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

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Abstract

Background: Specific symptom dimensions have been used to establish phenotypic subgroups in recent genetic studies of bipolar disorder. In preparation for a genetic linkage study of childhood-onset bipolar disorder (COBPD), we conducted an exploratory analysis of the concordance of prominent symptom dimensions between sibling pairs (N=260) who screened positive for COBPD. This report presents data on the potential usefulness of these dimensions in genotyping.

Method: A principal components factor analysis was conducted on the symptoms of 2795 children who screened positive for COBPD on the Child Bipolar Questionnaire (CBQ). The resulting factors were used in a concordance analysis between 260 proband/sibling pairs and 260 proband/matched comparison pairs.

Results: Ten factors were extracted. The strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between proband/sibling vs. proband/comparison pairs, were for Factor 9 (Fear of harm), Factor 5 (Aggression), Factor 10 (Anxiety), Factor 4 (Sensory sensitivity), Factor 6 (Sleep–wake cycle disturbances), and Factor 2 (Attention/Executive function deficits). Based on factor loadings and multivariate analyses, CBQ items were selected for a “Core Index” subscale that had a robust concordance estimate in the sibpair group (rho=0.514, 95% CI 0.450–0.577) as compared to the proband-matched comparison group (rho=0.093, 95% CI 0.008 to 0.178).

Limitations: Research diagnostic interviews (K-SADS P/L) were conducted to confirm bipolar diagnosis in only a subsample (N=100) of the children whose data were used for the concordance analysis.

Conclusions: Our data suggest a profile of heritable clinical dimensions in addition to classic mood symptomatology in COBPD. These features may represent a more homogeneous phenotypic subtype of COBPD that may prove more useful for delineating the neurobiology and genetics of the disorder than standard diagnostic models.

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1. Introduction

Over the past decade, several genetic loci have been mapped in bipolar disorder (BD), including 4p, 4q, 8q, 10p, 12q, 13q, 18q, 21q and 22q (reviewed by MacQueen et al., 2005; Payne et al., 2005). However, with the exception of the disruption of the DISC1 gene, which occurs as a consequence of a rare 1:11 (q42.1; q14.3) translocation identified in a Scottish family with schizophrenia and BD (St Clair et al., 1990), no functional alleles have been unequivocally identified. In addition, independent replication at positive loci is not universal, probably because of genetic heterogeneity and a lack of homogeneous phenotypes (Faraone and Tsuang, 2003; Tsuang et al., 2004; Lin et al., 2005; MacQueen et al., 2005).

It has been suggested that age of onset could be used to separate patients into more homogeneous phenotypic subgroups for genetic studies (reviewed by Leboyer et al., 2005). One subgroup of BD that holds promise for establishing a distinct, more uniform phenotype for genetic analysis is childhood-onset bipolar disorder (COBPD). Probands with COBPD have been found to have family pedigrees with higher rates of bipolar disorder in first degree relatives, including siblings with similar age of onset (Todd et al., 1993; Leboyer et al., 1998; Bellivier et al., 2003; Chang et al., 2003; Papolos, 2003; Faroane et al., 2004a; Leboyer et al., 2005). The study of COBPD may be particularly useful in identifying structural, biochemical and functional endophenotypic markers of the illness in the brain (Frazier et al., 2005).

It has also been suggested that dimensional criteria may prove more useful than categorical definitions in etiological research (Kendell and Jablensky, 2003). 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,” the individual symptoms or constellations of symptoms associated with a condition may yield important clues to its biological underpinnings. In their recent, extensive review of the findings of clinical, epidemiological, neurobiological, and genetic studies in bipolar disorder, Hasler et al. (2006) concluded that particular symptom dimensions, deficits, and physiological and neuroanatomical anomalies deserve further research focus as candidate endophenotypes that could improve the phenotypic definition of bipolar disorder.

