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Characteristics of depression among offspring at high and low familial risk of bipolar disorder

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Abstract

Objectives—Having a parent with bipolar disorder (BP) is a very strong risk factor to develop BP. Similarly, depression among youth is a clinical risk factor for subsequent BP. We evaluated whether mood symptomatology in depressed youth is different between those at high versus low familial risk to develop BP.

Methods—The most severe major depressive episode in BP offspring (N=61) and community control offspring (N=20) was evaluated using expanded depression and mania rating scales derived from the Schedule for Affective Disorders and Schizophrenia for Children Present Version. The results were adjusted for any between-group significant demographic differences and for multiple comparisons.

Results—The severity of depressive symptoms and percentage of offspring with severe depressive symptoms, especially atypical depressive features, were significantly higher in the depressed offspring of BP parents compared to the depressed controls ($p_s < 0.05$). The depressive symptoms were helpful to identify high risk group (e.g., odds ratio (OR) for hypersomnia: 22.4, Confidence Interval (CI): 1.3–404, $p=0.04$). In addition, there were significantly more depressed

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Conflict of Interest

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offspring of BP parents with subsyndromal manic symptoms than the controls (52.5% vs. 20%, OR: 4.2, CI: 1.2–14.7, $p < 0.01$).

Conclusions—Depressed BP offspring had more severe depression including atypical depressive symptoms, and were more likely to have subsyndromal mixed manic symptoms than depressed control offspring. Prospective studies to evaluate whether these youths are at high risk to develop BP are warranted. If replicated, the results of this study have important clinical (e.g., treatment of depression in depressed offspring of BP parents) and research implications.

Keywords

Depression; Atypical Symptoms; Mixed Features; Subsyndromal Manic Symptoms; Bipolar Offspring

1. Introduction

Approximately 20% of youths develop impairing symptoms of depression that substantially increase risk for suicidality, legal problems, and substance abuse and hampers normative psychosocial development (1–3). Depressive episodes are usually the first and the most common manifestation of bipolar disorder (BP) in youth (4–6), and 20%–40% of youth with early onset depression and family history of BP go on to develop BP (7–9). However, we do not know yet whether there are specific depressive symptoms that distinguish those youths at higher risk to develop BP.

Studies in offspring of parents with BP have shown significantly more mood dysregulation, subsyndromal manic symptoms, anxiety, and behavior problems in comparison with offspring of control parents (10, 11). Recently our group reported that offspring of BP parents with depression, anxiety, mood lability and subsyndromal symptoms of mania and whose parents had early-onset BP were at 50% risk to develop BP (12). However, despite accumulated knowledge about higher psychopathology rates of youth at risk to develop BP compared to controls (4, 7, 13–16), there are no studies examining the phenomenology of the depressive symptoms in high risk population, and whether these symptoms differentiate youth at lower risk to develop BP. The results of such studies could have important clinical as well as research implications.

Studies in adults suggest that atypical depressive symptoms (e.g., increased appetite/sleep, psychomotor retardation/leaden paralysis) are more common in BP depression compared to unipolar depression and may suggest increased risk for developing BP (17–24). The scarce literature in depressed youth suggests a prevalence of atypical symptoms in 16% of cases (25). These atypical features seem more common in BP depression than unipolar depressed youth (26). However, perhaps due to methodological limitations (e.g., not taking into account the effects of confounding factors such as comorbid clinical conditions, global functioning, and acute vs. past history of depression), the results of the above studies have been inconsistent (27).

In addition to the atypical features, there has been an increased interest in the field in identifying subsyndromal manic symptoms during an episode of depression that can help

distinguish BP (22, 24, 28, 29). In fact, up to 40% of depressed adults have co-occurring subsyndromal manic symptoms; these patients meet criteria for major depression with mixed features according to DSM 5 (30–35). Similar to the findings with atypical depressive symptoms, depressed adults with mixed presentations have poor treatment response to antidepressants and appear to be at higher risk for developing BP (23). Also, a recent study in depressed adolescents showed that the presence of mixed symptoms was associated with resistance to antidepressant treatment (36).

The Pittsburgh Bipolar Offspring Study (BIOS) provides an excellent opportunity to study the clinical presentation of depression among offspring of parents with BP as compared to offspring of community control parents (11, 37). Based on the scant literature (25, 36), we hypothesized that atypical depressive and subsyndromal manic symptoms would be more common in depressed offspring at familial risk for BP when compared with depressed offspring of community control parents even after adjusting for any between-group demographic differences.

