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Characteristics of Bipolar I Patients Grouped by Externalizing Disorders

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Abstract

Background—Bipolar disorder co-occurs with a number of disorders with externalizing features. The aim of this study is to determine whether Bipolar I (BPI) subjects with comorbid externalizing disorders and a subgroup with externalizing symptoms prior to age 15 have different clinical features than those without externalizing disorders and whether these could be attributed to specific genetic variations.

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Conflict of Interest

None

Methods—A large cohort (N=2505) of Bipolar I subjects was analyzed. Course of illness parameters were compared between an Externalizing Group, an Early-Onset Subgroup and a Non-Externalizing group in the Discovery sample (N=1268). Findings were validated using an independent set of 1237 BPI subjects (Validation sample). Genetic analyses were carried out.

Results—Subjects in the Externalizing Group (and Early-Onset Subgroup) tended to have a more severe clinical course, even in areas specifically related to mood disorder such as cycling frequency and rapid mood switching. Regression analysis showed that the differences are not completely explainable by substance use. Genetic analyses identified nominally associated SNPs; calcium channel genes were not enriched in the gene variants identified.

Limitations—Validation in independent samples is needed to confirm the genetic findings in the present study.

Conclusions—Our findings support the presence of an externalizing disorder subphenotype within BPI with greater severity of mood disorder and possible specific genetic features.

Keywords

Bipolar disorder; Externalizing disorders; Early onset; Comorbidity; Genome-wide association study (GWAS)

1. Introduction

Bipolar disorder (BP) includes distinct episodes with altered mood, activity, and thought patterns. The mean age at onset for Bipolar Disorder Type I (BPI) is 18.4 years and the lifetime prevalence is 0.6% (Merikangas et al., 2011). BP may occur in conjunction with a number of other disorders such as substance use and anxiety disorders (Merikangas et al., 2011). Substance use has been shown to be highly prevalent in BP patients (Merikangas et al., 2011; Regier et al., 1990). Prior studies have identified more severe outcomes among BP patients with co-occurring substance use disorders (Cardoso et al., 2008; Elizabeth Sublette et al., 2009; Frye and Salloum, 2006; Grunebaum et al., 2006). The presence of substance abuse also makes it more difficult to treat BP (Swann, 2010). The disorder has a substantial genetic component. Monozygotic twin concordance rates range from 45 to 70% and sibling recurrence risk ranges from 5 to 10% (Craddock and Forty, 2006). Genome Wide Association Studies (GWAS) have identified ten common variants with modest effects (Chen et al., 2013; Ferreira et al., 2008; Seifuddin et al., 2012; Sklar, 2013; Sklar et al., 2011; Smith et al., 2009; Smith et al., 2011), and analyses using the entire set of variants tested with common GWAS platforms suggest that many additional vulnerability genes remain to be identified as larger samples become available (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Lee et al., 2011). Many course of illness parameters have also been shown to be heritable (Potash et al., 2007). The aim of this study is to determine whether a subphenotype of BPI subjects can be defined based on the presence of externalizing disorders, and whether these subjects are clinically and/or genetically different from those who did not have externalizing disorders. We were particularly interested in whether the characteristics of the mood disorder itself (apart from externalizing symptoms) differentiated the subgroups. Two sets of BPI subjects ascertained by the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative and evaluated with the

Diagnostic Instrument for Genetic Studies (Nurnberger et al., 1994) were included (a Discovery sample and a Validation sample). We also performed GWAS analyses using the combined sample to identify genetic variations that may help characterize these groups.

2. Methods

2.1. Clinical parameters

BPI subjects were selected from those collected and characterized by the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative over the past 18 years. Subjects were from Indiana University, Johns Hopkins University, the National Institute of Mental Health Intramural (NIMH) Program, Washington University at St. Louis, University of Pennsylvania, University of California at San Diego, University of California at Irvine, University of California at San Francisco, University of Iowa, University of Chicago, Rush University, and Howard University.

The study protocol was approved by the Institutional Review Board of the respective universities. After description of the study to the subjects, written informed consent was obtained.