In genomics, the importance of the analysis of symptom dimensions as a strategy for genotyping is becoming more evident. In a recent genetic study of bipolar disorder pedigrees ascertained through adult probands, Faraone and colleagues (2004b) quantified dimensions of bipolar symptoms derived from a principal components factor analysis, determined their heritability, and used the heritable factors in a variance-components linkage analysis. More recently, Cheng et al. (2006) used both standard diagnostic models and 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 suggest that, “dissection of the disease phenotype can enrich the harvest of linkage signals and expedite the search for susceptibility genes.”

In previous work with data collected from the parents of a large sample of clinically diagnosed bipolar children (N=1601) via the Juvenile Bipolar Research Foundation (JBRF), we observed a strong relationship between frequent and intense fears about harm coming to self and others and overt aggressive acts toward self and others (Papolos et al., 2005). These data indicated that bipolar children/adolescents identified as having high fear-of-harm anxieties were 2.7-fold (RR=2.68) more likely to be identified by their parents as engaging in severely self-injurious behaviors than subjects with relatively low fear-of-harm anxieties; and these same children were 8-fold (RR=7.97) more likely to be identified as engaging in severely injurious assaults on others. There was a sharp difference in average fear-of-harm index between subjects with a clinical bipolar diagnosis (N=1601) and a sample of children in the JBRF database who did not have a clinical diagnosis of bipolar disorder (N=661) (p<0.0001).

Fear-of-harm, as a symptom dimension, appears to represent significant symptoms of anxiety and obsessiveness. Anxiety in COBPD has been the subject of several recent studies (Dilsaver and Chen, 2003; Masi et al., 2004; Post et al., 2004, Dickstein et al., 2005; Harpold et al., 2005). Consistent with Fear-of-harm as a primary symptom dimension in COBPD are findings from a recent study by Rich et al. (2006) that examined neural mechanisms mediating face processing in bipolar youth. These investigators found that in comparison to normal controls, patients perceived greater hostility in neutral faces and reported more fear when viewing them. Additionally, patients had greater activation in the left amygdala when rating face hostility, and their fear of the face, when compared to controls. Interestingly, neuroimaging findings in obsessive-compulsive disorder (OCD) and other anxiety disorders, such as social phobia, suggest parallels to the neuroimaging data in bipolar disorder (Stein et al., 2002; Mataix-Cols et al., 2003, 2004; Phillips and Mataix-Cols, 2004; Williams et
al., 2006). The comorbidity of panic and bipolar disorders has suggested to some a possible genetic subtype of bipolar illness (MacKinnon et al., 2002, 2003a,b; Rotondo et al., 2002; Cheng et al., 2006).

In order to gather preliminary data to test the hypothesis that the fear-of-harm symptom dimension may be a clinical marker germane to bipolar disorder heritability, especially COBPD heritability, we conducted an exploratory analysis of the concordance of it and other symptom dimensions between several hundred sibpairs enrolled in a JBRF-sponsored genetics study with a longitudinal component. Our findings suggest that a dimensional approach to COBPD will be an appropriate diagnostic strategy to pursue for future genetic studies.

2. Methods

2.1. Data acquisition

The JBRF has established an extensive Internet-based system for data acquisition on children clinically diagnosed with bipolar disorder. Parents and primary caregivers through national advocacy sites, online newsletters, and their children’s clinicians have entered clinical and demographic data on their children to a secure domain on the JBRF website. Parent report indicates that approximately 69% of these children have been diagnosed with bipolar disorder by a psychiatrist, psychologist, neurologist, or pediatrician in the community.

Families with more than one affected child are identified by the JBRF data acquisition program and are informed of their initial eligibility for a JBRF-sponsored genetic linkage study. Through this method, 445 affected sibling pairs were identified, including a proband and at least one full biological sibling who screened positive for bipolar disorder using the Child Bipolar Questionnaire.

