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ORIGINAL CONTRIBUTION

Temperament, life events, and psychopathology among the offspring of bipolar parents

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Abstract *Objectives* The present study examines the relationship between temperament, recent and remote life events, and psychopathology among the offspring of parents with bipolar disorder and well comparisons. *Methods* Offspring of bipolar and well parents were clinically assessed using KSADS-PL format interviews. Lifetime psychiatric diagnoses were made on a blind consensus basis in accordance with DSM-IV criteria. Depending on offspring age, either the child or their parent on their behalf, completed a semi-structured interview quantifying the number and impact of recent life events and remote permanent losses, as well as a measure of temperament. *Results* In this study, there was an association between psychopathology and the number of recent negative life events, but no association between psychopathology and the number of early losses. Emotionality was positively correlated with recent life events. However, in stepwise regression analyses, only emotionality significantly contributed to lifetime psychopathology in general and emotionality and age contributed to the risk of mood disorder in particular. *Conclusions* These findings, replicate in a sample of offspring at high risk for bipolar disorder, previously reported associations between high emotionality and unipolar depression. In this population, any effect of undesirable life events would appear to be mediated through the association with emotionality.

Key words bipolar disorder – high risk – offspring – temperament – life events

Introduction

Bipolar disorder is a complex illness likely resulting from the interaction of susceptibility genes yet to be determined, with other biological, psychological, and sociological determinants [3, 14, 34]. In order to fully understand the mechanism underlying illness onset and recurrence we need to study the

interactive effects among genetic and other known risk factors.

Substantial convergent evidence indicates an association between moderately to severely undesirable life events and the subsequent onset of major depressive episodes in both adults and adolescents with unipolar disorder. For example, in the classic series of studies by Brown and Harris it was determined that recent significant life events were strongly associated with subsequent depressive onsets [4, 5].

Adapting the Brown and Harris concepts, Goodyer and colleagues investigated the relationship between moderate to severely undesirable recent life events and subsequent episodes of unipolar depression in community samples of adolescents [15, 16, 18, 19]. They reported that such events were significantly more common in those who developed subsequent major depression. In particular, there was an association between events in the preceding month and new onsets, but only for around 60% of cases. There was no 'dose-response' relationship between the overall number of undesirable events in the year prior and new onsets of depression. Severely disappointing events, particularly with friends, over the follow-up period were associated with persisting disorder [20].

There is a growing appreciation for the interaction between life events and genetic risk for depression. For example, Kendler and colleagues have shown that adults at genetic risk for depression experience more stressful life events and are more sensitive to these events [27, 28, 30]. Consistent with this, Silberg and colleagues have reported that a part of the genetic risk for depression in adolescent girls is attributable to a genetic predisposition to experiencing particular stressful life events [35]. Sensitivity to stressful life events has been associated with having one or two copies of the short allele of the 5-HTT promoter polymorphism [7]. Genetic influences are not only expressed in the physiologic and psychological processes within, but extend into the behavioural phenotype and social environment in a reciprocal way [32].

The number of stressful life events reported by individuals over time has been shown to be quite stable and predicted by heritable personality and temperament characteristics [13]. Goodyer and colleagues have reported that high emotionality in adolescents is associated with the increased likelihood for developing a major psychiatric illness and depression in particular [17, 26]. There is also evidence supporting a multiplicative model in which the association between neuroticism (proxy for high emotionality) and depression is greatest at higher, rather than at lower, levels of adversity [29]. Further, in the studies by Henderson, perceived inadequacy of social relationships was a causal factor in the onset of neurosis in those experiencing high adversity [24].

There is an increasing interest in the idea that specific temperamental profiles or traits could predispose to bipolar disorder, perhaps in part through increasing exposure to stressful life events. Convergent data from family studies and prospective studies of adults and adolescents have supported the idea that temperament may be a reliable vulnerability marker [1, 2, 12, 31]. The role of stressful life events in the course of bipolar disorder is less clear, with some observations suggesting an association primarily with early episodes [33]; whereas other observations suggest an enduring association between stressful life events and recurrences [11, 23]. The early identification and intervention in individuals at risk for mood episodes is extremely important. With this in mind, we are interested in studying the relationship between affected status and both temperament and adversity among the offspring of bipolar parents.