2. Methods

2.1. Subjects

The methodology of the Bipolar Offspring Study (BIOS) was reported in detail elsewhere (11, 37). In summary, parents (probands) with BP-I or BP-II were recruited through advertisement (53%), adult BP studies (31%) and outpatient clinics (16%). Parents with lifetime diagnoses of schizophrenia, mental retardation, mood disorders secondary to substance abuse, medical conditions, or medications, and living more than 200 miles away from Pittsburgh were excluded. Control parents consisted of healthy parents or parents with non-BP pathology from the community, group matched by age, sex, and neighborhood with the BP parents. The control parents had the same exclusion criteria as the BP parents, but they could not have BP or have a first-degree relative with BP. BIOS recruited 233 BP parents and their 388 offspring aged 6–18 years and 143 control parents and their 251 offspring. For the purpose of this cross-sectional study, offspring who were experiencing a current major depressive episode at intake or at any of the study visits during the length of the study (6.8 ± 2.2 years) were included. For those with more than one depressive episode, we included the worst depressive episode as measured by the Depression Rating Scale (DRS) (38). Offspring who had already developed BP were excluded.

2.2. Clinical measures

After Institutional Review Board approval, consent was obtained from the parent and assent from the offspring. Proband parents and biological co-parents who participated in direct interviews (30%) were evaluated for Diagnostic and Statistical Manual- IV (DSM-IV) (39) psychiatric disorders using the Structured Clinical Interview-DSM-IV (SCID) (40). Attention Deficit Hyperactivity Disorder (ADHD), Disruptive Behavior Disorders (DBD), and Separation Anxiety Disorder (SAD) sections from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) were used to evaluate for these disorders (38). Socio-economic status (SES) was ascertained using the Hollingshead scale (41). The Family History-Research Diagnostic Criteria method

(FH-RDC) (42) plus ADHD and DBD items from the K-SADS-PL were used to ascertain the psychiatric history of biological co-parents not interviewed directly.

Parents were interviewed about their offspring, and the offspring were directly interviewed for the presence of past and current DSM-IV psychiatric disorders using the K-SADS-PL (38). As per the K-SADS-PL instructions, mood symptoms that were also in common with other psychiatric disorders (e.g., hyperactivity) were not rated as present in the mood sections unless they intensified with the onset of abnormal mood. Comorbid diagnoses were not assigned if they occurred exclusively during a mood episode. The depression rating scale (DRS) items derived from K-SADS-Present Version (38) and the K-SADS-Mania Rating Scale (MRS; derived from K-SADS-Present Version) (43) were used to ascertain depressive and manic symptoms, respectively. Both of these scales reflect the severity of mood symptoms one month before the interview. Scores of 4 and higher on DRS and MRS during the acute depressive episode indicate severe mood symptoms, whereas 1 indicates absence of that symptom, and 2–3 indicates subsyndromal presence of that mood symptom (43). Atypical mood symptoms were ascertained using DRS in accordance to the DSM 5 criteria: mood reactivity and two of the following depressive symptoms: increased appetite or weight gain, hypersomnia, leaden paralysis/psychomotor retardation, and rejection sensitivity (39). As per the DSM 5, mixed features were defined as 3 or more subsyndromal/syndromal manic symptoms present during the acute depressive episode (35). To diagnose a mixed episode, the DSM-IV requires both threshold manic and depressive symptoms. Thus, because this study aims to focus on acute major depressive episodes without threshold manic episodes, the DSM 5 criteria for mixed features were used to be able to report subsyndromal manic symptoms during the course of a depressive episode. Bachelors- or masters-level interviewers completed all assessments after intensive training for all instruments and after 80% agreement with a certified rater. The overall SCID and K-SADS kappas for psychiatric disorders including major depressive episodes were 0.8. This kappa was calculated for all major depression symptoms, and was not specific to items assessing atypical symptoms. All assessments were presented to psychiatrists who were ultimately responsible for all diagnoses. Interviewers and psychiatrists were blind to parents' and offspring's diagnoses.