2.2. Initial screening and diagnostic confirmation

The Child Bipolar Questionnaire (CBQ) is a parent-report form that was developed to assist in the rapid identification of homogeneous subgroups of children with BD (Papolos et al., 2006). The majority of the CBQ’s 65 items are drawn from DSM-IV symptom criteria for mania and major depression, but symptoms of common comorbid conditions, such as anxiety and behavior disorders, are also represented. Items are rated on a Likert scale: “1—never”, “2—sometimes”, “3—often”, or “4—very often or almost constantly”. In preliminary inquiries, the CBQ has demonstrated excellent reliability and validity in identifying subjects that meet a K-SADS diagnosis of bipolar disorder (inclusive of BPI, BPII, and BP-NOS) (Papolos et al., 2006).

The CBQ total score is the count of items rated “3” or “4”. Sibling pairs were considered initially eligible for participation in the genetic linkage study if they both scored ≥ 40 out of 65 items on the CBQ. Diagnostic confirmation of these sibling pairs by administration of the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime Version (K-SADS P/L) (Kaufman et al., 1997) is underway.

2.3. Factor analysis

In order to identify a set of prominent symptom dimensions that could be used to create homogeneous subgroups for genotyping, a series of principal component factor analyses with Varimax rotation were carried out on CBQ symptom data from the larger JBRF database of children with a CBQ total score ≥ 40 (N=2795).

2.4. Concordance analysis of factors

Concordance estimates between eligible sibpairs were then calculated for the factors resulting from the factor analysis. Multiple sibships were handled by selecting the sibling of the same sex as the proband and closest in age as the identified sibling for the concordance analysis. Inclusion criteria limited the siblings to be within 4 years of age of each other. If there was no affected sibling of the same sex as the proband, then the affected sibling of the opposite sex and closest in age was selected. For each identified affected sibpair, a comparison subject of the same age (in years) and sex as the proband was selected from the families in the database with only one child who screened positive for BD. This procedure resulted in the selection of sets of 3 subjects (probands, siblings, and non-related comparison subjects) that formed the study sample for this investigation.

Concordance estimates between responses of probands and siblings were obtained using the method of Lin (1989). This procedure yields a concordance coefficient (“rho”) and an estimate of its 95% confidence interval (95% CI). Concordance coefficients were estimated for both proband/sibling pairs and proband/comparison pairs. Because the proband/comparison concordance was dependent on the random (within age/sex category) selection of a comparison subject for each proband, we repeated the selection procedure multiple (1000) times, using bootstrap methods to obtain the estimated proband/comparison concordance.
coefficient and its standard error. These rho-estimates were then differenced to provide an estimate of the proband/sibling vs. proband/comparison concordances. An estimate of the standard error of this rho-difference estimate was obtained, and a z-statistic calculated as the ratio of the rho-difference to its standard error was obtained. The associated p-value was obtained from standard normal tables.

2.5. Concordance analysis of Y-BOCS derived fear-of-harm index

In our previous examination of the fear-of-harm symptom dimension (Papolos et al., 2005), we used a Y-BOCS measure that consisted of a count of six aggressive obsessions rated by the parent as occurring at a frequency of “3” (“often”) or “4” (“very often or almost constantly”): [1] Fear might harm self; [2] Fear might harm others; [3] Fear harm might come to self; [4] Fear will come to others (may be because of something child did or did not do); [5] Fear will act on unwanted impulses (e.g., to stab a family member); [6] Fear will be responsible for something else terrible happening (e.g., fire, burglary, flood). Where Y-BOCS data were available, this Y-BOCS-derived fear-of-harm index was included in the current concordance analysis between eligible sibpairs.

2.6. Concordance analysis of CBQ subscale of items found to correlate with fear-of-harm

In an effort to better characterize a phenotypic subgroup that had the fear-of-harm symptom dimension, a correlation analysis of CBQ items with the YBOCS fear-of-harm index was conducted to identify associated symptoms that could assist in genotyping. This analysis was limited to CBQ items not directly represented in the YBOCS data. The resulting items were used to comprise a scorable subscale of the CBQ, dubbed the Core index that was analyzed for concordance between proband/sibling and proband/comparison pairs.