2.1.1. Discovery sample—Subjects totaled 951 unrelated European American (EA) individuals and 317 unrelated African-American (AA) individuals. EA status was determined based on the subject's self-report that all four grandparents were of EA heritage. AA status was based on self-report of at least one grandparent being of AA heritage. The 1268 BPI subjects were divided into the following groups: 1) the Non-Externalizing Group-472 subjects; 2) the Externalizing Group-796 subjects who had at least one externalizing disorder and 3) the Early-Onset Subgroup-329 subjects in the Externalizing Group who had two or more symptoms of conduct disorder (CD) prior to age 15 (Table 1). Externalizing disorders included one or more of the following DSM-IV diagnoses: alcohol abuse/dependence, drug abuse/dependence, pathological gambling, anti-social personality disorder (ASPD), attention-deficit hyperactivity disorder (ADHD) and CD (Table 2). Of note, about 70% of subjects in this sample came from multiplex families (additional affected relatives with BPI disorder).

2.1.2. Validation sample—The validation sample consisted of 1237 unrelated EA BPI subjects from the same study. Based on the above mentioned criteria, these subjects were also divided into 1) the Non-Externalizing Group-436 subjects; 2) the Externalizing Group-801 subjects and 3) the early-onset sub-group-307 subjects (Table 1). Of note, about 20% of subjects in this sample came from multiplex families.

2.1.3. Clinical assessment—All subjects were interviewed with the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), a diagnostic instrument developed for determining mood disorders and related conditions and shown to have excellent test-retest reliability. Final diagnoses were made by two independent clinicians incorporating all available information using a best-estimate procedure.

2.2. Genome-wide association analyses

2.2.1. Genotyping and quality control of data available on dbGaP—Genotyping was carried out at the The Broad Institute Center for Genotyping and Analysis. PicoGreen fluorometry was used to check DNA quantity, and sample quality was initially assessed by genotyping a 24-single nucleotide polymorphism (SNP) panel on the Sequenom iPLEX platform containing a sex determining assay. Samples were plated at 50ng/ul in 96 well plates at the Rutgers University Cell and DNA Repository. The Centre d'Etude du Polymorphisme Human (CEPH; http://www.cephb.fr/en/cephdb/) sample NA12144 was placed on each production plate at the Broad Institute. Genotyping was carried out separately for the EA and AA samples using the Affymetrix Genome-Wide Human SNP Array 6.0. Allele calling was performed using the BirdSeed algorithm Affymetrix Power Tools version apt-1.8.6 and cluster models ('priors') file. Concordance between genotypes from the array and those from the initial quality control (QC) panel was evaluated to confirm sample ID. BPI EA Discovery and Validation samples were pooled together for the GWAS.

Samples were not used in the analysis if they had a low call rate (<98.5%) or incompatibility between reported gender and genetically determined gender. Pairwise identity-by-descent estimation was used to check for unexpected familial relationships in PLINK v1.07 (Purcell et al., 2007). SNPs were not analyzed if the minor allele frequency was <0.01, call rate <95%, Hardy Weinberg Equilibrium was violated ($P<10^{-6}$) in control samples, if there were three or more Mendelian errors, or if there was more than one discrepancy among duplicate samples. 2064 samples and 677,171 SNPs passed all QC tests. Further information on QC can be obtained in (Smith et al., 2009; Smith et al., 2011).

2.3. Statistical analyses

2.3.1. Clinical parameter analyses—Statistical analyses were performed between the Non-Externalizing Group and the Externalizing Group of BPI subjects (including both early-onset and later-onset subjects), and between the Non-Externalizing Group and the Early-Onset Subgroup. Categorical variables were analyzed using the Pearson chi-square test (two-sided) and continuous variables were analyzed using an independent samples t-test (two-sided). Levene's Test for Equality of Variances was performed to check the equality of variances assumption. All statistical analyses were performed in SPSS Statistics.

2.3.2. Genetic analyses—All genetic analyses were conducted using PLINK v1.07. The analyses involved testing the association of each SNP coded additively with externalizing and early-onset status, with subject sex included as a covariate in the logistic model employed.

3. Results

3.1. Subject distribution in the non-externalizing and Externalizing Groups

1268 BPI subjects (951 EA, 317 AA) were included in the Discovery phase of the analysis and the findings were validated using 1237 BPI subjects in the Validation sample (Table 1). The distribution of BPI subjects among the non-externalizing and Externalizing Groups, and the Early-Onset Subgroup was similar for the two samples.