2.3. Statistical analysis

Between-group demographic and clinical characteristics were compared using parametric and nonparametric methods as appropriate. For the cross-sectional analyses of mood symptoms, first we identified an acute episode of major depression with the highest DRS score (worst depression). This depressive episode needed to be present during a study visit. Subsequently, the mean total depressive and manic scores, and depressive and subsyndromal mixed manic symptoms equal or above threshold scores (DRS 4 and MRS 2, respectively) were analyzed. Logistic and cumulative logistic regression models were used to model the rates of threshold depressive and subsyndromal manic symptoms and the severity of symptom ratings, respectively. Differences in severity in depressive and subclinical manic symptoms were controlled for within-family correlation using the Generalized Estimating Equation (GEE) method. Firth's bias correction was used in all logistic regression models to mitigate potential bias from the low incidence of threshold depressive and subsyndromal manic symptoms in the offspring of control parents group (44). We adjusted our findings for

significant between-group differences in (offspring and parents) demographic characteristics by controlling for the demographic covariates that minimize the Akaike's Information Criterion (AIC), and calculated odd ratios (ORs) for each mood symptom. Since there are no studies examining the intensity and severity of depressive symptoms in youth at risk to develop BP in comparison with controls and we have a priori hypotheses, the main findings of this study with relatively small sample size are presented without controlling for multiple comparisons. However, for completeness, the tables also include p-values after corrections for multiple comparisons using the false discovery rate (FDR) (45). Additional analyses were conducted to explore the correlation between significant depressive and subsyndromal manic symptoms. The significance level was set at 0.05.

3. Results

Sixty-one depressed offspring of 57 BP parents and 20 depressed offspring of 16 control parents were included. In comparison to the depressed offspring of control parents, the depressed offspring of the BP parents had significantly fewer females ($p=0.02$), Caucasians ($p=0.03$), offspring living with biological parents ($p=0.03$), lower SES ($p=0.03$), and more past depressive episodes ($p=0.03$). There were no other between-group demographic and clinical differences (Table 1).

Depressive symptoms (Table 2)

Compared to the depressed offspring of control parents group, the depressed offspring of BP parents group had more severe depressive symptomatology including sad mood, irritability, fatigue, negative self-image, social withdrawal, anhedonia, rejection sensitivity, hypersomnia, increased appetite, hopelessness, guilt, psychomotor retardation, and suicidal ideation, ($p = 0.05$). In addition, depressed offspring of BP parents had higher total atypical depressive symptoms (14.26 ± 5.7 vs. 9.05 ± 2.3 , respectively, $p=0.0002$) and total depressive symptoms (27.5 ± 10.2 vs. 18.6 ± 7.8 , respectively, $p=0.006$). Except for increased appetite, the results remained similar after adjusting for significant between-group demographic variables (e.g., SES, living with biological parents, and offspring sex) (all adjusted $p = 0.05$). Adjusted Odd Ratios (ORs) ranged from 3.7 to 13.7 with some atypical depressive symptoms having the highest ORs (hypersomnia; 10.5 (confidence interval (CI): 2–56) and psychomotor retardation: 13.7 (CI: 2.3–81.2)). The adjusted OR for the rejection sensitivity was 3.8 (CI: 1.2–12). There were other depressive symptoms with significant adjusted ORs such as hopelessness (OR: 9.5, CI: 2.1–43.2), social withdrawal (OR: 7, CI: 2–23.8), negative self-image (OR: 6.7, CI: 2.1–21.4), guilty (OR: 6, CI: 1.4–25.3), irritability (OR: 4.9, CI: 1.7–14.2), anhedonia (OR: 4.5, CI: 1.5–13.6), and sad mood (OR: 4.1; CI: 1.4–11.9). Except for suicidal ideation, correcting for multiple comparisons yielded similar results. More depressed offspring of BP parents showed individual depressive scores above the threshold score (DRS ≥ 4) compared with depressed offspring of control parents including irritability (49.2 vs. 5%; OR: 9.2, CI: 1.5–55.3), fatigue (49.2% vs. 10%; OR: 5.9, CI: 1.4–25.8), and hypersomnia (34.4% vs. 0%; OR: 22.4, CI: 1.3–404) (all p -values ≤ 0.04). There were no significant between-group differences in offspring of BP parents vs. controls regarding use of medications during the period of depression (e.g., selective serotonin reuptake inhibitors 31.2% vs. 45%, mood stabilizers 13.1% vs. 10%, and ADHD medications 19.7% vs. 15%).

Excluding the 6 offspring of BP parents who developed BP during the BIOS study follow up did not change the results. None of the offspring of the controls converted into BP.

