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Research report

Fear of harm, a possible phenotype of pediatric bipolar disorder: A dimensional approach to diagnosis for genotyping psychiatric syndromes

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ABSTRACT

Background: In a prior concordance study of affected sibling pairs with a community diagnosis of pediatric bipolar disorder (PBD) a behavioral phenotype termed Fear of Harm (FOH) was found to have one of the strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between the rho-estimates for the proband/sibling vs. proband/comparison pairs [Papolos, D., Hennen, J., Cockerham, M.S, Lachman, H., 2007]. A strategy for identifying phenotypic subtypes: concordance of symptom dimensions between sibling pairs who met screening criteria for a genetic linkage study of childhood-onset bipolar disorder using the Child Bipolar Questionnaire (CBQ) was employed. J. Affect. Disord. 99, 27–36.]. We used the *Child Bipolar Questionnaire* (OUT) (CBQ) to further elucidate this behavioral phenotype of PBD. We hypothesized that selective factors including parent reported symptoms of mania and depression, would be distinguishing features of impairment between groups defined by 1) the magnitude of their score on a continuous measure of FOH, and 2) the high FOH group would have significantly greater levels of severity on course of illness variables. These measures included earlier age of onset of first psychiatric symptoms, first hospitalization, and frequency of psychiatric hospitalizations, as well as, degree of social impairment as determined by exposure to the juvenile justice system and school performance problems.
Methods: The sample was comprised of children with community diagnoses of bipolar disorder or at risk for the illness based on enriched family history with multiple first degree relatives diagnosed with BPD ($N=5335$). Included were all subjects who had >40 positively endorsed CBQ symptom items at frequencies of very often, almost always, and always. This group was divided randomly into two groups, the exploratory group ($N=2668$) and the hypothesis testing (study) group ($N=2666$). The exploratory group was used for the development of hypotheses and the study group was used to test these hypotheses on a new set of data. All results reported here derive from the latter group. In subsequent analyses, we classified each child as having a high degree of FOH, low FOH, or no FOH. We examined a subset of the sample for differences in age of onset of first psychiatric symptoms, course of illness and measures of symptom severity. These groups were compared using the chi-square procedure for categorical data and the Analysis of Variance (ANOVA) with Scheffe pair wise tests for continuous variables. The Child Bipolar Questionnaire V.2.0, the Yale-Brown Obsessive Compulsive Scale (YBOCS) and the Overt Aggression Scale (OAS) were the principal instruments used to obtain diagnostic information for this study.
Results: We found that children representative of the FOH phenotype when compared to children with PBD who lack this trait had higher indices of severity of mania and depression, as well as other

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indices that reflect severity and course of illness. Trait factors were derived from a factor analysis of CBQ in a large population of children diagnosed with or at risk for PBD, and used to further elucidate trait features of children with FOH. Children with the FOH traits were also more likely to be defined by six CBQ factors; Sleep/Arousal, Harm to Self and Others, Territorial Aggression, Anxiety, Self-esteem, Psychosis/Parasomnias/Sweet Cravings/Obsessions (PPSO).

Limitations: This data is derived from samples enriched with bipolar disorder cases. Further validation is needed with samples in which childhood-onset BD is rarer and diagnoses more diverse. Clinician diagnosis was not validated via research interview.

Conclusions: The FOH phenotype, as defined by a metric derived from combining items from the YBOCS/OAS, is a clinically homogeneous behavioral phenotype of PBD with early age of onset, severe manic and depressive symptoms, and significant social impairment that is strongly associated with 6 CBQ factors and can be easily identified using the CBQ. Through the examination of dimensional features of PBD in an enriched sample of large size, we were able to further refine a phenotype and identify clinical dimensions potentially linked to endophenotypic markers that may prove fruitful in differential diagnosis, treatment and etiological studies of PBD. The nature of the sets of specific symptoms that comprise the FOH factors enabled us to propose a biological model *for the phenotype* (OUT) that involves a complex orexigenic circuit which links hypothalamic, limbic, and other brain nuclei primarily responsible for the regulation of behavioral and proposed physiological features of the FOH phenotype.

1. Introduction

There is a general agreement within the clinical and research communities that the field of psychiatry is in a state of flux as advances in neuroscience, neuroimaging and genetics begin to challenge many of its current theoretical underpinnings, particularly those related to the definition and causation of mental disorders (Kendell and Jablensky, 2003; Charney et al., 2002). It is becoming increasingly apparent that the broad and imprecise nature of the current psychiatric diagnostic constructs is a limiting factor in the development of reproducible genetic and imaging research and in our understanding of the genetic basis of human behavioral abnormalities.

Recent findings from clinical studies have led some clinical investigators to conclude that psychiatric diagnosis such as obsessive–compulsive disorder and bipolar II disorder would be better conceptualized as a spectrum of overlapping syndromes (Hantouche and Akiskal, 2006) or much more well defined (Mataix-Cols et al., 2005; Leckman et al., 2007) than found in unitary nosologic entities as currently promulgated in DSM-IV. These studies are consistent with the idea that psychiatric syndromes may be better defined by an ordered matrix of symptom clusters or behavioral dimensions than by a set of discrete categories (Gusnard et al., 2003; Smoller et al., 2008). While categorical definitions tend to obscure symptoms not central to the construct of a particular disorder, i.e., the DSM-IV caveat, "Do not include if better accounted for by another disorder", clusters of individual symptoms that overlap with currently established diagnostic boundaries may define more homogeneous phenotypic subtypes for genetic studies. Future pharmacological treatments like CRF and NPY inhibitors and agonists and circadian interventions, such as sleep deprivation or full spectrum light for depression, that target specific functional systems in the brain will require a more differentiated classification of the clinical populations selected for treatment than the approaches that are currently available (Mathew et al., 2008; Ehlers et al., 1997; Robison et al., 2004; Zhou et al., 2008; Xapelli et al., 2006; Silva et al., 2005; Kishi and Elmquist, 2005; Benedetti et al., 2007; Kehne, 2007).

