Endophenotypes of a Core Phenotype of Pediatric Bipolar Disorder

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Background
Dimensional analysis of symptoms, neuropsychological testing, and neuromaging may reveal useful endophenotypic markers for identifying more homogeneous subtypes of childhood-onset BD. In a recent, extensive review of the findings of clinical, epidemiological, neurological, and genetic studies in bipolar disorder, Hawel et al (2006) concluded that attention deficits, deficits in working memory and learning, circadian rhythm instability, reduced anterior cingulate volume, and early-onset white matter abnormalities deserve further research as candidate endophenotypes that could improve the phenotypic definition of bipolar disorder. The Juvenile Bipolar Research Foundation (JBRF) has sponsored studies investigating the genetics, neuropsychology, neuroanatomy and clinical phenomenology of juvenile-onset BD. We report here on findings that support the proposal of a phenotypic subtype – the Core phenotype – characterized by ultra rapid cycling, attentional disturbance, behavioral aggression, and intense anxiety, as well as by specific neuropsychological deficits and neuroanatomical anomalies.

Method
Child Bipolar Questionnaire (CBQ) data were obtained on a sample of 2795 children aged 7-17 whose parents participated in the JBRF data acquisition program. These data were used in a principal component factor analysis with Varimax rotation to identify core symptom dimensions. The resulting factors were then analyzed for concordance between 339 affected sibling pairs enrolled in a JBRF-sponsored genetic study. A battery of neuropsychological tests was conducted with a subsample of subjects aged 7-11 with BD (N=44) and a second group with ADHD and no mood disorder (N=41) for a study of group differences. Of these study participants, 12 with BD were studied with structural MRI that included volumetric measurements of gray matter and diffusion tensor imaging of white matter tracts.

Results
Eleven clinical factors were identified with eigenvalues >1: poor frustration modulation of aggression, and dysregulation of arousal. A Core Index comprised of symptoms with high loadings on the most prominent factors was strongly concordant (rho=.514) between affected sibling pairs (see Table 1). Neuropsychological testing revealed a profile of deficits in sustained attention, verbal learning and memory, circadian rhythm instability, and reduced anterior cingulate volume, and early-onset white matter abnormalities described by several studies in clinical and preclinical populations. The clinical and neuropsychological profiles of the Core phenotype—deficits in threat perception, regulation of aggression and arousal states, motor control and sustained attention—are consistent with evidence from diverse fields of inquiry implicating anomalies in a neural circuit involving the amygdala and the anterior cingulate cortex, the structures found to be anomalous in the neuromaging findings reported here. The core phenotype may, therefore, represent a more homogeneous subtype of early-onset BD that could provide a more optimal venue for delineating the neurobiology of the disorder.

Conclusions
Contemporary categorical distinctions between BD subtypes have been primarily concerned with episode duration and the presence or absence of classic manic symptoms. Our data suggest a profile of clinical dimensions, cognitive deficits, and structural abnormalities associated with childhood-onset BD in addition to classical mood symptomatology. The clinical and neuropsychological profiles of the Core phenotype—deficits in threat perception, regulation of aggression and arousal states, motor control and sustained attention—are consistent with evidence from diverse fields of inquiry implicating anomalies in a neural circuit involving the amygdala and the anterior cingulate cortex, the structures found to be anomalous in the neuromaging findings reported here. The core phenotype may, therefore, represent a more homogeneous subtype of early-onset BD that could provide a more optimal venue for delineating the neurobiology of the disorder.

Table 1.
GBQ Core Index Content
1) displays excessive distress when separated from family
2) exhibits excessive anxiety or worry
3) has difficulty getting to sleep
4) has night terrors and/or nightmares
5) displays social blunting
6) complains of body temperature extremes or feeling hot despite neutral ambient temperature
7) has many ideas at once
8) interrupts or intrudes on others
9) displays abrupt, rapid mood swings
10) has irritable, grumpy, irritable/mood states
11) takes excessive risks
12) has periods of low energy and/or withdrawal or isolates self
13) has decreased initiative
14) experiences periods of self doubt and poor self-esteem
15) feels easily overwhelmed or overwhelmed
16) has anxiety about height and/or weight disturbances
17) displays aggressive behavior towards others
18) has acknowledged experiencing auditory and/or visual hallucinations
19) fears ants or anxiety about insects or food
20) has concerns with dirt, germs, or contamination

Table 2.
Comparison of Neuropsychological Tests between Pediatric Bipolar Group (n = 33) and ADHD-only Group (n = 20).

Test | Mean (sd) | PBD | ADHD | Difference in mean (se) | 95% confidence interval | p
--- | --- | --- | --- | --- | --- | ---
WISC-IV Processing Speed Index | 89 (13) | 104 (11) | -15 (4) | (22, -4) | 0.001
CPS II

Non-Preferred Hand  | 88 (20) | 98 (11) | -10 (4) | (-19, -2) | 0.020
Inhibition/Switching  | 7.1 | 9.5 (3.4) | -2.4 (1.1) | (-4.6, -0.2) | 0.033
Word Reading  | 8.7 | 11.0 | -2.3 (0.9) | (-4.1, -0.6) | 0.009
Color Naming  | 7.8 | 10.7 | -2.9 (1.0) | (-4.8, -1.0) | 0.004
Delayed Recognition  | -0.17 | 0.50 | -0.67 (0.2) | (-1.1, -0.2) | 0.004
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Figure 1
Highly significant correlations of amygdala and hippocampal asymmetry with decreased FA were identified in children with identical white matter regions. These areas include bilateral parietal white matter (figure 1, thin arrows), bilateral prefrontal white matter (figures 1 and 2, wide arrows), an area of anterior-occipital white matter (figure 2, thin arrow), right medial temporal white matter (figure 3, large arrow), and inferior frontal white matter adjacent to olfactory cortex (figure 3, small arrow).

Figure 2

Figure 3