Juvenile Bipolar Research Foundation

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Endophenotypes of a Core Phenotype of Pediatric Bipolar Disorder

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Background

Dimensional analysis of symptoms, neuropsychological testing, and neuroimaging 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, neurobiological, and genetic studies in bipolar disorder, Hasler et al (2006) concluded that attention deficits, deficits in verbal learning and memory, circadian rhythm instability, reduced anterior cingulate volume, and early-onset white matter abnormalities deserve further research focus 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 5-17 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 7-15 with BD (N=39) and a second group with ADHD and no mood disorder (N=21) 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 tolerance, attention deficit, depression, dysregulation of arousal, poor modulation of aggression, circadian rhythm instability, grandiosity/hypersexuality, mania, anxiety/aggression (fear of harm), anxiety/non-aggressive. All but two of the concordance coefficients differed significantly from zero. Concordances were strongest for fear of harm, poor 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, mobilization of arousal, and motor sequencing in the BD group as compared to the ADHD-only group (See Table 2). Neuroimaging revealed significant asymmetry of several medial temporal lobe structures in all 12 individuals in the BD subsample (See Figures 1-3). Left side amygdala, right anterior hippocampus and right anterior and mid cingulate cortex were significantly asymmetrically smaller than their contralateral homologues, a finding not present in normal young subjects. Additionally, loss of white matter integrity was detected as lower fractional anisotropy (FA) in prefrontal and right temporal white matter using DTI.

Limitations

Diagnoses based on clinical interview (K-SADS P/L) are available only on those children who participated in neuropsychological and neuroimaging studies. While considered initially eligible for the genetic study based on CBQ score, only a subset of sibling pairs have been interviewed as yet. The CBQ has been validated against the K-SADS P/L (k=.84).

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 classic mood symptomatology. The clinical and neuropsychological dimensions 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 neuroimaging 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.

CBQ Core Index Item Content

1) displays excessive distress when separated from family
2) exhibits excessive anxiety or worry
6) has difficulty getting to sleep
8) has night terrors and/or nightmares
10) craves sweet-tasting foods
23) complains of body temperature extremes or feeling hot despite neutral ambient temperature
26) has many ideas at once
27) interrupts or intrudes on others
31) displays abrupt, rapid mood swings
32) has irritable mood states
33) has elated or silly, goofy, giddy mood states
36) takes excessive risks
38) has periods of low energy and/or withdraws or isolates self
39) has decreased initiative
40) experiences periods of self doubt and poor self-esteem
42) feels easily humiliated or shamed
52) lies to avoid consequences of his/her actions
53) has protracted, explosive temper tantrums
55) displays aggressive behavior towards others
62) has acknowledged experiencing auditory and/or visual hallucinations
63) hoards or avidly seeks to collect objects or food
64) has concern 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	Mean (sd) ADHD	Difference in mean (se)	95% confidence interval	p
WISC-IV					
Processing Speed Index	89 (15)	104 (11)	-14 (4)	(-22, -6)	0.001
CPT-II					
No. of Omissions	58 (17)	46 (6)	13 (3)	(6, 19)	< 0.001
Hit RT	56 (14)	46 (12)	10 (4)	(3, 17)	0.008
Hit RT Standard Error	56 (12)	45 (9)	12 (3)	(5, 18)	0.001
Variability	54 (11)	44 (9)	10 (3)	(4, 16)	0.002
Response Style B	55 (13)	48 (7)	7 (3)	(1, 14)	0.028
Perseverations	53 (14)	47 (3)	6 (2)	(1, 11)	0.015
Hit RT ISI Change	58 (13)	46 (6)	12 (3)	(7, 18)	< 0.001
Hit SE ISI Change	54 (9)	46 (7)	8 (2)	(3, 13)	0.001
CVLT					
Short Delay Free Recall	-0.58 (1.1)	0.25 (0.8)	-0.83 (0.3)	(-1.4, -0.2)	0.006
Short Delay Cued Recall	-0.64 (1.1)	0.25 (1.1)	-0.88 (0.3)	(-1.5, -0.3)	0.006
Long Delay Free Recall	-0.67 (1.1)	0.30 (1.0)	-0.97 (0.3)	(-1.6, -0.3)	0.003
Long Delay Cued Recall	-0.53 (1.1)	0.08 (0.8)	-0.60 (0.3)	(-1.2, -0.03)	0.039
Delayed Recognition Hits	-0.17 (1.1)	0.50 (0.5)	-0.67 (0.2)	(-1.1, -0.2)	0.004
Response Bias	-0.48	0.13	-0.61)0.3)	(-1.2, -0.03)	0.039
DKEFS Color-Word Interference					
Color Naming	7.8 (4.1)	10.7 (2.9)	-2.9 (1.0)	(-4.8, -1.0)	0.004
Word Reading	8.7 (3.7)	11.0 (2.5)	-2.3 (0.9)	(-4.1, -0.6)	0.009
Inhibition/Switching	7.1 (4.1)	9.5 (3.4)	-2.4 (1.1)	(-4.6, -0.2)	0.033
Purdue Pegboard					
Non-Preferred Hand	88 (20)	98 (11)	-10 (4)	(-19, -2)	0.020
Both Hands	85 (16)	93 (13)	-8.8 (4.3)	(-17, -0.2)	0.045

Figures 1-3.

Highly significant correlations of amygdala and hippocampal asymmetry with decreased FA were identified in several subcortical 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 parieto-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).

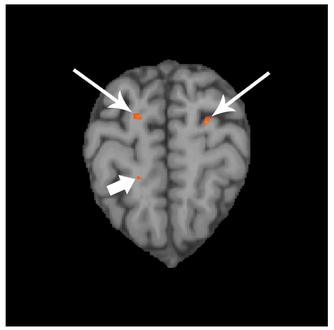

Figure 1

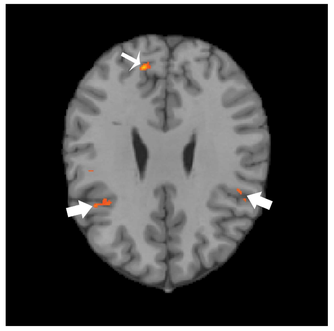

Figure 2

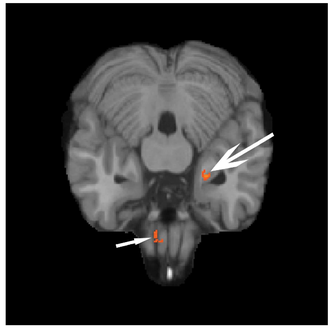

Figure 3