The current study is a cross-sectional investigation of the association between undesirable recent life events, early permanent losses, temperament and psychopathology among the offspring of well-characterized bipolar and well parents. The high risk groups were further sub-classified on the basis of having a parent with either a lithium responsive (LiR) or a lithium non-responsive (LiNR) bipolar disorder. Long term response to lithium monotherapy is one way to reduce heterogeneity [22] and may therefore distinguish variations in vulnerability for the disorder among offspring.

Method

Participants

Parents

Proband parents included in this study were identified through ongoing genetic studies of bipolar disorder and are described in detail elsewhere [8–10, 36]. They were recruited through an outpatient mood disorders program at the Royal Ottawa Hospital and the Hamilton Psychiatric Hospital. Briefly, probands met DSM-IV criteria for bipolar I disorder based on SADS-L interview by two research psychiatrists. Response to long-term lithium monotherapy was based on research evaluations using standardized protocol. All probands had a recurrent illness prior to lithium treatment. Lithium responders were completely stabilized, requiring no additional medication, on therapeutic lithium (plasma levels > 0.7 mmol/l) for a minimum of three years, while lithium non-responders had an additional two recurrences while

on therapeutic plasma levels of lithium. All diagnoses and treatment response decisions were reviewed on a blind consensus basis by a panel including at least one additional research psychiatrist. In four cases, we included an affected first degree relative of a lithium responsive bipolar I proband as a parent in this study. These were individuals who suffer from a bipolar illness with a typical lithium responsive profile [21].

For this study, we included a comparison sample of parents and their children from two local schools in Ottawa, following the methods of Goodyer et al. [17]. Briefly, families completed demographic screening questionnaires detailing family composition and medical and psychiatric histories of the parents. Families indicating no lifetime psychopathology in either parent were invited to take part in this study. At least one parent from each comparison family completed a SADS-L interview confirming no lifetime psychopathology. If the other parent did not complete the interview, their unaffected status was confirmed using the interviewed spouse as the informant following the Family History- RDC method.

Offspring

All consenting offspring of identified bipolar and well parents of age 8–25 years were enrolled in this study. These offsprings have been described in previous reports [8–10] and as a part of the high risk study, they are followed prospectively and repeatedly assessed. For this cross-sectional study, offspring were included if they had completed the life events, permanent losses and temperament measures at the same time as a clinical assessment based on a semi-structured interview (see below). Of the high risk and comparison offspring eligible and approached for this study, none refused to take part.

Measures

Diagnostic measures

All high-risk and comparison offspring were interviewed by a child and adolescent research psychiatrist (AD) according to KSADS-PL/SADS-L format (depending on their age). They or their parent on their behalf (see methods below) completed permanent losses and life event measures on the basis of a semi-structured interview, as well as completing the temperament questionnaire. DSM-IV diagnoses were made on the basis of a consensus review including an additional research psychiatrist and a child and adolescent sub-specialist blind to parent group (control or high risk) and to parent treatment response.

Recent life events and difficulties

Recent life events and friendship difficulties were assessed for the preceding year at the clinical assessment in a semi-structured interview procedure adapted from Goodyer et al. [15, 20]. Significant negative events were recorded by the interviewer and rated by the offspring or parent (for those under age 13) in terms of negative impact (quite pleasant, pleasant, neutral, unpleasant, very unpleasant). Briefly, this interview assessed 12 domains of life events and only counted those experiences subjectively rated as having an unpleasant or very unpleasant impact, lasting for at least 2 weeks. Total life event scores for each individual were calculated by summing the number of criterion life events. All events were recorded for the preceding 12 month period.