Smoller and Tsuang (1998) have suggested that the success of psychiatric genetics may require the development of a genetic nosology that can classify individuals in terms of the heritable aspects of psychopathology. Fruitful endophenotype studies depend on the selection of heritable, quantitative traits that can be objectively and reliably measured. However, to date, there are no agreed upon methods by which candidate behavioral phenotypes can be chosen and applied (Bearden and Freimer, 2006; van Praag, 1993). An important dividend from an effort to define the boundaries of heritable phenotypes for genetic studies would be a refinement in the nosology of psychiatric conditions (Smoller and Tsuang, 1998; Kendell and Jablensky, 2003; Finegan, 1998).

Clearly, in psychiatry, the goal over the next decade will be to establish behavioral phenotypes strongly associated with biologically based anchor endophenotypes that respond to specific pharmacological or circadian treatments (Drevets et al., 2006). This need is no more critical than in the area of pediatric bipolar disorder (PBD) as there is no current consensus in the field about diagnosis. A recent study reports that the estimated annual number of youth office-based visits with a diagnosis of bipolar disorder in the US increased from 25 (1994–1995) to 1003 (2002–2003) visits per 100,000 population — a 40-fold rise (Moreno et al., 2007). Though several phenotypes have been proposed (Geller and Tillman, 2005; Leibenluft et al., 2003; Papolos, 2003; Biederman et al., 2004), there remains some controversy about how the illness is diagnosed in childhood. Regardless of the differences between research groups regarding how bipolar disorder in children is defined, it is agreed that PBD is a serious and pernicious illness. With early intervention during the period of time in which youths are exhibiting subsyndromal symptoms of PBD, it appears that the progression of the illness to the more malignant manifestation of the disorder may be avoided (Demeter et al., 2008; Holtmann et al., 2008; Geller and Tillman, 2005; Craney and Geller, 2003; Biederman et al., 2000; Dilsaver, 2001; Kim and Miklowitz, 2002; Schapiro, 2005; Youngstrom et al., 2005).

Two parallel but separate traditions have sought to define behavioral phenotypes: the first, more closely identified with clinical psychiatry, has utilized categorical diagnoses (e.g., bipolar disorder, obsessive–compulsive disorder, panic disorder and social phobia) that sharply delineate sets of psychiatric symptoms into putatively non-overlapping diagnoses. The other, more closely identified with psychological studies of personality development, has examined dimensional traits (e.g., approach/avoidance, neuroticism and anxious temperament, behavioral inhibition, self-directedness, persistence, novelty seeking, reward dependence, fear of harm, Brown et al., 1992; Eysenck, 1997; Papolos et al., 2006; De Fruyt et al., 2006; Gusnard et al., 2003). A genetic nosology of bipolar disorder could incorporate features of both traditions to provide a strategy for optimizing genetic approaches to bipolar disorder (BPD). We have attempted to do that in this study.

By systematically selecting features of a disorder that might result from distinct genetic influences, and by carefully defining the target phenotype, we can hope to narrow the range of genes that influence risk for the trait in a study population, thereby increasing the likelihood of finding them. We have taken an approach that we believe gives us the best opportunity to determine the genetic associates of PBD. We ascertained cases of early onset PBD from families with multiple first degree relatives diagnosed with BPD and determined heritability factors by performing concordance studies on affected sibling pairs and twins.

In genomics, the importance of the analysis of symptom dimensions as a strategy for genotyping is becoming more evident. Cheng et al. (2006) used both standard diagnostic models and the comorbid symptoms of psychosis, suicidal behavior and panic disorder to identify phenotypic subtypes for a genome-wide linkage scan in a large bipolar sample. Over half the regions implicated by the strongest linkage signals (genome-wide significance) were identified using phenotypic subtypes. Cheng and colleagues concluded that a dissection of the disease phenotype can enrich the harvest of linkage signals and expedite the search for susceptibility genes. In a genetic study of BPD pedigrees ascertained through adult probands, Faraone et al. (2006) quantified dimensions of BPD symptoms derived from a principal component factor analysis, determined their heritability, and used the heritable factors in a variance-components linkage analysis.

Using a similar methodology, we found that a behavioral dimension that encompasses aggressive obsessions and aggressive behavior directed towards others and self defined as Fear of Harm (FOH) had one of the strongest concordance coefficients (rho) between probands and siblings compared with age and sex matched singletons, and the widest contrasts between the rho-estimates for the proband/sibling vs. proband/comparison pairs (Papolos et al., 2007). In the present study, we sought to further examine this behavioral phenotype defined by a metric adopted from the YBOCS and OAS, well-standardized scales that measure obsessive–compulsive and aggressive behaviors. We hypothesized that selective factors including mania and depression, would be distinguishing features of impairment between groups defined by the magnitude of their score on a continuous measure of FOH. Additionally, we hypothesized that parent-reported symptom severity as measured by earlier age of onset of first psychiatric symptoms, first hospitalization, and frequency of psychiatric hospitalizations, as well as, degree of social impairment, as determined by exposure to the juvenile justice system and school performance problems, would be greater in the high FOH phenotype group when compared to the low or no FOH group.