2.7. General statistical methods

Averaged continuous data are reported as means with standard deviations (mean±SD) or 95% CI. Binary data are reported as N (%) or N/denominator (% with 95% CI). Some continuous variables were logarithmically transformed to achieve more nearly Gaussian distributions. Robust standard error (SE) estimates were obtained whenever feasible. Statistical significance required 2-tailed p ≤ 0.05. Analyses employed commercial microcomputer programs (Stata®, Stata Corporation, College Station, TX).

3. Results

3.1. Age and sex data

Twenty-three hundred forty-six parents provided CBQ data for 2795 children/adolescents via the JBRF internet-based system. Of these, 70% (1957) were singletons, 688 were full biological sibling pairs; and the remaining 150 children were members of multiple affected sibships. As noted in Methods, inclusion criteria limited the siblings to be within 4 years of age of each other and sibpair selection was prioritized by sex. That is, for male probands, the selection algorithm gave preference to male matching siblings, provided that the 4-year age criterion was satisfied; and similarly, for female probands, priority was assigned to female siblings. Using these methods, 260 sibpair (proband/sibling) groups were selected. Comparison subjects were randomly selected within age/sex strata from the subset of the available set of subjects that scored N≥40 on the CBQ for whom the parents did not provide data on a sibling (N=1957). The random selection resulted in 260 comparison subjects matched by age (same age by year) and sex to the probands selected for inclusion in the study sample Age/sex and previous diagnosis data for the probands/siblings/comparisons are summarized in Table 1. It is noticeable that the selection algorithm yielded a set of study triples (probands/siblings/comparisons) for whom the within-sibling age differences and sex ratios were quite minor.

3.2. Results of factor analysis of CBQ item-level data

Ten factors with eigenvalues >1.0 were identified based on CBQ data for the entire sample of 2795 subjects. These ten factors are listed in Table 2 along with their corresponding CBQ items. The factors are named based on item content. Among the symptom dimensions represented by the factors are a combination of anxiety symptoms and overt aggressive behaviors (Factor 9) that parallels our previous findings with the Y-BOCS fear-of-harm data. In addition, there is a factor representing aggressive behavior without the anxiety component (Factor 5) and one representing anxiety symptoms without the aggressive component (Factor 10).

3.3. Results of concordance analysis of 11 factors

Concordance coefficients (Lin, 1989) for these CBQ factors were estimated between probands and siblings.
Table 2
CBQ principal component factors