Subsyndromal manic symptoms (Table 3)

Depressed offspring of BP parents had significantly higher subsyndromal manic symptoms compared to the depressed offspring of control parents including mood lability, irritability/anger, racing thoughts, and total subsyndromal mixed manic symptoms (all p -values < 0.04). These subsyndromal manic symptoms remained significant (all adjusted $p < 0.05$) after correcting for between-group demographic differences (e.g., parental SES, living with biological parents, and gender of offspring) with ORs of 7.6 (CI: 1.3–44) for racing thoughts and 6.3 (CI: 1.2–33.4) for mood lability. After correcting for multiple comparisons there were no significant between-group differences in subsyndromal manic symptoms. In comparison with the depressed offspring of the control parents, significantly more depressed offspring of BP parents had mood lability (36% vs. 10%; corrected OR: 4.6, CI: 1.01–21.3) and mixed features (3 or more subsyndromal manic symptoms; 52.5% vs. 20%; corrected OR: 4.2, CI: 1.2–14.7) (all p -values < 0.04) (Figure 1). The results did not change after excluding the 6 offspring who developed BP during the BIOS study follow up.

Correlations between depressive and subsyndromal manic symptoms

Total atypical depressive symptoms were significantly correlated with mood lability ($r=0.32$, $p=0.004$) and total subsyndromal manic symptoms ($r=0.24$, $p=0.03$). Total subsyndromal manic symptoms were significantly correlated with irritability ($r=0.37$, $p=0.01$), fatigue ($r=0.35$, $p=0.001$), and psychomotor retardation ($r=0.27$, $p=0.02$).

4. Discussion

This study found that depressed offspring at high familial risk for BP can be differentiated from depressed offspring at lower risk for BP in that they had significantly more past depressive episodes, severe depressive and atypical depressive symptoms, and subsyndromal manic symptomatology during the depressive episodes. As per the DSM 5 criteria (35), more depressed offspring of BP parents met criteria for “with mixed features” than the depressed offspring of the controls. These differences remained significant after controlling for between group demographic differences. The single strongest factor associated with high risk for developing BP is high family loading for this disorder, and BP usually manifests for the first time with depression (6, 7, 13). Thus, the presence of more severe depression, especially with atypical symptoms and more subsyndromal manic symptoms, may help identify high risk for BP onset in depressed youth and indicate careful monitoring for potential emergence of this disorder.

It is important to take into account the study’s limitations before considering the implications of the above-noted findings. The sample size for depressed offspring of control parents was small and the study is cross-sectional. The majority of the adolescents in this study were Caucasian, limiting the generalizability of the findings. Similar to other adult and pediatric studies, we found that 19.7% of depressed offspring of BP parents had atypical depression (25, 46). Other studies in unipolar depressed adults have suggested that atypical

features are associated with more comorbidity, more severe depressive symptoms, worse course, less treatment response, and higher risk for conversion to BP (23, 47, 48). However, these publications did not report whether depressed patients with atypical symptoms also had more family history of BP. This is important because in our study only 5% of the depressed control offspring showed atypical depressive symptomatology. The atypical symptoms including rejection sensitivity, hypersomnia, psychomotor retardation, and increased appetite were significantly more severe and (except for rejection sensitivity) more prevalent in depressed BP offspring of parents with BP than the offspring of the controls. Similarly, a recent study in adults suggested that depressed patients who converted to BP during 5-year follow up after index hospitalization had higher atypical depressive features relative to those who remained unipolar depressed (OR=6.414, 95% CI=3.228–12.743) (49). These findings indicate the need for careful evaluation for the presence of these symptoms, particularly in youth with early-onset depression and family history of BP, because these factors also increase the risk of developing BP (7–9, 50).

In addition to its clinical significance, our findings have research implications. It is well accepted that studies involving high-risk subgroups have the advantage of identifying distinct psychopathology profiles prior to the onset of the disorder and offer the ability to identify the emerging psychopathological condition (51). For example, compared to healthy controls, offspring of BP parents have different patterns of neurocognitive functioning (52) and brain activation (53) even when they did not have a BP diagnosis. Thus, their findings of increased atypical depressive symptomatology in depressed offspring of BP parents can also help guide biological and longitudinal research in depression regarding the associations of these symptoms with the emergence of BP.