This potentially heritable behavioral dimension or trait feature of FOH overlaps with DSM-IV definitions of bipolar disorder, obsessive–compulsive and other anxiety disorders, oppositional defiant, conduct disorder and impulse-control disorder, as well as, parasomnias and REM sleep behavior disorder with symptoms of suicidality and psychosis. Thus, the trait FOH, does not pertain to any specific set of current DSM-IV criteria and, therefore, cannot be diagnosed using the categorical nosology promulgated by DSM-IV.

2. Methods

The sample was comprised of children with community diagnoses of bipolar disorder or at risk for the illness based on enriched family history with multiple first degree relatives diagnosed with BPD ($N=5335$). Included were all subjects who had >40 positively endorsed CBQ symptom items at frequencies of very often, almost always, and always. This group was divided randomly into two groups, the exploratory group ($N=2668$) and the study group ($N=2666$). The exploratory group was used for exploratory data analysis and the development of hypotheses. A study group was used to test these hypotheses using a new and uncontaminated set of data. All results reported here are derived from the latter group. In subsequent analyses, we examined a subset of the study group sample for differences in age of onset of first psychiatric symptoms, course of illness and measures of symptom severity. These groups were compared using the chi-square procedure for categorical data and the Analysis of Variance (ANOVA) with Scheffe pair wise tests for continuous variables. The Child Bipolar Questionnaire V.2.0, the Yale–Brown Obsessive Compulsive Scale (YBOCS) and the Overt Aggression Scale (OAS) were the principal instruments used to obtain diagnostic information for this study.

To assess the relationship between membership in an FOH group and symptoms of mood dysregulation and psychiatric disorders, the CBQ was administered to all subjects ($N=1726$). The CBQ is a 65 item, self-administered, parent-report measure originally developed to establish initial eligibility for clinical and genetic studies of PBD (Papolos et al., 2006) It was constructed based on the model proposed by Depue et al. (1981), who, with the development and validation of the General Behavior Inventory (GBI), derived a dimensional approach for the definition of BPD in adults. Behaviors and symptoms are measured on 1–4 Likert scale. A rapid screening instrument with a Core Index subscale of key symptom dimensions frequently reported in PBD, the CBQ includes scoring algorithms for DSM-IV BD, with and without attention deficit/hyperactivity disorder (ADHD). Test/retest data showed excellent reliability for both the CBQ total score ($r=0.82$) and the Core Index subscale ($r=0.86$). CBQ screening algorithms were performed with a specificity of 97% and a sensitivity of 76% in classifying subjects with Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS P/L) diagnosis of BD vs. no BD (Papolos et al., 2006). The Core

Index subscale had excellent agreement with K-SADS P/L diagnosis (k = 0.84) in classifying BD, ADHD-only, and no diagnosis and demonstrated 100% sensitivity and 86% specificity in classifying BD vs. no BD. Consistent with a previous examination of the FOH symptom dimension (Papolos et al., 2005a), we used a YBOCS measure that consisted of a count of six aggressive obsessions rated by the parent as occurring at a frequency of "often" or "very often" or "almost constantly": [1] fear might harm self; [2] fear might harm others; [3] fear harm might come to self; [4] fear harm will come to others (may be because of something child did or did not do); [8] fear will act on unwanted impulses (e.g., to stab a family member); [10] fear will be responsible for something else terrible happening (e.g., fire, burglary, flood). The FOH index was calculated by summing six YBOCS items that had scored greater or equal to 3 and two items from OAS that had scored greater or equal to 2. The items from the OAS are: [11] mutilates self, causes deep cuts, bites that bleed internal injury, fracture, loss of consciousness, loss of teeth and [15] attacks others, causing severe physical injury.

Consistent with a previous examination of the FOH symptom dimension (Papolos et al., 2005a,b) YBOCS items that had scored greater or equal to 3 and two items from OAS that scored greater or equal to 2 defined the phenotype. A principal component factor analysis with Varimax rotation was used to determine what other traits are associated with the FOH trait by examining the independent factors derived from the CBQ. To determine the nature and extent to which each of these factors were associated with the FOH trait, a total score for each factor was calculated by summing all items for each factor and the factors were named based on item content. Cronbach's alpha was also calculated per factor. These factors were used in a multiple regression model to predict the Fear of Harm Index using a stepwise method. Some questions were not applicable to all subjects, resulting in different sample size per variable. The SPSS version 15 was used for all these analyses.

3. Results

Of the 2666 subjects, 1729 were found to have FOH data. When we examined the distribution of the FOH index in this sample, one of the most striking findings was that a full third of the group had no FOH ($X^2 = 169.14$, df = 1, $p < .001$). The total group of 1729 children was, therefore, divided into three groups. A group with no FOH symptoms (NoFOH), values of 0 positively endorsed items (NoFOH: 0 ± 0, $N = 621$, 36%), and subjects with values from 1 through 7 (LowFOH: 4.5 ± 2 $N = 555$, 32%) were designated as the low FOH group. The high FOH group included subjects with values greater than or equal to seven (HighFOH: 14.1 ± 5, $N = 553$, 32%).

