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Research report

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.

Keywords: Childhood-onset bipolar disorder; Pediatric bipolar disorder; Sib-pair concordance; Behavioural phenotype; Anxiety; Aggression; Child Bipolar Questionnaire

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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