Juvenile Bipolar Research Foundation

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# Behavioral Dimensions of a Core Phenotype of Pediatric Bipolar Disorder

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## Background

In 2001, an NIMH Roundtable on Prepubertal Bipolar Disorder recommended that the DSM-IV diagnosis: Bipolar Disorder, Not Otherwise Specified (BP-NOS) serve as a "working diagnosis" for studies of children who suffer severe mood disturbance but present differently than adults. The Roundtable cautioned, however, that the dimensions of impairment associated with marked mood disturbance in children, including attention deficits, anxiety symptoms, and aggressive behavior, need further investigation (Special Communication, 2001). Since then, an NIMH intramural program has proposed the Narrow, Broad and Intermediate phenotypes to form more specific diagnostic categories (Liebenluft, 2003). We propose an additional phenotype that combines established DSM-IV categories with the specific functional impairments observed in a large sample of children with incipient or fully progressed juvenile-onset bipolar disorder. The hallmark features of this Core phenotype include not only mood symptoms but accompanying behavioral dimensions, including poor modulation of aggression, poor frustration tolerance, low threshold for anxiety, and attention/executive function deficits (Figure 1). The inclusion of specific functional impairments in the diagnostic criteria set of the Core phenotype is an effort to reduce what is, in our view, an unfortunate splintering of the dimensions of a single condition into multiple diagnoses with disparate, potentially counterproductive treatment approaches. This report summarizes the findings of a factor analysis of behavioral symptoms reported by parents who completed an online questionnaire on their children, the majority of whom carried a community diagnosis of bipolar disorder.

## Methods

Via a secure, internet-based data acquisition system established and maintained by the Juvenile Bipolar Research Foundation (JBRF), data were collected on 2,795 subjects screened for bipolar disorder using the Child Bipolar Parent Questionnaire (CBQ) (Papolos and Papolos, 2002). Items on the CBQ are keyed to the behavioral features of several DSM-IV categories for childhood and adult psychiatric disorders including separation anxiety disorder, generalized anxiety disorder, phobias, obsessive compulsive disorder, oppositional defiant disorder, conduct disorder, attention-deficit disorder, major depression and bipolar disorder. These items were selected from a larger behavioral checklist because of their frequency of endorsement by parents of a clinical sample of children diagnosed with bipolar disorder using DSM-IV criteria.

CBQ data were analyzed using factor analytic methods with Varimax rotation. Six factors with eigenvalues > 1.0 were extracted in the factor analysis. The CBQ items most strongly loading on these six factors are summarized in Table 1. Inspection of these items suggested 6 dimensions of impairment, provisionally labeled as follows:

1. Aggression/poor frustration tolerance
2. Attention/executive function deficit
3. Depression/dysphoria
4. Fear of harm/lparanoia
5. Social anxiety/inhibition
6. Sleep/wake cycle disturbances

These 6 dimensions of impairment were correlated with a bipolar diagnosis indicator ("BPD") in a subsample with a community diagnosis of bipolar disorder (N=1945, 69.9%). We then looked at how these dimensions correlated with DSM-IV diagnoses from KSADS-P/L interviews conducted with 65 of these subjects. Finally, we contrasted factor scores based on the 6 factors among the three phenotypes proposed as diagnostic alternatives to DSM-IV Bipolar Disorder for categorizing juvenile-onset bipolar disorder.

## Results

Four factors were found to discriminate between children with and without a community diagnosis of bipolar disorder (see Table 2). These were Factor 1 (aggression/poor frustration tolerance), Factor 4 (fear of harm/paranoia), Factor 5 (social anxiety/inhibition) and, in the opposite direction, Factor 6 (sleep disturbance). The dimensions of impairment found to have the strongest associations with a community diagnosis of bipolar disorder were aggressive behaviors/poor frustration tolerance (Factor 1) and fear-of-harm/paranoia (Factor 4).

In subjects who received a DSM-IV diagnosis of bipolar disorder on the KSADS-P/L, we found significant associations between impairment in attention/executive function (Factor 2) and a comorbid diagnosis of Attention Deficit Hyperactivity Disorder ($p < .003$) and between aggression/poor frustration tolerance (Factor 1) and a comorbid diagnosis of Oppositional Defiant Disorder ($p < .03$).