Although there were no significant differences between rates of males and females on the Fear of Harm Index (female: 5.7 ± 6, male: 6.2 ± 7, $f = 2.1$, df = 1,1640, $p = .148$), there were significantly more male subjects in the LowFOH group (NoFOH: 35%, LowFOH: 45%, and HighFOH: 34%, $X^2 = 6.41$, df = 2, $p = .041$). There is no significant age difference among groups (NoFOH = 10.0 ± 4, $N = 585$; LowFOH = 10.2 ± 4, $N = 528$; HighFOH = 10.4 ± 4; $f = 1.7$; df = 2,1636; $p = .182$). However, there were significantly more ADHD subjects in the NoFOH group compared to HighFOH (NoFOH = 19%, LowFOH = 16%, HighFOH = 11%, $X^2 = 7.9$, df = 1, $p = .005$).

Despite the fact that the three groups did not differ on the number of subjects diagnosed with bipolar disorder (NoFOH = 83%, LowFOH = 86%, HighFOH = 86%, $X^2 = 1.13$, df = 2, $p = .57$), or major depressive disorder (NoFOH = 4%, LowFOH = 2%, HighFOH = 2%, $X^2 = 2.69$, df = 2, $p = .26$), using CBQ item scores we found that there was a significantly greater frequency of manic (NoFOH = 5.0 ± 2, LowFOH = 5.7 ± 1, HighFOH = 5.6 ± 2; $f = 79.43$; df = 2,1726; $p < .0001$) and depressive symptoms (NoFOH = 3.9 ± 2, LowFOH = 4.6 ± 2, HighFOH = 4.9 ± 2; $f = 60.53$; df = 2,1726; $p < .0001$) in the high FOH group when compared to the low or no FOH groups. Pair wise tests indicate that all groups are significantly different from each other on these variables. These differences are also evident when the dimensions were dichotomized (Table 1). The HighFOH group has a significantly greater number of subjects with five or more manic/hypomanic symptoms, 91%, compared to the LowFOH group of 83% and NoFOH group of 69% of subjects ($X^2 = 93.8$, df = 2, $p < .000$). All pair wise comparisons were also significant. The differences persisted when analyzed for depressive symptoms; 84% of the HighFOH group exhibited four or more symptoms of depression in comparison to 78% of the LowFOH and 62% of NoFOH groups ($X^2 = 76.4$, df = 2, $p < .0001$). All pair wise comparisons were also significant. Similar results were found when groups were compared separately for male and female subjects (Table 1).

Course of illness data was available for 967 children. Within this subgroup we applied the same criteria for FOH status. Similar to the larger pool of children, this smaller group contained about a third of children who endorsed 0 items of FOH ($N = 334$, 35%), a third endorsed 1 through 7 items ($N = 322$, 33%) and a third endorsed more than 7 items ($N = 311$, 32%). The similarity of the distribution of FOH in each group raises one's confidence that this smaller subset of children is a representative sample of the larger sample.

The three groups endorsed CBQ items significantly differently from each other ($f = 137.69$; df = 2,981; $p < .001$). The NoFOH group positively endorsed 37.9 ± 11 items, LowFOH 45.8 ± 8 items and the HighFOH group positively endorsed 49.6 ± 8 items. These differences were similar to the larger group. The groups were not significantly different in age (NoFOH = 9.7 ± 4, LowFOH = 9.9 ± 4, HighFOH = 10.3 ± 4; $f = 2.10$; df = 2,896; $p = .122$). The groups had a similar distribution of male subjects (NoFOH: 33%, LowFOH: 30%, and HighFOH: 36%, $X^2 = 5.11$, df = 2, $p = .077$).

These groups had a similar age of onset of first reported psychiatric symptoms, age of initial psychiatric evaluation, age of initial diagnosis and age at first psychiatric hospitalization. However, they were significantly different on the number of hospitalizations (Table 2). The NoFOH group has

Table 1
Group differences on symptoms of mania and depression mania and depression symptoms ($N = 1729$).

	NoFOH	LowFOH	HighFOH	X^2 *
Manic symptoms greater or equal to 5	69% (426)	83% (459)	91% (502)	93.8
Depressive symptoms greater or equal to 4	62% (387)	78% (431)	84% (464)	76.4

* $p < .001$.

Table 2
Course of illness ($N=967$).

	NoFOH	LowFOH	HighFOH	f	$p<.01$
Age of 1st symptoms (years)	2.7±2 ($N=334$)	2.6±3 ($N=322$)	2.5±2 ($N=311$)	1.12	.326
Age of initial psychiatric evaluation (years)	6.0±3 ($N=316$)	6.0±3 ($N=312$)	6.0±3 ($N=300$)	.037	.963
Age of initial diagnosis (years)	6.3±3 ($N=306$)	6.5±5 ($N=313$)	6.3±4 ($N=302$)	.365	.694
Age of 1st psychiatric hospitalization (years)	9.7±4 ($N=78$)	9.6±4 ($N=114$)	9.4±4 ($N=164$)	.337	.713
Number of hospitalizations	1.5±1 ($N=86$)	1.8±2 ($N=118$)	2.4±2 ($N=172$)	6.31	.002 *

* Significant pair wise comparisons based on Scheffe formula: NoFOH vs. LowFOH ($p=.005$) and vs. HighFOH ($p=.044$).

a significantly fewer number of hospitalization than the other two groups.