3.2. Prevalence of externalizing disorders

We then examined the distribution of externalizing disorders in the Externalizing Group of BPI subjects in the two studies (Table 2). A majority of subjects had alcohol abuse/dependence and/or drug abuse/dependence. A higher proportion ($P<0.05$) of Discovery subjects had drug abuse/dependence and ASPD compared to Validation sample subjects. Conversely, a higher proportion ($P<0.05$) of Validation sample subjects had ADHD compared to Discovery subjects, but this may be related to assessment methodology (see Discussion). Further information on the breakdown of substance use disorders in the sample cohort can be found in Table S1.

3.3. Clinical characteristics

A number of clinical parameters were found to be significantly ($P<0.05$) different when comparing the Externalizing Group to the Non-Externalizing Group of BPI subjects in the Discovery sample (Tables 3 and 4). Subjects in the Externalizing Group were more likely to be male ($\chi^2=9.012$, $df=1$, $P=0.003$), to be disabled ($\chi^2=6.932$, $df=1$, $P=0.008$) and to have fewer years of schooling ($t=6.694$, $df=1217$, $P<0.001$). They had an earlier age at onset of BPI ($t=7.250$, $df=776.393$, $P<0.001$) (including earlier onset ages for both depression ($t=5.533$, $df=796.274$, $P<0.001$) and mania ($t=5.807$, $df=837.128$, $P<0.001$)), a higher number of depressive ($\chi^2=20.902$, $df=1$, $P<0.001$) and manic episodes ($\chi^2=12.613$, $df=1$, $P<0.001$, excluding episodes judged to be secondary to substance use) and a higher frequency of episodes ($\chi^2=9.763$, $df=1$, $P=0.002$; $\chi^2=4.179$, $df=1$, $P=0.041$). The subjects in the Externalizing Group had an increased frequency of incidents of (non-suicidal) self-harm ($\chi^2=25.797$, $df=1$, $P<0.001$) and more suicide attempts ($t=-2.680$, $df=478.609$, $P=0.008$). They were rated as more impaired on the interepisode Global Assessment Scale (GAS) ($t=3.771$, $df=474$, $P<0.001$) and were more likely to report a history of rapid switching ($\chi^2=21.696$, $df=1$, $P<0.001$) and rapid cycling ($\chi^2=25.516$, $df=1$, $P<0.001$). We have investigated the effect of ethnicity in externalizing disorders and we find similar results for EA and AA except for disability, frequency of depressive episodes, number and frequency of manic episodes, and age of first tobacco use in case of AA (Tables S2, S3, S4 and S5). The findings in BPI subjects in the overall Discovery sample (Tables 3 and 4) were replicated in BPI subjects in the Validation sample (Tables S6 and S7).

Examination of the clinical variables in the Early-Onset Subgroup shows the same pattern as in the Externalizing Group as a whole, but in general the differences are greater. Non-suicidal self-harm was seen in 30.2% of early-onset subjects as compared to 10.0% of non-externalizing subjects (and 26.0% of externalizing subjects as a whole). Rapid switching was seen in 70.6% of early-onset subjects as compared to 48.6% of non-externalizing subjects (and 62.8% of externalizing subjects). Although they are younger, 56.7% of early-onset externalizing subjects have had >8 non-substance-related depressive episodes in their lifetime compared with 35.5% of non-externalizing subjects (and 49.5% of externalizing subjects); 55.1% have had >4 non-substance-related manic episodes in their lifetime compared with 42.8% of non-externalizing subjects (and 53.5% of externalizing subjects). They have an earlier age of onset of bipolar disorder by more than 5 years (at 16.0 years compared to 20.4 years) and these ages are similar to the ages of first depressive episode; age of first mania is also advanced by more than 5 years (21.3 years compared to 26.6

years). Number of suicide attempts is greater (3.6 vs 2.6) and age of first attempt is >4 years earlier (20.3 years vs 24.5 years). Patterns are very similar in the Validation sample.