Early permanent losses

Permanent lifetime losses were measured in a semi-structured interview procedure adapted from Goodyer and colleagues. Early permanent losses were recorded by the interviewer and rated by the offspring or parent (for those under age 13) in terms of negative impact. This interview assessed 10 types of permanent losses including death of a parent, sibling, grandparent, other family relative, family friend, and/or personal friend, as well as permanent separation from a parent, sibling, other family member, and/or close friend. The negative impact was rated on a scale of 0 to 3, and only events considered moderate or severe (scores of 2 or 3 out of 3) were counted.

Temperament

The Emotionality, Activity, Sociability and Shyness Temperament Questionnaire (EAS), developed by Buss and Plomin [6], was used to measure these four dimensions of temperament. This measure consisted of a 20-item self-report form, and individuals were asked to rate themselves using a 5-point Likert scale (ranging from "not typical" to "very typical"). Summing the items within each subscale and dividing by 5 derived subscale scores for each dimension of temperament. The respondent in this case was either a parent (for children under 13 years of age) or the offspring themselves. This scale has been extensively studied in children and adolescents and has shown itself to be a reliable and valid measure of temperament [6, 37].

Statistical methods

Chi square analyses were performed on categorical descriptive data. Analysis of variance and Tukey's post hoc comparisons were used to assess differences across

groups on age at assessment. Kruskal–Wallis test was used to assess group differences in negative life events, permanent losses and temperament scores. Spearman's rank correlation was used to test an association between emotionality and both undesirable life events and permanent losses. Two step-wise logistic regression analyses using SAS software were performed with diagnosis of any psychiatric disorder and diagnosis of mood disorder as the dependent variables. The independent variables included: age at assessment, sex, lithium response of the parent, early permanent losses, recent negative life events, and emotionality scores.

Results

Descriptive statistics

Of the high risk group, 50 offspring were considered affected (to have met a lifetime DSM-IV diagnosis) and 25 offspring were unaffected (see Table 1). The comparison sample included 37 psychiatrically unaffected offspring from well parents. This was not a result of selection of well offspring, as the absence of psychiatric disorder was required only in the parents of the comparison families.

The comparison group offspring were younger on average than the high risk offspring, however there was no difference in age between the high risk unaffected and affected offspring subgroups (see Table 2). There were no sex ratio differences between the study groups.

In all three groups, the majority of families remained intact. There were differences in the education levels of the parents across the groups (see Table 2) such that for both mothers and fathers, the high risk unaffected group was less likely to have completed university than was the comparison group.

Table 1 DSM-IV lifetime diagnoses in offspring

*Diagnosis	Offspring of LiR	Offspring of LiNR
Bipolar disorder (I, II, NOS)	12	5
Recurrent major depression	2	7
Depression NOS	5	0
Single MD episode	2	1
Anxiety disorder	2	5
Sleep disorder	2	5
Adjustment disorder	2	2
Eating disorder	0	2
Psychotic spectrum disorder	0	0
Substance use disorder	5	7
Cluster A/B personality traits	1	3
Learning disability	1	0
ADD/ADHD	1	1
Unaffected high-risk offspring	12	13

*Some individuals meet criteria for more than one diagnosis.

Table 2 Demographic information

	Offspring			
	High-Risk affected (n = 50)	High-Risk unaffected (n = 25)	Comparison (n = 37)	
Sex ratio (male:female)	21:29	11:14	18:19	$\chi^2(2) = 0.39$, $P = .83$
Average age at last assessment	21.4 years SD = 5.84	18.7 years SD = 6.48	14.4 years SD = 2.95	$F(2,109) = 19.39$, $P < .001$[a]
Percentage intact families	66.70%	76.90%	84.60%	$\chi^2(2) = 2.44$, $P = .30$
Family income				
$0 – $39,999	10	7		
$40,000 – $59,999	6	5	n/a	$\chi^2(3) = 1.61$, $P = .66$
$60,000 – $79,999	12	7		
$80,000 +	17	6		
	High risk offspring (n = 75)		Comparison Offspring (n = 37)	
Mother's education[b]				
University not completed	12	8	2	$\chi^2(2) = 6.86$, $P = .03$[c]
Undergraduate or graduate degree completed	35	17	31	
Father's education[b]				
University not completed	6	12	1	$\chi^2(2) = 25.40$, $P < .001$[d]
Undergraduate or graduate degree completed	42	10	32	