On measures of severity of illness presented in Table 3, there were significant differences found among the FOH groups on the severity of illness variables; Ever Hospitalized, Held Back a Grade, and Suspended from School. However, the groups were not significantly different on home schooling and their involvement with the juvenile justice system. All groups were significantly different from each other on ever hospitalized with HighFOH has the largest percentage of subjects (52%). Significantly more subjects from the HighFOH group were also held back a grade compared to NoFOH ($X^2=8.49$, df = 1, $p=.004$) and significantly more subjects from HighFOH and LowFOH were suspended from school than NoFOH ($X^2=8.48$, df = 1, $p=.004$; $X^2=6.24$, df = 1, $p=.012$). There was a strong trend between held back a grade and suspended from school. 47% of subjects who were held back a grade were also suspended from school ($X^2=2.75$, df = 1, $p=.098$). 14% of subjects from HighFOH groups were suspended from school and held back a grade compared to 7% from NoFOH ($X^2=7.39$, df = 1, $p=.007$) and 6% subjects from LowFOH groups ($X^2=11.30$, df = 1, $p=.001$).

Using all of the children in the study, a principal component factor analysis was used to identify a set of independent dimensions associated with the FOH trait of children ($N=1729$; NoFOH = 621, LowFOH = 555, HighFOH = 553). The factor analysis yielded thirteen factors with eigenvalues greater than 1.0 that explained a total of 61% of variance. By combining 3 of the factors with the lowest Cronbach's alpha with other factors to which they also contributed, we reduced the 13 factors to 10. These ten factors their CBQ items, eigenvalues, percentage of variance and the Cronbach's alphas are listed in Table 4.

Descriptive information for each CBQ factor for the three FOH groups are presented in Table 5.

The mean number of CBQ items endorsed by the three FOH groups was significantly different from each other. The NoFOH group positively endorsed 37.9±11 items (out of 65 items), LowFOH 45.05±9 items and the HighFOH group positively endorsed 49.99±8 items ($f=243.27$; df = 2,1726; $p<.001$). Subjects who scored either HighFOH or LowFOH were found to have more severe symptoms on all of these CBQ factors than children without the FOH trait.

We sought to determine what other traits are associated with the FOH trait by examining the 10 independent factors derived from the CBQ using a multiple regression analysis. The regression analysis resulted in a six factor model being the best fit. The 6 factors that emerged accounted for 45% of the variance (Step 6: F = 148.65; df = 6,1076; p = .000). These factors are: Territorial Aggression, Harm to Self and Others, Self-esteem, Psychosis/Parasomnias/Sweet Craving/Obsessions (PPSO), Sleep, and Anxiety.

4. Discussion

In this study we sought to further elucidate a dimensional behavioral phenotype of PBD. This phenotype was originally defined in a concordance study of affected sibling pairs that examined the heritability of CBQ factors in a group of subjects with a community diagnosis of PBD (Papolos et al., 2007). Six of these factors, including a Core Index of 22 CBQ items, exhibited the strongest concordance coefficients between probands and siblings and the widest contrasts between proband/sibling vs. proband/comparison pairs. These factors were: Fear of harm, Aggression, Anxiety, Sensory sensitivity, Sleep/wake cycle disturbances, and Attention/Executive function deficits. This suggested to us a profile of heritable clusters of CBQ symptoms, that, in addition to classic mood symptoms, could provide distinguishing features of novel phenotypes of PBD (Papolos et al., 2007). We hypothesized that in addition to mania and depression, heritable trait features such as FOH could be instrumental in elucidating a specific behavioral phenotype derived from a factor analysis of CBQ symptom dimensions. Indeed, we found that subjects with FOH had significantly higher frequencies of both manic and depressive symptoms than the no or low FOH groups, suggesting that the subjects who carry this trait feature fall clearly within the domain of classical manic-depression, and that the presence and severity of FOH symptoms is a defining feature of this phenotype (Kraepelin, 1976; Goodwin and Jamison, 2007).

It has been suggested that an earlier age of onset may further separate patients with BD into more homogeneous

Table 3
Group differences on measures of severity of illness.

	Yes	NoFOH (%)	LowFOH (%)	HighFOH (%)	X^2	p value
Ever hospitalized ($N=984$)	352	22	34	52	63.7	.001
Home schooled ($N=984$)	40	5.4	4.3	2.2	4.7	.094
Held back a grade ($N=880$)	171	15	20	24	8.5	.014
Ever suspended from school ($N=905$)	366	36	38	48	9.9	.007
Involved with the juvenile justice system ($N=984$)	110	91	89	86	5.1	.079