To determine whether the differences in the clinical parameters between subjects in the non-externalizing and Externalizing Groups can be accounted for by substance use disorders, separate linear regression analyses were performed using frequency of clean depressive episodes/clean manic episodes as the dependent variable, and externalizing disorder status, presence of alcohol abuse/dependence, presence of drug abuse/dependence, ethnicity, presence/absence of first degree relatives with BPI and cohort (years of ascertainment) as independent variables controlling for age and gender in the Discovery sample. The frequency of depressive episodes was found to be a function of externalizing disorder status (standardized β=0.119, P=0.021), but was not completely explained by the presence of alcohol abuse/dependence (P>0.05) or drug abuse/dependence (P>0.05). The frequency of manic episodes was not found to be a function of externalizing disorder status (P>0.05), the presence of alcohol abuse/dependence (P>0.05) or the presence of drug abuse/dependence (P>0.05), but appeared to be related to cohort (P<0.05). This may be related to the preponderance of multiplex families in the earlier cohorts. We further examined the effect of externalizing disorder status controlling for alcohol abuse/dependence in one analysis and drug abuse/dependence in a separate analysis on age at onset of BPI, one of the clinical parameters observed to be significantly different between the non-externalizing and Externalizing Groups. A significant (P<0.05) effect of externalizing disorder status was still observed even when controlling for alcohol and drug use disorders in the two analyses (data not shown). This suggests that other externalizing disorders such as ASPD (Swann et al., 2010), pathological gambling (Kim et al., 2006), ADHD and CD (Masi et al., 2008) may explain a substantial part of the differences seen in the clinical parameters between the externalizing and Non-Externalizing Groups.

3.4. Genetic association analyses

Two GWAS analyses were performed comparing: 1) 784 subjects in the Non-Externalizing Group vs. 1280 subjects in the Externalizing Group; 2) 784 subjects in the Non-Externalizing Group vs. 502 subjects in the Early-Onset Subgroup. QC was performed on all subjects and all SNPs, as summarized above. Although no SNP reached genome-wide significance ($P<5 \times 10^{-8}$) from the two analyses, a number of SNPs were found to be associated at a P-value of 10^{-5} or lower. Details of 20 SNPs with the strongest association signals from each of the two analyses are shown in Table 5. Since gene variants associated with bipolar disorder have been reported to be enriched for calcium channel genes, we examined that pathway (Cross-Disorder Group of the Psychiatric Genomics, 2013; Sklar et al., 2011) but saw no evidence for enrichment of calcium channel genes in either analysis. We also performed GWAS analyses comparing each of the three groups with the control group, but did not identify any genome-wide significant SNPs in any of these comparisons (data not shown).

4. Discussion

The purpose of this study was to determine clinical and genetic differences between BPI subjects who had externalizing disorders and those who did not have externalizing disorders.

We found that a majority of Discovery and Validation sample BPI subjects had externalizing disorders. We believe that this is the largest cohort of BPI subjects (total N=2505) analyzed for factors associated with externalizing symptomatology. Two factors: internalizing and externalizing, appear to substantially account for psychiatric comorbidity among BPI subjects (Monahan et al., in press).

A significant difference in a majority of clinical parameters were found when we compared subjects in the non-externalizing and Externalizing Groups as well as subjects in the Non-Externalizing Group and the Early-Onset Subgroup (Tables 3 and 4, online Tables S6 and S7). A possible explanation for the differences seen between these groups is the high proportion of subjects with alcohol abuse/dependence and/or drug abuse/dependence (Table 2). However, our regression studies show that the differences in clinical parameters are not completely explained by the presence or absence of substance use disorders.

The most remarkable result of this study was the increased severity and frequency of mood disorder symptoms and episodes in the Externalizing Group and particularly in the early-onset externalizing subgroup. In every parameter tested, subjects with externalizing disorders show evidence of greater symptomatology, earlier onset, and more impairment. This is true even when care is taken to exclude the direct effects of substances (e.g. the exclusion of substance-related depressive or manic episodes). In general the chronology suggests that substance use precedes episodes of major mood disorder but it is not clear whether minor mood problems may precede substance use or abuse. In any case, the divisions highlighted in this report appear to be clinically salient.