[a]Tukey's post hoc comparisons showed that comparison offspring were younger than both affected and unaffected offspring
[b]Education information was not available for all subjects
[c]Follow-up pairwise chi square analyses indicated that mothers of unaffected high risk offspring differed from mothers of comparison offspring
[d]Follow-up pairwise chi square analyses indicated that fathers of unaffected high risk offspring differed from both fathers of affected high risk offspring and from fathers of comparison offspring

In addition, for fathers, the high risk unaffected group was less likely to have completed university than was the high risk affected group. Income information was not available on the comparison group, therefore only the two high-risk groups were compared. There was no relationship between family income and affected status.

Primary results

As the two high-risk offspring cohorts were similar demographically and as lithium response of the parent did not differentiate the high-risk offspring groups on the primary variables of interest, we collapsed the high-risk subgroups to examine affected versus unaffected offspring.

In order to test whether those offspring affected with an Axis I disorder would report more negative life events, early permanent losses, and higher emotionality compared to unaffected high-risk offspring and comparison offspring, Kruskal–Wallis non-parametric tests were performed using an alpha of .05 for the overall comparison as well as for post hoc pairwise comparisons where necessary.

Means and standard deviations for the three groups for numbers of negative life events and permanent losses are reported in Table 3. There was a significant overall difference ($P = .02$) across the three groups in number of negative life events. Post hoc pairwise comparisons showed that affected high risk offspring experienced more negative life events than did both unaffected high risk offspring ($P = .03$) and comparison offspring ($P = .02$). There was no difference in number of negative life events between the unaffected high risk and comparison offspring ($P = .90$). There were no significant differences ($P = .88$) across the three groups in number of permanent losses.

Means and standard deviations for the three groups for the temperament scales are also reported in Table 3. There was a significant difference ($P < .001$) in emotionality across the three groups. Post hoc pairwise comparisons showed that affected high risk offspring were higher in emotionality than both unaffected high risk offspring ($P < .001$) and comparison offspring ($P < .001$). There were no significant differences across the three groups in shyness ($P = .83$), sociability ($P = .32$), or activity ($P = .65$).

Within the high risk cohort, there was a correlation between emotionality scores and number of negative life events, Spearman's rho = .28, $P = .02$. This was also the case among all offspring including controls. However, there was no significant correlation between emotionality and number of permanent losses in either the total group of offspring or in the high risk group, Spearman's rho = .21, $P = .08$.

Two stepwise logistic regressions were conducted in order to test whether negative life events, emotionality, sex and lithium response of parent would predict (i) presence of a psychiatric illness, in general, and (ii) presence of a mood disorder, specifically. Age at last assessment was used to control for the age-dependent prevalence of psychiatric disorders by "forcing" the age variable into the model before any other explanatory variables. In analyzing the contribution of the above predictor variables to lifetime diagnosis of psychiatric illness in general, only emotionality was associated with the risk of having any Axis I disorder with age showing only a trend (see Table 4). For the analysis of factors contributing to presence of a lifetime mood disorder, both age at last assessment and emotionality were significant predictors (see Table 4). Overall, emotionality was positively associated with both the risk of any psychiatric illness and of mood disorders specifically.