Table 4

Factor	CBQ items	Eigenvalues	% Variance	α
Factor 1: Territorial Aggression	46) is willful and refuses to be subordinated by others 47) argues with adults 49) defies or refuses to comply with rules 51) is easily angered in response to limit setting 48) is bossy towards others 45) relentlessly pursues own needs and is demanding of others 50) blames others for his/her mistakes 53) has protracted, explosive temper tantrums 55) displays aggressive behavior towards others 32) has irritable mood states 52) lies to avoid consequences of his/her actions 44) is intolerant of delays 54) has difficulty maintaining friendships	16.56	25.5	.91
Factor 2: Attention/Executive function	17) has difficulty organizing tasks 13) demonstrates inability to concentrate at school 12) is easily distracted during repetitive chores and lessons 14) attempts to avoid homework assignments 16) has poor handwriting 11) is easily distracted by extraneous stimuli 19) has difficulty estimating time 15) able to focus intently on subjects of interest and yet at times is easily distractible 20) has auditory processing or short-term memory deficit 18) has difficulty making transitions	3.71	5.7	.87
Factor 3: Mania	25) has periods of high, frenetic energy and motor activation 28) has periods of excessive and rapid speech 26) has many ideas at once 33) has elated or silly, goofy, giddy mood states 24) is easily excitable 27) interrupts or intrudes on others 04) is hyperactive and easily excited in the PM 31) displays abrupt, rapid mood swings 43) fidgets with hands or feet 65) is very intuitive and/or very creative 30) tells tall tales; embellishes or exaggerates 29) has exaggerated ideas about self or abilities	3.24	4.9	.87
Factor 4: Harm to Self/Others	59) makes clear threats of violence to others or self 58) makes moderate threats to others or self 60) has made clear threats of suicide 57) curses viciously, uses foul language in anger 56) has destroyed property intentionally 61) is fascinated with gore, blood, or violent imagery	2.93		.83
Factor 5: Self-esteem	41) feels easily criticized and/or rejected 42) feels easily humiliated or shamed 40) experiences periods of self doubt and poor self-esteem 37) complains of being bored 38) has periods of low energy and/or withdraws or isolates self 39) has decreased initiative	2.40		.84
Factor 6: Sleep	06) has difficulty getting to sleep 05) has difficulty settling at night 07) sleeps fitfully and/or awakens in the middle of the night 03) has difficulty arising in the AM	1.93		.74
Factor 7: Sensory	21) is extremely sensitive to textures of clothes, labels, and tightness of fit of socks or shoes 22) exhibits extreme sensitivity to sound and noise 23) complains of body temperature extremes or feeling hot despite neutral ambient temperature	1.78		.71
Factor 8: Hypersexuality	34) displays precocious sexual curiosity 35) exhibits inappropriate sexual behaviors, e.g. openly touches self or others' private parts 36) takes excessive risks	1.50		.74
Factor 9: Psychosis, Parasomnias, Sweet Cravings, and Obsessions	09) wets bed 08) has night terrors and/or nightmares 63) hoards or avidly seeks to collect objects or food 62) has acknowledged experiencing auditory and/or	1.23		.59

(continued on next page)

Table 4 (*continued*)

Factor	CBQ items	Eigenvalues	% Variance	α
	visual hallucinations			
	10) craves sweet-tasting foods			
	64) has concern with dirt, germs, or contamination			
Factor 10: Anxiety	01) displays excessive distress when separated from family	1.03		.66
	02) exhibits excessive anxiety or worry			

α: Cronbach's alpha.

phenotypic subgroups for genetic studies (Todd et al., 1993; Leboyer et al., 1998; Bellivier, 2003; Papolos, 2003; Faraone et al., 2004; Leboyer et al., 2005; Engstrom et al., 2003). While the low and high FOH groups did not differ from the NoFOH group on age of first psychiatric symptoms and diagnosis, nor on age at first psychiatric hospitalization they had a significantly greater number of hospitalizations. The median ages for all three groups on first onset of symptoms for the first psychiatric diagnosis (NoFOH 2.7±2 LowFOH 2.6±3, and High FOH 2.5±2), or first psychiatric hospitalization respectively (NoFOH 9.7±4, LowFOH 9.6±4, and HighFOH 9.4±4) was surprisingly young. We also examined the difference between groups on course of illness variables. On measures of school performance, subjects positive for FOH were significantly more likely to be held back a grade and to be suspended from school. Taken together these findings suggest that all groups are of significant clinical importance. These children have severe psychiatric illness and impairment, very early age of onset, are highly socially impaired, and may have learning deficits. There was a greater incidence of comorbid ADHD in children without the FOH trait. The FOH group therefore, may represent a more homogeneous and perhaps more severe phenotype given the higher rates of hospitalization, and greater likelihood of school performance difficulties. In an extensive review of clinical, epidemiological, neurobiological, and genetic studies in bipolar disorder, Hasler et al. (2006) concluded that particular symptom dimensions, deficits, and physiological anomalies deserve further research focus as candidate endophenotypes that could improve the phenotypic definition of bipolar disorder. Such an approach has proved fruitful in the study of obsessive–compulsive (OCD) symptoms. By stepping outside the traditional DSM-IV diagnostic boundaries and applying findings from factor-analytic studies that consistently identified four temporally stable symptom dimensions: contamination/washing, aggressive/checking, hoarding, and symmetry/ordering (1–7), and examining these OCD symptom dimensions independently, Mataix-Cols et al. (2004, 2005, 2007, 2008) determined that a different activation pattern on fMRI is associated with each symptom dimension of OCD. Furthermore, they found that different dimensions are mediated by relatively distinct components of frontostriatothalamic circuits. They concluded that OCD may be best conceptualized as a spectrum of multiple, potentially overlapping syndromes rather than a unitary nosologic entity. Similarly, we utilized a factor-analytic approach of symptom dimensions of PBD derived from the CBQ that we believe provides further support for this method as a means to dissect phenotypes of complex psychiatric disorders. As currently defined, PBD is a clinically heterogeneous condition. This heterogeneity can reduce the power and obscure the findings from natural history studies to genome scans, neuroimaging, and clinical trials. It has been suggested that when the boundaries of a syndrome are in question, as in the case with PBD, dimensional analysis may yield more information about the specific symptoms or constellations of symptoms that define a syndrome (Kendell and Jablensky, 2003). We believe this approach finds further support from this study and underscores the farsightedness of Mataix-Cols and colleagues for pointing the field in this direction. By examining other dimensional features of the FOH trait in enriched samples of large size we were able to further refine what appears to be a subphenotype of pediatric bipolar disorder. The complex clinical presentation of PBD can be understood as a spectrum of potentially overlapping syndromes that may 1) coexist in any patient, 2) be continuous with classical manic and depressive symptoms and 3) extend beyond the traditional nosological boundaries of BPD that tend to obscure symptoms not central to the construct of a particular disorder.