We noted a higher proportion of subjects in the Validation sample with ADHD compared to the Discovery sample. A section for adult ADHD was included in DIGS 4.0 used for later cohorts but the earlier versions had only a retrospective report of childhood ADHD. Inclusion of the adult ADHD section may be expected to have increased the frequency of ADHD reports (including retrospective childhood ADHD). It is not clear to us how to explain the decrease in ASPD diagnoses and drug abuse/dependence diagnoses in the Validation Sample compared to the Discovery sample. Site effects cannot be ruled out (as the four original sites contributed to a larger proportion of the Discovery sample in comparison to the Validation sample), and such effects have been demonstrated in other studies of bipolar subphenotypes (Saunders et al., 2008). However it is reassuring to note the similarity of the proportions of externalizing and early-onset subjects in the two samples, as well as the very similar results with respect to clinical variables (Tables 3 and 4, Tables S6 and S7).

Although no SNP reached genome-wide significance ($P<5 \times 10^{-8}$) in the two GWAS analyses, a number of potential candidate SNPs were found to be nominally associated ($P<10^{-5}$) (Table 5). Two intronic SNPs (rs9359856 and rs6934804) and one coding SNP (rs2273238) were identified in the *ANKRD6* (ankyrin repeat domain 6) gene on chromosome 6. Also known as Diversin, the gene has been shown to be an essential component of the Wnt-signaling pathway, controlling fusion of heart precursors and gastrulation movements in zebrafish embryogenesis (Moeller et al., 2006; Schwarz-Romond et al., 2002). It has been shown to be prominently expressed in the developing mouse brain suggesting a role during

brain development and variants in the gene have been associated with muscle performance and habitual physical activity (Tissir et al., 2002; Van Deveire et al., 2012). A SNP in a gene in the same family (*ANKRD26*) was also noted in this short list. Variants in other identified genes have been associated with fasting glucose-related traits (*GLIS3*, *TMEM195* and *ZMAT4*) (Dupuis et al., 2010; Meigs et al., 2007) and Alzheimer's disease (*MTHFD1L*) (Naj et al., 2010). Cerebral glucose metabolic rates are known to be altered in mood disorders (Baxter et al., 1985; Drevets et al., 1997). SNPs in or near *ST6GALNAC3*, associated with carbohydrate metabolism, are seen three times in this list of 40. Thus, a number of SNPs associated with other diseases/complex traits may play a role in predisposition to externalizing disorders in the presence of bipolar illness. There is no evidence of an enrichment of calcium channel genes, suggesting that this pathway is not likely to explain the difference between externalizing and non-externalizing subtypes of BPI disorder.

The present study includes 2505 unrelated BPI subjects in two samples with clinical and genetic data. Subjects from two different ethnic populations (EA and AA) were analyzed for clinical parameters. However, this is a modest sample size for GWAS analyses and possible significant associations are likely to have been missed. Validation at genome-wide significance levels would be needed to confirm the suggestive associations identified in the present study.

5. Conclusion

In sum, we have demonstrated that BPI subjects with externalizing disorders tend to have a poorer clinical outcome then those without externalizing disorders; this is particularly true of those subjects with early onset of conduct disorder symptoms. Although no SNP reached genome-wide significance in the GWAS analyses, it does seem important to us that calcium channel genes do not appear to explain the genetic variance between externalizing and Non-Externalizing Groups of BPI subjects. The clinical results in particular suggest the presence of an externalizing disorder subphenotype within BPI warranting further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

BPI subject distribution.

	Non-Externalizing Group		Externalizing Group		Total N	Early-Onset Subgroup	
	N	% of Total N	N	% of Total N		N	% of Externalizing Group N
Discovery subjects	472	37.2	796	62.8	1268	329	41.3
European Americans	385	40.5	566	59.5	951	235	41.5
African Americans	87	27.4	230	72.6	317	93	40.4
Validation sample subjects	436	35.2	801	64.8	1237	307	38.3

Table 2

Breakdown of externalizing disorders in the Externalizing Group of Discovery and Validation sample BPI subjects.

Discovery and Validation sample subjects							
Externalizing disorder	**Discovery sample (N=796)**		**Validation sample (N=801)**		χ^2	**df**	***P* (two-sided)**
	N	**%**	**N**	**%**			
Alcohol abuse/dependence	591	74.2	607	75.8	0.501	1	0.479
Drug abuse/dependence	528	66.3	475	59.3	8.448	1	0.004
Pathological gambling	43	5.4	44	5.5	0.006	1	0.936
Anti-social personality disorder	110	13.8	58	7.2	18.353	1	<0.001
Attention-deficit hyperactivity disorder	153	19.2	263	32.8	38.407	1	<0.001
Conduct disorder	29	3.6	28	3.5	0.025	1	0.874

Table 3

Clinical features in Discovery sample BPI subjects grouped by externalizing disorders (categorical parameters).

