 (0.14)	1.49 (0.16)	40.41	<0.0001 [*]	0.1808	<0.0001	<0.0001			
Total Effect		0.90 (0.15)	0.48 (0.27)	0.68 (0.27)	4.38	0.112						

b.: Association between SLES and current pathology, parent responses

	Current Any Axis I				Current MDE				Current ADHD				Current DBD				Current SUD				Current Anxiety			
	Odds Ratio *	t stat	p-value	Odds Ratio <i>a</i>	t stat	p-value	Odds Ratio *	t stat	p-value	Odds Ratio <i>a</i>	t stat	p-value	Odds Ratio *	t stat	p-value	Odds Ratio <i>a</i>	t stat	p-value	Odds Ratio *	t stat	p-value	Odds Ratio <i>a</i>	t stat	p-value
total # of events	1.10369	5.43	<0.0001 *	1.062389	2.91	0.0039	1.03975	2.56	0.0115	1.08912	4.85	<0.0001 *	1.10838	4.02	<0.0001 *	1.03263	2.14	0.0341						
# of events with effect = 4	1.18875	5.16	<0.0001 *	1.184712	4.43	<0.0001 *	1.04979	1.66	0.0992	1.08807	2.96	0.0033	1.15269	3.56	0.0004 *	1.13701	4.42	<0.0001 *						
# of events with effect >= 3	1.12908	5.43	<0.0001 *	1.113825	4.15	<0.0001 *	1.03905	1.93	0.0551	1.05919	2.96	0.0033	1.1284	4.4	<0.0001 *	1.06669	3.36	0.001 *						
Independent	1.11952	3.89	0.0002 *	1.069381	1.56	0.1203	1.05096	1.77	0.0783	1.1031	3.34	0.0009	1.18258	3.79	0.0002 *	1.04889	1.72	0.0885						
Uncertain	1.48216	5.4	<0.0001 *	1.289688	2.24	0.0257	1.24321	2.97	0.0035	1.4579	4.72	<0.0001 *	1.68035	4.01	0.0001 *	1.15073	1.94	0.054						
Dependent	1.27724	5.57	<0.0001 *	1.237632	3.88	0.0001 *	1.10893	2.65	0.009	1.29719	5.76	<0.0001 *	1.29033	4.03	<0.0001 *	1.0854	2.13	0.035						
Negative	1.12131	5.47	<0.0001 *	1.080399	3.05	0.0024 *	1.04677	2.54	0.0124	1.10098	4.72	<0.0001 *	1.13906	4.28	<0.0001 *	1.04263	2.33	0.0211						
Neutral	1.25571	3.25	0.0015	1.107716	0.85	0.395	1.15431	2.02	0.0455	1.36602	3.98	<0.0001	1.26934	2.22	0.0285	1.06061	0.81	0.4194						
Positive	1.73429	2.3	0.0233	3.227152	2.59	0.0099	1.23479	0.72	0.472	2.10665	2.55	0.0113	5.03544	3.01	0.0031	1.05488	0.18	0.8544						
Independent	1.04152	4.04	<0.0001 *	1.030485	1.95	0.0519	1.02052	1.98	0.0503	1.03277	3.08	0.0022	1.07024	4.16	<0.0001 *	1.02654	2.55	0.0121						
Uncertain	1.14294	5.51	<0.0001 *	1.129189	3.17	0.0016 *	1.06426	2.47	0.0147	1.11505	4.19	<0.0001 *	1.21179	4.39	<0.0001 *	1.05759	2.26	0.0254						
Dependent	1.07914	5.25	<0.0001 *	1.078251	4.29	<0.0001 *	1.02542	1.92	0.0573	1.06607	4.76	<0.0001 *	1.08965	4.46	<0.0001 *	1.03846	2.96	0.0037						
Negative	1.03765	5.35	<0.0001 *	1.031228	3.47	0.0006 *	1.01407	2.23	0.0275	1.02751	4.26	<0.0001 *	1.05209	5.15	<0.0001 *	1.02004	3.18	0.0019						
Neutral	1.08904	3.4	0.0009	1.070633	1.83	0.068	1.04739	1.77	0.0793	1.09986	3.55	0.0004	1.10672	2.33	0.0216	1.04324	1.63	0.1063						
Total Effect Positive	1.21046	2.5	0.0137	1.444264	2.82	0.005	1.02623	0.28	0.7806	1.1474	1.48	0.1386	1.45107	2.46	0.0152	1.07873	0.86	0.394						

^aStandard errors are in log scale.

^bOccurrence of positive event was modeled differently.

* Significant after multivariate adjustment and FDR correction

^aControlling for parent group only

* Significant at 0.05 level after multivariate adjustment and FDR correction