The FOH phenotype is a clinically homogeneous behavioral phenotype of PBD with early age of onset, severe manic and depressive symptoms, early and frequent psychiatric hospitalizations, significant social impairment and school problems that can be identified using 6 factors derived from the CBQ with 96% accuracy. Given the potential for early intervention in such a group of very severely ill children that engender an enormous psychic, social, and financial burden to parents, teachers, medical and social agencies that have responsibility for their care, the CBQ is being widely used as an early screening tool by child psychiatrists, child psychologists, social workers, and pediatricians (The Juvenile Bipolar Research Foundation (http://www.bpchildresearch.org/cpp/index.html)). Although the dimensional structure of symptoms derived from the CBQ to define a subtype of PBD is imperfect, this quantitative approach to the identification of phenotypic traits has the potential to advance our

Table 5
Bipolar Child Questionnaire Factor Scores: Mean Standard Deviations Across FOH Groups.

	NoFOH	LowFOH	HighFOH	Factor group mean
Territorial Aggression [a]	39.8±9	43.5±7	46.5±5	43.1±8
Attention/Executive function	30.9±7	33.1±5	34.5±5	32.8±6
Mania	36.1±7	39.0±6	41.3±5	38.7±7
Harm to Self/Others [a]	11.9±4	14.5±4	17.6±4	14.5±5
Self-esteem [a]	17.3±4	18.9±4	20.1±4	18.7±4
Sleep [a]	11.5±3	12.5±3	13.0±3	12.3±3
Sensory	7.4±3	8.1±3	8.8±3	8.1±3
Hypersexuality	5.7±2	6.5±3	7.3±3	6.5±3
Psychosis/Parasomnias/Sweet Cravings/Obsessions [a]	11.5±3	13.2±3	14.6±4	13.0±4
Anxiety [a]	4.7±2	5.5±2	5.9±2	5.3±2

[a] These are the significant factors that emerged with multiple regression analysis of the factor structure.

understanding of PBD and may prove fruitful in both differential diagnosis and etiological studies. The specificity of the CBQ factor items that define the FOH subtype including, Territorial Aggression, Harm to Self and Others, Self-esteem, and Psychosis/Parasomnias/Sweet Craving/Obsessions (PPSO) has lead us to propose a hypothesis that predicts the biological underpinnings of the endophenotype.

The PPSO factor comprises a unique cluster of symptoms that includes psychosis, parasomnias (enuresis and night terrors), craving for sweets, food hoarding and contamination fears, and suggests the phenotype is characterized by disturbances in appetite, as well as sleep/arousal systems. In juvenile bipolar disorder, disturbances in the quality of both sleep and wakefulness are prominent. Preliminary data from parental reports of children with PBD indicate that a diverse set of sleep problems particularly sleep-onset delay and sleep fragmentation and morning sleep inertia are severe and more frequent relative to children with other psychiatric disorders, primary sleep disorders, in a community sample of children. (Harvey et al., 2006; Mehl et al., 2006a,b; Murphy et al., in press).

Preliminary data from temperature/actigraphy studies of pediatric bipolar disorder suggest that one of the features of the condition is a delay of circadian sleep and temperature rhythms that would produce symptoms of initial insomnia and sleep inertia (sleep onset and sleep offset) (unpublished data). Also, pilot data from children with the FOH phenotype suggest that there is a circadian phase delay in sleep timing and temperature dysregulation at sleep onset. Difficulty arising in the AM (sleep inertia), settling at night, getting to sleep and sleeping fitfully or awakening in the middle of the night constitute sleep initiation and maintenance problems that specifically characterize the FOH Sleep/Arousal factor. In addition, arousal parasomnias, including enuresis, hypnogogic and hypnopompic hallucinations, night terrors and vivid nightmares — often containing images of gore and mutilation, themes of pursuit, bodily threat and parental abandonment are features of the PPSO factor. Taken together this set of symptoms is indicative of both primary sleep problems and sleep pertubations secondary to altered circadian and ultradian rhythms of sleep, wakefulness and temperature (Lack et al., 2008; Poceta et al., 2009; Pal and Mallick, 2007). Disturbances in areas that regulate these rhythms would likely result in difficulties with transitions from sleep to waking, waking to sleep and between REM and NREM sleep phases.

Cumulative evidence indicates that hypothalamic preoptic area orexigenic neurons are active during sleep and in response to the increase in homeostatic pressure for sleep. They orchestrate onset, offset and maintenance of sleep as well as the regulation of REM/nonNREM sleep transitions by inhibitory modulation of multiple arousal systems (de Lecea et al., 1998; Willie et al., 2001; Fujiki et al., 2009; Mieda et al., 2004; Yamanaka et al., 2003; Oldfield et al., 2007; Hirota, 2007; Szymusiak and McGinty, 2008; Galvão et al., 2009). Regulation of vigilance states by orexin neurons operates through two orexin receptor subtypes. Noradrenergic neurons in the locus coeruleus express orexin A, and histaminergic neurons in the tuberomammillary neurons (TMN) express orexin B, while serotonergic neurons in the dorsal raphe express both receptor subtypes. Orexin neurons in the lateral hypothalamic nucleus send excitatory projections to monoaminergic neurons. Studies in knockout mice suggest that activation of (TMN) histaminergic neurons via orexin B is crucial for maintenance of arousal and gating of non-REM sleep, while both receptors may prevent entry into REM sleep (de Lecea et al., 1998; Hagan et al., 1999; Ohno and Sakurai, 2008).