Non-Externalizing Group vs. Externalizing Group									
Parameter	**Non-Externalizing**		**Externalizing**		**χ^2 (1 df)**	***P* (two-sided)**	**Odds Ratio: Value**	**Odds Ratio: 95% CI**	
	N	**%**	**N**	**%**				**Lower**	**Upper**
Gender									
Male	185	39.2	381	47.9	9.012	0.003	0.702	0.557	0.885
Female	287	60.8	415	52.1					
Disabled									
Yes	92	20.4	208	27.2	6.932	0.008	0.688	0.521	0.910
No	358	79.6	557	60.9					
Self harm									
Yes	25	10.0	122	26.0	25.797	<0.001	0.316	0.199	0.501
No	226	90.0	348	74.0					
Rapid switching									
Yes	205	48.6	434	62.8	21.696	<0.001	0.559	0.438	0.715
No	217	51.4	257	37.2					
Rapid cycling									
Yes	182	44.6	403	60.4	25.516	<0.001	0.528	0.411	0.677
No	226	55.4	264	39.6					
Number of clean depressive episodes[a]									
1 to 8	267	64.5	364	50.5	20.902	<0.001	1.781	1.389	2.284
>8	147	35.5	357	49.5					
Number of clean depressive episodes per year[b]									
0 to 0.4	224	55.3	317	45.5	9.763	0.002	1.480	1.157	1.893
>0.4	181	44.7	379	54.5					
Number of clean manic episodes[b]									
1 to 4	254	57.2	343	46.5	12.613	<0.001	1.536	1.211	1.947
>4	190	42.8	394	53.5					
Number of clean manic episodes per year[b]									

Non-Externalizing Group vs. Externalizing Group

Parameter	Non-Externalizing		Externalizing		χ^2 (1 df)	*P* (two-sided)	Odds Ratio: Value	Odds Ratio: 95% CI	
	N	%	N	%				Lower	Upper
0 to 0.4	240	55.7	345	49.4	4.179	0.041	1.286	1.010	1.636
>0.4	191	44.3	353	50.6					

Non-Externalizing Group vs. Early-Onset Subgroup

Parameter	Non-Externalizing		Early-Onset		χ^2 (1 df)	*P* (two-sided)	Odds Ratio:	Odds Ratio: 95% CI	
	N	%	N	%				Lower	Upper
Gender									
Male	185	39.2	172	52.3	13.435	<0.001	0.588	0.443	0.782
Female	287	60.8	157	47.7					
Disabled									
Yes	92	20.4	97	30.0	9.355	0.002	0.599	0.430	0.833
No	358	79.6	226	70.0					
Self harm									
Yes	25	10.0	73	32.0	35.719	<0.001	0.235	0.143	0.386
No	226	90.0	155	68.0					
Rapid switching									
Yes	205	48.6	218	70.6	35.321	<0.001	0.394	0.289	0.538
No	217	51.4	91	29.4					
Rapid cycling									
Yes	182	44.6	201	68.1	38.216	<0.001	0.377	0.275	0.515
No	226	55.4	94	31.9					
Number of clean depressive episodes[a]									
1 to 8	267	64.5	130	43.3	31.548	<0.001	2.375	1.752	3.220
>8	147	35.5	170	56.7					
Number of clean depressive episodes per year[a]									
0 to 0.4	224	55.3	130	44.5	7.901	0.005	1.542	1.139	2.087
>0.4	181	44.7	162	55.5					
Number of clean manic episodes[b]									

Non-Externalizing Group vs. Early-Onset Subgroup

Parameter	Non-Externalizing		Early-Onset		χ^2 (1 df)	*P* (two-sided)	Odds Ratio:	Odds Ratio: 95% CI	
	N	%	N	%				Lower	Upper
1 to 4	254	57.2	136	44.9	10.960	0.001	1.642	1.223	2.203
>4	190	42.8	167	55.1					
Number of clean manic episodes per year[b]									
0 to 0.4	240	55.7	144	49.5	2.682	0.101	1.283	0.952	1.728
>0.4	191	44.3	147	50.5					

[a] According to the DSM-IV, a clean depressive episode is a depressive episode without prior physical illness, drug or alcohol abuse, organic precipitants, or bereavement.