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Eigenvalue</th>
<th>Mean±SD</th>
<th>CBQ item content</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Oppositional/Poor frustration tolerance</td>
<td>14.0</td>
<td>8.1±2.5</td>
<td>Is intolerant of delays; Relentlessly pursues needs/demanding of others; Is willful, refuses to subordinate to others; Argues with adults; Is bossy towards others; Defies or refuses to comply with rules; Blames others for his/her mistakes; Is easily angered in response to limit setting; Has protracted, explosive temper tantrums*</td>
</tr>
<tr>
<td>II. Attention/Executive functions deficit</td>
<td>3.9</td>
<td>7.8±2.4</td>
<td>Is easily distracted by extraneous stimuli; Is easily distracted during repetitive chores; Demonstrates inability to concentrate at school; Attempts to avoid homework assignments; Able to focus well but also easily distractible; Has poor handwriting; Has difficulty organizing tasks; Has difficulty making transitions; Has difficulty estimating time; Has auditory processing/short-term memory deficit</td>
</tr>
<tr>
<td>III. Depression</td>
<td>3.6</td>
<td>5.4±2.0</td>
<td>Complains of being bored; Has periods of low energy or withdrawal; * Has decreased initiative; * Has periods of self-doubt/poor self-esteem; * Feels easily criticized and/or rejected; Feels easily humiliated or shamed; * Has made clear threats of suicide</td>
</tr>
<tr>
<td>IV. Sensory sensitivity</td>
<td>3.0</td>
<td>2.3±1.5</td>
<td>Is extremely sensitive to textures of clothes; Exhibits extreme sensitivity to sound; Complains of body temperature extremes; * Has concern with dirt, germs, contamination*</td>
</tr>
<tr>
<td>V. Aggression</td>
<td>2.5</td>
<td>4.9±2.7</td>
<td>Has difficulty maintaining friendships; Displays aggressive behavior towards Others; * Has destroyed property intentionally; Makes moderate threats to others or self; Makes clear threats of violence to others/self; Has made clear threats of suicide; Fascinated with gore, blood, violent imagery</td>
</tr>
<tr>
<td>VI. Sleep cycle problems</td>
<td>2.1</td>
<td>4.0±1.7</td>
<td>Has difficulty arising in the AM; Is hyperactive and easily excited in the PM; Has difficulty settling at night; Has difficulty getting to sleep; * Sleeps fitfully and/or awakens in the night; Has night terrors and/or nightmares*</td>
</tr>
<tr>
<td>VII. Grandiose/Hypersex</td>
<td>1.6</td>
<td>2.6±1.5</td>
<td>Has exaggerated ideas about self or abilities; Tells tall tales/embellishes or exaggerates; Displays precocious sexual curiosity; Exhibits inappropriate sexual behaviors; Lies to avoid consequences of actions*</td>
</tr>
<tr>
<td>VIII. Mania</td>
<td>1.3</td>
<td>6.5±1.9</td>
<td>Is hyperactive and easily excited in the PM; Is easily excitable has periods of high energy, frenetic activity; Has many ideas at once; * Interrupts or intrudes on others; * Has periods of excessive and rapid speech; Displays abrupt, rapid mood swings; * Has elated or silly/giddy mood states*</td>
</tr>
<tr>
<td>VIII. Fear of harm</td>
<td>1.3</td>
<td>5.2±2.8</td>
<td>Displays excessive distress when separated; * Exhibits excessive anxiety or worry; * Has night terrors and/or nightmares; * Displays aggressive behavior towards others; * Has destroyed property intentionally; Makes moderate threats to others or self; Makes clear threats of violence to others/self; Displays excessive distress when separated from family; Exhibits excessive anxiety and worry; Has night terrors and/or nightmares</td>
</tr>
<tr>
<td>X. Anxiety</td>
<td>1.1</td>
<td>1.5±1.0</td>
<td></td>
</tr>
</tbody>
</table>

* Item chosen for Core Index subscale.

a Factors identified limited to factors with eigenvalues ≥ 1.0.

b Factor summary scores (mean±SD) are based on the several CBQ items most closely correlated with each factor.
and, separately, between probands and matched comparison subjects. These data are summarized in Table 3.

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 were for Factor 9 (Fear of harm), Factor 5 (Aggression), Factor 10 (Anxiety), Factor 4 (Sensory sensitivity), Factor 6 (Sleep–wake cycle disturbances), and Factor 2 (Attention deficits). For example, for Factor 9 (Fear of harm), the proband/sibling rho estimate (0.287) was substantially larger than the corresponding proband/comparison rho estimate (0.018), and this difference was statistically significant (z=3.19, p<0.001; Table 3). Similarly, for Factor 5 (Aggression), the two estimates for rho were 0.246 vs. 0.014, and this difference was statistically significant (z=2.74, p=0.006; Table 3). It is noteworthy that all of the rho coefficients for the proband vs. comparison pairs were near zero (as expected because of the random selection of comparisons).

For several of the CBQ factors, the proband vs. sibling concordances were found to be relatively weak. For the factor assessing classic adult manic symptoms (Factor 8), the rho coefficient was smaller than 0.10, although the majority of the larger group (N=2795) were reported to often or almost always experience the eight symptoms included in this factor (Displays abrupt, rapid mood swings [88.8%], Interrupts or intrudes on others [87.4%], Has periods of high frenetic energy [84.4%], Is easily excitable [86.2%], Has elated or silly/giddy mood states [80.6%], Is hyperactive in the PM [78.8%], Has many ideas at once [76.4%], Has periods of excessive and rapid speech [73.3%]), and the mean number of these symptoms reported was 6.52. Possible reasons for this finding are examined in Discussion.