Discussion

This study examined the relationship between psychiatric disorder, temperament, recent undesirable life events, and permanent losses among offspring of bipolar and well parents. Consistent with previous reports from studies of unipolar depressed patients and their relatives, we found an association between

Table 3 Means and standard deviations for number of negative life events, permanent losses, and temperament scores

	Offspring		
	High-Risk affected ($n = 50$)	High-Risk unaffected ($n = 25$)	Comparison ($n = 37$)
Negative Life Events	1.50[a] (1.42)	0.76[b] (0.97)	0.92[b] (1.48)
Permanent Losses	0.92 (1.12)	0.92 (1.19)	1.08 (1.26)
Emotionality	2.74[a] (0.86)	1.97[b] (0.89)	2.26[b] (0.66)
Shyness	2.43 (0.82)	2.50 (0.84)	2.38 (0.70)
Sociability	3.39 (0.67)	3.31 (0.61)	3.52 (0.72)
Activity	3.52 (0.67)	3.68 (0.45)	3.52 (0.72)

Values enclosed in parentheses represent standard deviations
Means with different superscripts differ significantly, $P < .05$

Table 4 Summary of step-wise logistic regression analyses

Variables	Wald test (Chi square)	*B*	SE *B*	Odds ratio	95% CI Upper	95% CI Lower
Predicting presence of any psychiatric illness						
Age	2.69†	0.08	0.05	1.08	1.18	0.99
Emotionality	9.81**	1.06	0.34	2.89	5.61	1.49
Life events	1.68	–	–	–	–	–
Losses	0.88	–	–	–	–	–
Response	0.15	–	–	–	–	–
Sex	0.71	–	–	–	–	–
Predicting presence of mood disorder						
Age	6.42*	0.12	0.05	1.13	1.24	1.03
Emotionality	8.35**	0.91	0.31	2.47	4.56	1.34
Life Events	2.71	–	–	–	–	–
Losses	2.37	–	–	–	–	–
Response	0.21	–	–	–	–	–
Sex	0.08	–	–	–	–	–

†$P = 0.1$; *$P < 0.05$; **$P < 0.01$

emotionality and the presence of psychiatric disorder in general, and mood disorder in particular. Aside from age at assessment, emotionality explained most of the variance in psychiatric outcome in the high risk cohort. It is not clear from this study, whether high emotionality in this high risk population reflects subsyndromal illness or a true temperamental variant found in the normal population [25].

In this study, affected high risk offspring experienced more undesirable recent life events. However, it appears that in this population, recent undesirable life events in and of themselves, did not significantly directly contribute to the outcome of psychopathology. Rather, recent undesirable life events appeared to be related to psychopathology through their association with emotionality. This differs from the literature on unipolar disorders, but agrees with the general observation that the course of bipolar disorder appears relatively independent of life events, especially after the index mood episode [33].

Finally, there were no differences between the offspring of lithium responders and the offspring of lithium non-responders with regard to their temperamental profiles or number of recent or remote life events. This suggests that the striking group differences in the early childhood functioning and in the nature and course of psychopathology previously described, is not mediated through differences in these psychosocial risk factors [8–10].

The main limitation of this study was that all offspring who met lifetime criteria for a mood or other psychiatric disorder had already manifested the illness prior to the measurement of temperament and recent life events. This complicates the interpretation of the findings, as we cannot determine from this study whether or not high emotionality is a precursor to or a consequence of psychopathology. For example, it may be that affected offspring develop heightened emotional reactivity as a consequence of their illness.

A lesser limitation includes the fact that the interviewer was not blind to whether or not the offspring was from a high risk or comparison family. However, lifetime diagnoses were based on blind consensus review for all offspring and the independent variables were self report and self ranked measures.

This study represents an initial step towards understanding the interplay between social and psychological factors and psychopathology among the offspring of bipolar and well parents. The next step will be to study these factors in younger offspring, prior to the manifestation of any major psychiatric disturbance, with repeated prospective reassessment to identify differential outcomes. It would be important to definitively test whether high emotionality, measured prior to the onset of illness, predicts for subsequent psychopathology in children at risk for bipolar disorder [25]. It would also be important to determine if particular temperamental profiles were associated with differential risks of psychopathology within the high risk cohort. Finally, it would be most helpful to explore the temporal relationship between life events and the onset of antecedent psychopathology and the recurrence of mood episodes very early in the course.

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