[b] According to the DSM-IV, a clean manic episode is a manic episode without prior physical illness, drug or alcohol abuse, or organic precipitants.

Table 4

Clinical features in Discovery sample BPI subjects grouped by externalizing disorders (continuous parameters).

Non-Externalizing Group vs. Externalizing Group							
Parameter	**Non-Externalizing**		**Externalizing**		***t***	**df**	***P* (two-sided)[b]**
	Mean	**SD**	**Mean**	**SD**			
Age	44.01 (N=467)	13.49	41.06 (N=782)	11.52	3.954	862.231	<0.001
Years of school	15.18 (N=452)	2.81	14.06 (N=767)	2.84	6.694	1217	<0.001
Age at onset of illness	21.36 (N=447)	9.92	17.38 (N=774)	7.94	7.250	776.393	<0.001
Age at onset of depression	21.93 (N=425)	10.70	18.48 (N=746)	9.46	5.533	796.274	<0.001
Age at onset of mania	26.61 (N=452)	11.52	22.83 (N=750)	9.84	5.807	837.128	<0.001
Age of first drink	16.72 (N=197)	4.68	14.06 (N=422)	4.88	6.392	617	<0.001
Age of first tobacco use	16.03 (N=244)	5.35	14.89 (N=579)	5.23	2.855	821	0.004
Number of suicide attempts	2.62 (N=144)	2.55	3.51 (N=380)	4.99	−2.680	478.609	0.008
Age of first suicide attempt	24.46 (N=74)	10.32	21.26 (N=229)	8.44	2.676	301	0.008
Interepisode GAS[a]	75.30 (N=206)	14.94	70.14 (N=270)	14.64	3.771	474	<0.001

Non-Externalizing Group vs. Early-Onset Subgroup							
Parameter	**Non-Externalizing**		**Early-Onset**		***t***	**df**	***P* (two-sided)[b]**
	Mean	**SD**	**Mean**	**SD**			
Age	44.01 (N=467)	13.49	39.80 (N=325)	11.00	4.825	770.462	<0.001
Years of school	15.18 (N=452)	2.81	13.45 (N=325)	2.82	8.464	775	<0.001
Age at onset of illness	21.36 (N=447)	9.92	16.03 (N=322)	7.55	8.460	764.467	<0.001
Age at onset of depression	21.93 (N=425)	10.70	16.93 (N=312)	9.10	6.840	719.155	<0.001
Age at onset of mania	26.61 (N=452)	11.52	21.29 (N=309)	9.46	6.962	733.888	<0.001
Age of first drink	16.72 (N=197)	4.68	12.98 (N=206)	4.32	8.345	401	<0.001
Age of first tobacco use	16.03 (N=244)	5.35	14.02 (N=269)	5.47	4.208	511	<0.001
Number of suicide attempts	2.62 (N=144)	2.55	3.64 (N=181)	4.27	−2.661	301.360	0.008
Age of first suicide attempt	24.46 (N=74)	10.32	20.30 (N=115)	8.54	3.012	187	0.003
Interepisode GAS[a]	75.30 (N=206)	14.94	69.29 (N=108)	14.89	3.389	312	0.001

[a]GAS, Global Assessment Scale.

[b] P-values were determined after performing Levene's Test for Equality of Variances to check equality of variances assumption.

Table 5

SNPs with the strongest association signals from the GWAS analyses of BPI subjects.