Impairment in the dimension of aggression/poor frustration tolerance strongly discriminated the Narrow and Core phenotypes from the Broad. The correlations of the 6 factors with each of these phenotypes are summarized in Table 3.

## Conclusions

In a large dataset of children screened for bipolar disorder, we found substantial evidence of the validity of a "Core" phenotype of pediatric bipolar disorder with hallmark features including poor modulation of aggression and fear of harm. These dimensions of impairment were successfully able to discriminate children with a community diagnosis of bipolar disorder from those without. Preliminary data from a small subsample for whom we have DSM-IV diagnoses provides evidence supporting these dimensions of impairment in the form of comorbid disorders.

The role of aggression/poor frustration tolerance in differentiating the Narrow and Core phenotypes from the Broad was intriguing in light of the centrality of explosive rage and aggression to the diagnosis of the Broad phenotype, which excludes elation/grandiosity. This finding may be explained by the prevalence of aggression reported on the CBQ, even for subjects satisfying the Narrow phenotype requirement of elation and/or grandiosity. It appears that parents of the large majority of subjects in this dataset reported both elation and aggression in their children, thus excluding them from a Broad phenotype diagnosis. This is consistent with our view, represented in the Core phenotype diagnostic criteria, that poor modulation of aggression is pathognomonic of juvenile-onset bipolar disorder as is (hypo)manic mood.

As recommended by the NIMH Roundtable in 2001, a further understanding of the dimensions of bipolar disorder as it presents in children will lead to more accurate and more parsimonious diagnosis and treatment.

**References**

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Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. (2003) Defining clinical phenotypes of juvenile mania. Am J Psychiatry, 160(3):430-437.
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## Table 1.

CBQ factor structure

| Factor and Items | Loading | % of Overall Variance: This factor | Cumulative |
|---|---|---|---|
| 1. Aggression/poor frustration tolerance | ---- | 44.9% | 44.9% |
| 49. defies or refuses to comply with rules | 0.556 | | |
| 47. argues with adults | 0.549 | | |
| 46. willful and refuses to be subordinated | 0.549 | | |
| 58. makes moderate threats to others/self | 0.522 | | |
| 29. tells tall tales | 0.512 | | |
| 55. aggressive behavior towards others | 0.512 | | |
| 56. has destroyed property intentionally | 0.499 | | |
| 2. Attention/executive function deficit | | 11.3% | 56.2% |
| 17. has difficulty organizing | 0.436 | | |
| 13. inability to concentrate | 0.416 | | |
| 12. easily distracted | 0.399 | | |
| 16. poor handwriting | 0.390 | | |
| 14. avoids homework | 0.310 | | |
| 49. defies/refuses to comply with rules* | –0.302 | | |
| 3. Depression/dysphoria | | 10.2% | 66.4% |
| 40. experiences self-doubt, poor self-esteem | 0.416 | | |
| 41. easily feels rejected | 0.353 | | |
| 4. hyperactive in p.m.* | –0.418 | | |
| 25. high frenetic energy* | –0.418 | | |
| 24. easily excitable* | –0.399 | | |
| 4. Fear of harm/paranoia | | 8.1% | 74.5% |
| 8. has night terrors | 0.358 | | |
| 62. experienced auditory/visual hallucinations | 0.334 | | |
| 64. concerned with dirt/germs/contamination | 0.261 | | |
| 60. has made clear threats of suicide | 0.264 | | |
| 2. excessive anxiety/worry | 0.140 | | |
| 17. has difficulty organizing tasks* | –0.193 | | |
| 5. Social anxiety/inhibition | | 6.6% | 81.1% |
| 41. feels easily rejected | 0.398 | | |
| 42. feels easily humiliated | 0.377 | | |
| 42. self-doubt/poor self-esteem | 0.301 | | |
| 2. excessive anxiety/worry | 0.290 | | |
| 36. takes excessive risks* | –0.196 | | |
| 35. inappropriate sexual behaviors* | –0.195 | | |
| 34. precocious sexual curiosity* | –0.163 | | |
| 6. Sleep/wake cycle disturbances | | 5.2% | 86.3% |
| 6. has difficulty getting to sleep | 0.582 | | |
| 5. has difficulty settling at night | 0.551 | | |
| 3. has difficulty arising in the morning | 0.296 | | |
| 7. sleeps fitfully/awakens in middle of night | 0.199 | | |
| 39. has decreased initiative | 0.193 | | |

*Items marked with * have negative factor loadings.