Despite that 20% of the control offspring also had subsyndromal manic symptoms, subsyndromal manic symptoms (e.g., mood lability, irritability, racing thoughts) were more common in depressed offspring of BP parents suggesting that subsyndromal manic symptoms are already present in depressed offspring at high risk to develop BP. The increased subsyndromal symptoms could have been confounded by the presence of atypical symptoms. However, the correlation between subsyndromal manic and atypical depressive symptoms was moderate, suggesting that both the atypical and subsyndromal manic symptoms are prevalent in depressive offspring of bipolar parents.

Similar to our findings, studies in adults have reported that up to two thirds of depressed adults with BP had significant co-occurring subsyndromal mixed manic symptoms during the course of an acute depression, suggesting the possibility that a previous manic episode would increase subsequent mixed manic symptoms during an acute depression (22, 28, 54). Because some clinical and neurobiological abnormalities emerge only after the onset of the manic episode (55, 56), future longitudinal studies investigating co-occurring subsyndromal mixed manic features in depression are needed to better understand the intertwined trajectories of depressive and manic psychopathology (57).

Our study and others have shown that subsyndromal manic symptoms, mood lability and severe depressive symptomatology are associated with increased risk for offspring of parents with BP to develop BP (6, 11, 37, 51). These findings raise the question regarding the most

appropriate treatment of the acute depression in youth at high risk to develop BP. This is critical because subsyndromal manic symptoms that accompany an episode of depression are associated with poor treatment response and increase the risk for mood destabilization with antidepressant treatment (12, 29, 36, 58, 59). Thus, there is a need for treatment studies (pharmacological and psychosocial) for the acute treatment of depression in youth at risk to develop BP.

In conclusion, depression in offspring of BP parents is manifested by more severe and higher rates of depressive, atypical, and subsyndromal manic symptoms indicating the need of detailed assessment of these symptoms. Further cross-sectional and especially longitudinal studies are warranted to replicate our findings and provide clinical markers for the identification of depressed youth who are at risk to develop BP. This information will be informative for research as well as development of treatment for these youth.

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Fig. 1.
Comparison of rates (%) of depressed offspring with subsyndromal mixed manic symptoms.

Demographic and Clinical Characteristics of Depressed Offspring of Parents with Bipolar Disorder and Depressed Offspring of Community Control Parents

Table 1

	Depressed Offspring of BP parents		Depressed Offspring of Control Parents		Statistics	
	N=61		N=20		χ^2 or Fisher's exact	P-values
Mean age (years) (SD)	14.7 (3.1)		14.9 (2.6)		F=0.07	.80
Living with both bio-parents (%)	23.5		50		$\chi^2=4.7$	.03
Race (% White)	72.1		95		Fisher	.03
Sex (% female)	45.9		75		$\chi^2=5.1$	.02
CGAS (SD)	62.4 (14)		68.2 (8.8)		F=2.9	.09
SES (SD)	29.6(13.1)		38.9(14.5)		F=2.2	.03
Age of onset for depression (years) (SD)	11.3 (3.3)		12.9 (2.8)		F=3.5	.07
Past depressive episodes (%)	31.9		5.3		Fisher	.03
Dysthymia (%)	1.64		5		Fisher	.44
Anxiety disorders (%)	54.1		35		$\chi^2=2.2$	.14
ADHD (%)	39.3		25		$\chi^2=1.3$	.25
DBD (%)	44.3		25		$\chi^2=2.3$	.13
SUD (%)	14.8		15		Fisher	1

ADHD= Attention Deficit Hyperactive Disorder; BP= Bipolar Disorder; DBD= Disruptive Behavioral Disorders (e.g., oppositional defiant disorder or conduct disorder), SUD= Substance Use Disorders, SD= Standard Deviation, CGAS= Child Global Assessment Scale. Significant differences with $p < 0.05$ were indicated in bold.