SNP	Chromosome	Base pair position[a]	Closest gene[a,b]	SNP location relative to gene[a]	Minor Allele Frequency	*P*	Odds Ratio
Externalizing Group vs. Non-Externalizing Group							
rs17099448	1	76921007	*ST6GALNAC3*	51.79kb downstream	0.025	2.56E-06	0.4633
rs17622252	6	21439886	*CDKAL1*	100.15kb downstream	0.1333	4.39E-06	1.658
rs2764655	1	76942171	*ST6GALNAC3*	72.96kb downstream	0.025	6.62E-06	0.4774
rs10090419	8	124097812	*DERL1*	Intron	0.175	1.94E-05	0.7077
rs2071842	22	41313726	*POLDIP3*	Intron	0.1667	2.16E-05	0.661
rs2958709	8	106838246	*ZFPM2*	Intron	0.1417	2.31E-05	0.6872
rs2273238	6	90383081	*ANKRD6*	Coding region	0.0417	2.33E-05	0.5065
rs11015506	10	27409689	*ANKRD26*	Intron	0.025	2.65E-05	3.33
rs2997227	10	122575842	*WDR11*	24.85kb upstream	0.0778	2.98E-05	0.7426
rs6461161	7	15239240	*TMEM195*	Intron	0.3083	3.00E-05	1.327
rs4869963	6	151341417	*MTHFD1L*	Intron	0.2833	3.48E-05	0.7507
rs7913464	10	23551309	*PTF1A*	28.13kb downstream	0.0583	3.76E-05	0.5527
rs16851722	2	166741590	*SCN9A*	18.36kb downstream	0.0583	4.40E-05	1.655
rs333846	2	117695664	-	-	0.025	4.44E-05	4.72
rs4341952	2	166728262	*SCN9A*	31.68kb downstream	0.1917	4.47E-05	1.393
rs1779518	14	40797200	-	-	0.3222	4.61E-05	1.424
rs7739248	6	151323361	*MTHFD1L*	Intron	0.15	4.85E-05	0.7254
rs11997383	8	40574573	*ZMAT4*	Intron	0.1889	4.85E-05	0.618
rs16831019	2	135259447	*ACMSD*	53.21kb upstream	0.025	4.91E-05	0.4319
rs11013397	10	23660815	*C10orf67*	Intron	0.0667	5.10E-05	0.5823
Early-Onset Subgroup vs. Non-Externalizing Group							
rs9359856	6	90364704	*ANKRD6*	Intron	0.2	4.52E-06	0.6091
rs4761053	12	127072154	-	-	0.2583	6.95E-06	1.525
rs6934804	6	90372739	*ANKRD6*	Intron	0.1833	1.18E-05	0.6201
rs1438108	20	1792858	*SIRPA*	29.96kb upstream	0.0417	1.45E-05	0.4555
rs1526303	2	174151593	-	-	0.3778	1.93E-05	0.7042
rs1871946	2	213587652	*IKZF2*	Intron	0.4407	2.24E-05	1.413

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SNP	Chromosome	Base pair position[a]	Closest gene[a,b]	SNP location relative to gene[a]	Minor Allele Frequency	*P*	Odds Ratio
rs2665452	7	97285019	*ASNS*	34.36kb downstream	0.2333	2.39E-05	0.6398
rs17622252	6	21439886	*CDKAL1*	100.15kb downstream	0.1333	2.71E-05	1.746
rs13080973	3	140078740	*FOXL2*	67.02kb downstream	0.1583	2.89E-05	1.553
rs12538214	7	154969302	*CNPY1*	17.42kb downstream	0.2167	2.91E-05	1.484
rs2289439	15	87486790	*ABHD2*	Intron	0.1083	3.15E-05	0.5478
rs4726457	7	139269639	*TBXAS1*	Intron	0.275	3.45E-05	0.6856
rs2242400	12	24989341	*BCAT1*	Intron	0.1167	3.48E-05	1.733
rs742002	22	25765086	-	-	0.2917	4.14E-05	0.683
rs4339696	9	4285880	*GLIS3*	Intron	0.4333	4.27E-05	1.403
rs2216316	7	53451934	-	-	0.1083	4.31E-05	1.539
rs2530132	7	97286662	*ASNS*	32.72kb downstream	0.2333	4.37E-05	0.6502
rs10868082	9	85828929	*RMI1*	20.12kb downstream	0.1833	4.38E-05	0.6671
rs17099448	1	76921007	*ST6GALNAC3*	51.79kb downstream	0.025	4.51E-05	0.3724
rs1560651	5	167530850	*ODZ2*	Intron	0.4833	4.59E-05	1.392

[a] Genomic locations are based on NCBI Build 36.3.

[b] Closest genes were genes in which the SNP was present or genes located within 200kb (kilobases) of the SNP.