3.4. Results of concordance analysis of Y-BOCS-derived fear-of-harm index

Y-BOCS data were available on 249 sibling pairs. The concordance estimate for the Y-BOCS-derived fear-of-harm index was also substantially and significantly different from zero (rho=0.341, 95% CI 0.231–0.451, p<0.001).

3.5. Results of correlation analysis of CBQ items with fear-of-harm

We hypothesized that 17 CBQ items would be strongly associated with fear of harm in the children that screened positive for bipolar disorder: 2) exhibits excessive anxiety or worry; 8) has night terrors and/or nightmares; 41) feels easily criticized and/or rejected; 42) feels easily humiliated or shamed; 45) relentlessly pursues own needs and is demanding of others; 46) is willful and refuses to be subordinated by others; 50) blames others for his/her mistakes; 51) is easily angered in response to limit setting; 53) has protracted, explosive temper tantrums; 55) displays aggressive behavior towards others; 56) has destroyed property intentionally; 57) curses viciously, uses foul language in anger; 58) makes moderate threats to others or self; 59) makes clear threats of violence to others or self; 61) is fascinated with gore, blood, or violent imagery; 62) has acknowledged experiencing auditory and/or visual hallucinations; 64) has concern with dirt, germs, or contamination. In bivariate analyses, all 17 of these

<table>
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<tr>
<th>Table 3: CBQ factor concordance contrasted between sibpairs (proband vs. sibling) and non-sibpairs (proband vs. comparison)</th>
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<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>Factor 9 Fear of harm</td>
</tr>
<tr>
<td>Factor 5 Aggression</td>
</tr>
<tr>
<td>Factor 10 Anxiety</td>
</tr>
<tr>
<td>Factor 4 Sensory sensitivity</td>
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<td>Factor 3 Depression</td>
</tr>
<tr>
<td>Factor 7 Grandiose/ Hypersexual</td>
</tr>
<tr>
<td>Factor 8 Mania</td>
</tr>
<tr>
<td>Factor 1 Oppositional/Poor frustration</td>
</tr>
<tr>
<td>CBQ Total Score</td>
</tr>
</tbody>
</table>

* a-z-statistic obtained by generalized linear regression modeling methods, with adjustment for clustering within matched proband/sibling/control set.

* b-rho is concordance coefficient (Lin, 1989), together with its 95% confidence interval (95% CI).
CBQ items were found to be strongly correlated with the Y-BOCS-derived fear-of-harm score. All 17 of these bivariate associations, examined with Poisson modeling methods (because the fear-of-harm score is a count with Poisson-like properties), were found to be strongly statistically significant. When these 17 items were examined in a series of multivariate analyses that included age and sex to estimate their correlations with the Y-BOCS fear-of-harm indicator, 12 items were found to have the most predictive value.

3.6. Results of concordance of CBQ Core Index subscale

In addition to the 12 items that remained after multivariate analyses, 10 CBQ items were identified based on the strength of their individual correlations with the Y-BOCS-derived fear-of-harm measure, their factor loadings, and the relevance of their content. Through this method, a single scorable subscale was created that could be used to rapidly identify a phenotypic subtype. The items included in this subscale, called the “Core Index,” are listed in Table 4. The Core Index was found in preliminary investigations to have excellent validity (Papolos et al., 2006). The concordance estimate for the CBQ Core Index score (number of items rated “3—often” or “4—almost always”) was found to be quite robust in the sibpair group (rho=0.514, 95% CI 0.450–0.577). In contrast, the corresponding concordance coefficient for proband vs. matched comparison on this measure was near zero (rho=0.093, 95% CI 0.008–0.178).