## Table 2.

Summary factor scores—by community diagnosis of bipolar disorder

| Factor | Community Diagnosis: Present | Absent | z | p |
|---|---|---|---|---|
| 1. Aggression | 0.14 ± 0.90 | –0.31 ± 1.05 | 11.6 | <0.001 |
| 2. Attention | 0.04 ± 0.89 | –0.10 ± 1.03 | 1.38 | 0.17 |
| 3. Depression | 0.04 ± 0.88 | –0.09 ± 1.04 | 0.01 | 0.99 |
| 4. Fear of harm/paranoia | 0.05 ± 0.91 | –0.11 ± 0.91 | 4.48 | <0.001 |
| 5. Social anxiety/inhibition | 0.03 ± 0.87 | –0.08 ± 0.95 | 2.28 | 0.023 |
| 6. Sleep disturbance | –0.03 ± 0.88 | 0.07 ± 0.89 | –4.97 | <0.001 |

Among subjects with sufficient CBQ data to form the 6 factors, there were N=1945 subjects with a community diagnosis of bipolar disorder, and N = 838 subjects absent this diagnosis.
Z-statistics and p-values estimated by multivariate linear modeling with adjustment for age and sex.

## Table 3.

Summary factor scores—among three proposed phenotypes

| | Proposed Phenotype: Narrow | | Broad | | Core | |
|---|---|---|---|---|---|---|
| Factor | z | p | z | p | z | p |
| 1. Aggression | 21.2 | <0.001 | 8.47 | <0.001 | 11.8 | <0.001 |
| 2. Attention | 0.34 | 0.73 | –0.39 | 0.70 | 0.44 | 0.66 |
| 3. Depression | –10.8 | <0.001 | –4.31 | <0.001 | 3.88 | <0.001 |
| 4. Fear of harm | –0.02 | 0.99 | –1.09 | 0.28 | –2.43 | 0.015 |
| 5. Social inhibition | –0.38 | 0.70 | –3.81 | <0.001 | –5.13 | <0.001 |
| 6. Sleep disturbance | 1.57 | 0.12 | 1.20 | 0.23 | 0.18 | 0.85 |

Z-statistics and p-values estimated by multivariate linear modeling with adjustment for age and sex.

## Figure 1. A Core Phenotype for Pediatric Bipolar Disorder

### Core Phenotype Diagnostic Criteria

**Must meet Criteria A-D for diagnosis**

A. Episodic and abrupt transitions in mood states accompanied by rapid alternations in levels of arousal, emotional excitability, sensory sensitivity, and motor activity. Manic/hypomanic or mixed episode required for diagnosis. Episodes are defined by DSM-IV symptom criteria but not by DSM-IV duration criteria.

B. Poor modulation of drives (aggressive, sexual, appetitive, acquisitive) resulting in behaviors that are excessive for age and/or context: aggressive/fight-based behaviors and/or self-directed aggression, fear/flight-based behaviors, premature and intense sexual feelings and behaviors, excessive craving for carbohydrates and sweets, and poor control over acquisitive impulses.

Criteria A and B are present most days for at lease 12 months, without any symptom free periods exceeding 2 months in duration, and cause functional impairment in 1 or more settings (e.g., significant behavioral problems at home but not necessarily in the school setting).

C. Four (or more) of the following disturbances have been present during the same 12 month period:
   1. Excessive anger and oppositional/aggressive responses to situation that elicit frustration.
   2. Poor self-esteem regulation.
   3. Sleep/wake cycle disturbances; at least one of the following: 1) Sleep discontinuity 2) sleep arousal disorders 3) Sleep/wake reversals
   4. Fear of harm/low threshold for anxiety.
   5. Disturbance in the capacity to habituate to sensory stimuli often when exposed to novel, repetitive or monotonous sensory stimulation; thermoregulatory disturbance.
   6. Executive Function Deficits; One or more of the following: 1) Mental Inflexibility, 2) Emotional Inflexibility, 3) Inflexibility of Motor Activity.
   7. A family history of recurrent mood disorder and/or alcoholism, as well as other bipolar spectrum disorders.

D. Symptoms are not due to a general medical condition (e.g. hypothyroidism).