Table 2
Comparison of mean depressive scores in Depressed Offspring of Bipolar Parents and Depressed Offspring of Community Control Parents

Depressive symptoms	Depressed Offspring of BP Parents N=61		Depressed Offspring of Control Parents N=20				Statistics			
	Mean (SD)		Mean (SD)		χ^2	P-values	Adjusted P-values [‡]	FDR	ORs	95% CI
Sad mood	3.41 (1.7)		2.20 (1.6)		8.49	0.004	0.007	0.02	4.1	(1.4–11.9)
Irritability	3.10 (1.5)		1.80 (1.1)		11.63	0.0006	0.002	0.008	4.9	(1.7–14.2)
Reactivity of depression *	2.74 (1.7)		2 (1.5)		3.59	0.06	0.04	0.08	3	(1.03–8.6)
Diurnal mood changes (morning)	1.26 (0.7)		1.20 (0.5)		0.03	0.86	0.88	0.88	0.9	(0.2–3.9)
Guilt	2.10 (1.3)		1.50 (1.1)		4.41	0.04	0.006	0.02	6	(1.4–25.3)
Negative self-image	2.74 (1.6)		1.85 (1)		4.57	0.03	0.0006	0.004	6.7	(2.1–21.4)
Hopelessness	2.23 (1.4)		1.50 (1.1)		6.79	0.009	0.0008	0.004	9.5	(2.1–43.2)
Body aches	2.10 (1.3)		1.80 (1.5)		1.76	0.18	0.05	0.10	3.2	(0.9–11)
Anhedonia	2.59 (1.4)		1.79 (1.2)		7.16	0.007	0.006	0.02	4.5	(1.5–13.6)
Fatigue	2.89 (1.6)		1.45 (1.1)		16.39	<0.0001	0.0001	0.003	10.8	(2.7–43.3)
Difficulty concentrating	2.51 (1.6)		1.85 (1.3)		3.45	0.06	0.19	0.27	2.2	(0.8–6.9)
Psychomotor agitation	1.85 (1.3)		1.5 (1.1)		2.16	0.14	0.45	0.55	1.7	(0.4–6.9)
Psychomotor retardation *	2 (1.2)		1.10 (0.3)		10.47	0.001	0.0005	0.004	13.7	(2.3–81.2)
Social withdrawal	2.70 (1.4)		1.65 (1.1)		9.53	0.002	0.0008	0.004	7	(2–23.8)
Insomnia	2.57 (1.4)		2.15 (1.5)		1.37	0.24	0.18	0.27	2	(0.7–5.6)
Terminal insomnia	1.38 (0.8)		1.30 (0.9)		0.65	0.42	0.74	0.79	13	(0.3–5.8)
Hypersomnia *	2.44 (1.8)		1.15 (0.5)		10.92	0.001	0.0009	0.004	10.5	(2–56)
Anorexia	1.64 (1.3)		1.50 (1.1)		0.11	0.74	0.54	0.62	1.5	(0.4–5.5)
Weight loss	1.25 (0.9)		1.20 (0.7)		0.03	0.87	0.87	0.88	0.9	(0.2–4.5)
Increased appetite *	1.72 (1.2)		1.15 (0.5)		4.43	0.04	0.08	0.13	3.7	(0.8–18.4)
Craving for sweets	1.38 (0.8)		1.10 (0.3)		1.39	0.24	0.21	0.29	2.8	(0.5–14.8)
Weight gain *	1.40 (1.2)		1.10 (0.4)		0.68	0.41	0.34	0.45	2.2	(0.4–12.7)
Leadren paralysis	1.44 (1)		1.05 (0.2)		2.69	0.10	0.08	0.13	6.3	(0.6–65.9)
Rejection sensitivity *	2.54 (1.5)		1.50 (0.9)		7.98	0.005	0.02	0.04	3.8	(1.2–12)
Suicidal ideation	1.87 (1.2)		1.30 (0.7)		4.34	0.04	0.04	0.08	3.7	(0.99–13.5)

	Depressed Offspring of BP Parents N=61		Depressed Offspring of Control Parents N=20		Statistics					
	Mean (SD)		Mean (SD)		χ^2	P-values	Adjusted P-values ^y	FDR	ORs	95% CI
Depressive symptoms										
Number of suicidal acts	0.30 (1.1)		0.05 (0.2)		0.88	0.35	0.43	0.55	2.4	(0.2–23.1)
Suicidal acts seriousness	0.20 (0.7)		0.15 (0.4)		0.51	0.47	0.73	0.79	0.8	(0.1–4)
Suicide medical lethality	0.21 (0.5)		0.15 (0.5)		0.47	0.49	0.49	0.58	1.8	(0.3–10.2)
Recurrent. thoughts of death	1.72 (1.2)		1.20 (0.5)		3.44	0.06	0.05	0.10	4.1	(0.9–18.5)
Self-damaging acts	1.38 (1)		1.06 (0.2)		3.76	0.05	0.09	0.14	4.2	(0.7–24.6)
All atypical depressive symptoms	14.26 (5.7)		9.05 (2.3)		15.70	0.0002	0.0004	0.004	-	
All depressive symptoms	27.54 (10.2)		18.55 (7.8)		12.92	0.0006	0.0004	0.004	-	

Depressive symptoms were derived from the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS)-Present Version (38).