Disruption of the orexin system results in human narcolepsy, characterized by excessive daytime sleepiness, premature transitions to REM sleep (sleep-onset REM), and cataplexy (Mieda et al., 2004; Fujiki et al., 2009; Mishima et al., 2008; Douglass, 2003). A transgenic method that mapped upstream neuronal populations with synaptic connections to orexin neurons revealed that these neurons receive input from several brain areas, including the amygdala, basal forebrain cholinergic neurons, GABAergic neurons in the preoptic area, and serotonergic neurons in the median/paramedian raphe nuclei (Ohno and Sakurai, 2008). Produced in a very sparse population of cells in the lateral and posterior hypothalamus, orexin neurons send widespread projections throughout the brain and heavily innervate many wake-promoting regions such as the locus coeruleus as well as those regions involved in food-seeking behaviors and the ventral tegmental area (VTA), the origin of dopamine projections implicated in motivation and reward (Peyron et al., 1998; de Lecea et al., 1998; Marcus et al., 2001; Sutcliffe and de Lecea, 2000; Mochizuki et al., 2006). In addition, orexin neurons project densely to the preoptic area which is involved in thermoregulation (Parmeggiani et al., 1986; Boulant, 2000; Yoshimichi et al., 2001; Capitani et al., 2005; Burdakov and González, 2008; Morrison et al., 2008). An emerging body of evidence from both adults and children support the notion that thermoregulatory processes are critical in the regulation of sleep. Specifically, the ability to dissipate heat efficiently at night is permissive of sleep onset, and the capacity to conserve heat efficiently in the morning reduces sleep inertia and promotes wakefulness. The PPSO and Sleep/Arousal symptoms can be viewed as a reflection of dysregulation of homeostatic functions that are closely associated with the rise and fall of body temperatures — the relationship between these thermoregulatory variables at the appropriate time of day promote sleep onset and sleep offset and potentially the timing function that alternates between NREM and REM sleep phases.

Sweet craving and food hoarding are primary symptoms of the PPSO FOH factor. Orexin A and NPY-induced orexigenic actions modulate behavioral state and state-dependent processes. Evidence suggests that the mechanism of orexin action is directly related to synaptic regulation of the NPY system (Horvath et al., 1999; Tavas et al., 1999; Kalra et al., 1999; Yamanaka et al., 2000; Kalra and Kalra, 2004; Glavas et al., 2008). NPY is the most robust physiological appetite transducer known (Day et al., 2009). Orexin A also induces acute feeding (Preti, 2002). The circadian and ultradian rhythmicities in NPY secretion imprint the daily circadian and episodic feeding patterns. NPY is a potent peptide that increases food foraging and hoarding (appetitive behavior) and food intake (consummatory behavior) (Williams et al., 2001; Jain et al., 2000; Yoshida et al., 2001; Kalra and Kalra, 2004; Day et al., 2005; Keen-Rhinehart and Bartness, 2007; Olszewski et al., 2009; Day et al., 2009).

The CBQ factors, Territorial Aggression and Harm to Self and Others are two other significant traits that define the FOH phenotype. These two factors comprised of symptoms that

reflect high levels of aggression and fear as well as defensive or reactive aggressive behaviors. Karl et al. (2004) established a relationship between territorial aggression and feeding behavior in animals through the identification of a neural circuit by which the NPY Y1 receptors may affect both behaviors. Fear arousal, initiated by a perceived threat, leads to activation of the stress response, a state of alarm that promotes an array of cortico-limbic, autonomic pathways and endocrine changes associated with fight or flight behaviors designed to aid self-preservation (Zhou et al., 2008; Rodrigues et al., 2009). NPY release is induced by stress, decreases fear-related behaviors in various animal models of anxiety and is abundantly expressed in regions of the limbic system that are implicated in arousal and in the assignment of emotional valences to fear stimuli and memories (long term potentiation) (Jiménez-Vasquez et al., 2001; Sørensen et al., 2008, 2009; Gutman et al., 2008). NPY dampens the excitability of amygdaloid neurons and inhibits both baseline acoustic startle and the expression of fear-potentiated startle behaviors, and is anticonvulsant (Sosulina et al., 2008; Rodrigues et al., 2009). This neuropeptide circuit is clearly involved in territorial aggressive behaviors, fear sensitization, foraging and hoarding behaviors in animals.

In sum, we suggest that a complex orexigenic neuropeptide circuit first delineated by Emeson and Morabito (2005), that links the hypothalamic nuclei, the median preoptic nucleus (MnPO), ventrolateral preoptic nucleus (VLPO), and the suprachiasmatic nucleus (SCN), as well as the olfactory bulb, amygdala, ventral tegmental nucleus, nucleus accumbens, median and dorsal raphe nuclei, and the locus coeruleus, is primarily responsible for the regulation of the behavioral and proposed physiological features of the FOH phenotype.

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Conflict of interest

Dr. Papolos developed the Child Bipolar Questionnaire which was the primary instrument used in this research. He derives minimal financial benefit from the use of the questionnaire by clinicians. The survey is also used in research free of charge.

Dr. Golshan reports no financial or personal conflicts of interest that could inappropriately influence, or be perceived to influence the work reported here.

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