4. Discussion

The methodology reported here is in keeping with the direction that a number of researchers who study the genetics of psychiatric illness have taken to further refine phenotypes for genotyping. Advances in genomics, cognitive neuropsychology, and brain imaging techniques offer new possibilities for the in vivo study of the pathophysiology of neuropsychiatric disorders, including bipolar disorder. Researchers may now combine endophenotypic markers with refined clinical correlates to establish more distinct behavioral phenotypes. The identification of symptom dimensions such as fear-of-harm, strongly concordant in sibpairs who screened positive for COBPD, may suggest endophenotypes that could prove useful in clinical and etiological research.

In this group of preliminary analyses performed in preparation for a genetic linkage study of COBPD, 10 factors were extracted from a very large set of symptom level data reported by parents of children who met initial screening criteria for bipolar disorder. These factors were then analyzed for concordance between probands and siblings. 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, were for Factor 9 (Fear of harm), Factor 5 (Aggression), Factor 10 (Anxiety), Factor 4 (Sensory sensitivity), Factor 6 (Sleep—wake cycle disturbances), and Factor 2 (Attention/Executive function deficits). None of the factors with the strongest concordance contribute to current categorical definitions of bipolar disorder. The concordance estimate for Factor 8 (Mania), which includes CBQ items representing classic adult manic symptomatology, was relatively low. Yet of the eight items included in the mania factor, the mean number rated “3—often” or “4—almost always” was 6.52 in the larger sample from with the sibpair subjects were drawn.

The explanation for this intriguing finding may involve both age- of-onset and developmental changes in symptom presentation. Systematic clinical investigations and family/genetic studies have provided increasing evidence that the clinical presentation and naturalistic course of COBPD is substantially different from the adult-onset form of the disorder (Faedda et al., 1995, 2004; Wozniak et al., 1995; McElroy et al., 1997;
fits our current understanding of CNS systems and their behavioral correlates.

4.1. Limitations and caveats

Research diagnostic interviews (K-SADS P/L) were conducted to confirm bipolar diagnosis in only a subsample \(N=100\) of the children whose data was used for the concordance analysis. For pragmatic reasons, it was impossible to conduct diagnostic interviews with the entire sample \(N=2795\) who screened positive for BD on the CBQ. Therefore, the majority of the CBQ data used in the principal components analysis and in the concordance estimates is contingent upon accuracy of parent report. The CBQ has been validated against the K-SADS P/L \(k=0.84\), and recent research demonstrates a positive association between parent-rated mania symptoms and consensus BD diagnosis in adolescents (Hunt et al., 2005).

4.2. Conclusions

Traditionally, diagnostic definitions of bipolar disorder embedded in our psychiatric nomenclature have embodied the Kraepelinian concepts of mania and depression. Contemporary categorical distinctions between BD subtypes have been primarily concerned with episode duration and the presence or absence of classic manic symptoms. Standard diagnostic interviews are designed to make categorical decisions based on these definitions while either subsuming symptom dimensions not considered central to the construct of bipolar disorder or diagnosing them as central to a comorbid disorder. Thus, our assessment tools continue to support the current categorical definitions, perhaps masking information that might be crucial to understanding the etiology of the disorder. The use of rating scales covering multiple symptom dimensions allows symptoms that might be viewed as frequently co-occurring, but not central to a disorder, to become a focus of study. Our data suggest a heritable profile of clinical dimensions in COBPD that parallels commonly observed features of adult-onset bipolar disorder. Although not included in the categorical definition of mania, these symptom dimensions are consistent with evidence from diverse fields of inquiry implicating anomalies in a neural circuit involving the amygdala and the anterior cingulate cortex in the neurobiology of bipolar disorder (Davidson, 2000; Hariri et al., 2000, 2003; Allman et al., 2001; Phan et al., 2002; Strakowski et al., 2004; Haller et al., 2005; Blumberg et al., 2005; Chen et al., 2006; Rich et al., 2006). As phenotypic features, they may,
therefore, assist in identifying a homogeneous subtype of COBPD that could provide a more optimal venue for delineating the genetics of the disorder.

References