* represents atypical depressive symptoms.

[‡] Adjusted for significant between-group demographic differences (e.g., parental SES, living with biological parents, and gender of offspring). After adjusting for between group demographic differences, multiple comparisons were corrected using False Discovery Rate (FDR). ORs=Odds Ratios.

Table 3
Comparison of mean manic scores in Depressed Offspring of Bipolar Parents with and Depressed Offspring of Community Control Parents

Manic symptoms	Depressed Offspring of BP Parents N=61		Depressed Offspring of Control Parents N=20		Statistics					
	Mean (SD)		Mean (SD)		χ ²	P-values	Adjusted P-values [‡]	FDR	ORs	95% CI
Elation	1.43 (0.8)		1 (0)		11.05	-	-	-	-	-
Irritability/anger	1.69 (1.1)		1.10 (0.4)		6.96	0.008	0.05	0.20	6	(0.7–51)
Decreased sleep	1.28 (0.7)		1.30 (1.1)		0.29	0.59	0.59	0.67	1.6	(0.3–9.2)
Energetic	1.43 (0.8)		1.25 (0.9)		2.38	0.12	0.13	0.40	3.2	(0.6–16.5)
Goal directed activity	1.11 (0.4)		1.10 (0.3)		0	1	0.29	0.51	0.33	(0.1–2.3)
Motor hyperactivity	1.57 (1)		1.30 (1)		3.06	0.08	0.42	0.51	2	(0.4–10.7)
Grandiosity	1.11 (0.4)		1 (0)		3.56	-	-	-	-	-
Pressured speech	1.38 (0.8)		1.15 (0.4)		0.82	0.36	0.39	0.51	1.9	(0.4–8)
Racing thoughts	1.54 (1)		1.10 (0.3)		4.05	0.04	0.008	0.11	7.6	(1.3–44)
Flight of ideas	1.30 (0.6)		1.20 (0.7)		1.59	0.21	0.29	0.51	2.4	(0.4–13.5)
Poor judgment	1.57 (1.2)		1.25 (0.9)		1.77	0.18	0.16	0.41	3	(0.6–16.4)
Inappropriate laughing	1.25 (0.6)		1 (0)		6.79	-	-	-	-	-
Uninhibited people seeking	1.11 (0.3)		1.25 (0.6)		0.3	0.58	0.25	0.51	0.4	(0.1–2)
Increased productivity	1.16 (0.5)		1.10 (0.4)		1.05	0.31	0.27	0.51	3.3	(0.3–32.4)
Sharpened thinking	1.23 (0.6)		1.05 (0.2)		1.65	0.20	0.38	0.51	2.4	(0.3–22.1)
Hypersexuality	1.15 (0.5)		1.25 (0.8)		0.09	0.76	0.31	0.51	0.3	(0.04–2.8)
Distractibility	1.89 (1.1)		1.50 (0.9)		2.41	0.12	0.43	0.51	1.6	(0.5–4.8)
Hallucinations	1.15 (0.5)		1.05 (0.2)		0.28	0.60	0.76	0.76	1.4	(0.1–15.1)
Delusions	1.05 (0.3)		1.05 (0.2)		0.11	0.75	0.75	0.76	0.7	(0.1–7.7)
Sentence incoherence	1.03 (0.3)		1 (0)		0.57	-	-	-	-	-
Thought derailment	1.03 (0.3)		1 (0)		0.57	-	-	-	-	-
Mood lability	1.74 (1.2)		1.15 (0.5)		5.87	0.02	0.01	0.11	6.3	(1.2–33.4)
All manic symptoms	6.05 (6.2)		2.45 (4.3)		5.80	0.02	0.02	0.11	-	-

Manic symptoms were recorded on Mania Rating Scale (MRS) (43) derived from the K-SADS-P (38). K-SADS-MRS also measures psychotic symptoms.

[‡] Adjusted for significant between-group demographic differences (e.g., parental SES, living with biological parents, and gender of offspring). After adjusting for between group demographic differences, multiple comparisons were corrected using False Discovery Rate (FDR). ORs=Odds Ratios. C.I: confident intervals