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Research report

Dimensional endophenotypes in bipolar disorder: Affective dysregulation and psychosis proneness

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ABSTRACT

Background: The clinical phenotype of bipolar disorder (BPD) is heterogeneous and the genetic architecture of the disorder is complex and not well understood. Given these complications, it is possible that the identification of intermediate phenotypes ("endophenotypes") will be useful in elucidating the complex genetic mechanisms that result in the disorder. The examination of unaffected relatives is critical in determining whether a particular trait is genetically-relevant to BPD. However, few dimensional traits related to BPD have been assessed in unaffected relatives of patients.
Methods: We assessed affective temperament and schizotypy in 55 discordant sibling pairs and 113 healthy controls (HCs) using the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego, Auto-questionnaire version (TEMPS-A) to assess affective temperament and the Schizotypal Personality Questionnaire (SPQ) to assess schizotypy.
Results: BPD patients scored significantly higher than HCs on all subscales of the SPQ and on all but one subscale (hyperthymic) of the TEMPS-A (all $p < 0.01$). Siblings demonstrated scores that were significantly intermediate to patients and HCs on the anxious subscale of the TEMPS-A and on the interpersonal deficits and disorganized subscales of the SPQ.
Limitations: We did not investigate the BPD spectrum as most patients were diagnosed with BPD I ($n=47$). Most of the patients had experienced psychosis ($n=42$) and so we were unable to examine whether psychosis status impacted upon affective temperament or schizotypy in patients or their siblings.
Conclusion: These data suggest that schizotypy and affective temperament represent dimensional traits that are likely to underlie the genetic risk for BPD.

1. Introduction

Proneness to psychopathology can be conceptualized from the perspective of quantitative genetic models, such that variability along dimensional traits contributes to an individual's risk for developing a clinical disorder. The identification of genetically-relevant dimensional traits is an important step in understanding the functional relevance of risk variants. Bipolar disorder (BPD), in particular, has repeatedly been found to be associated with characteristic variations in personality and temperament (e.g. Savitz and Ramesar, 2006). Less is known, however, about the endophenotypic status of such variations and, specifically, whether unaffected relatives of patients with BPD demonstrate similar alterations in personality and temperament. Moreover, few studies have examined how different aspects of temperament may be related to one another within and across patients, relatives, and healthy participants.

Temperament is comprised of a complex set of traits reflecting, among other things, one's general activity level, worldview, and interpersonal style. Two important aspects of this construct that have been found to be associated with risk for psychopathology are affective temperament (e.g. Akiskal and Mallya, 1987; Cassano et al., 1992) and psychosis proneness (Claridge et al., 1996; Raine, 1991; Rossi and Daneluzzo, 2002). Decades of research by Akiskal and others have led to the delineation of five main affective temperaments: hyperthymic, cyclothymic, depressive, irritable, and anxious (e.g. Akiskal, 1998; Akiskal and Mallya, 1987; Placidi et al., 1998). When compared with healthy controls, patients with BPD have been found to have higher rates of affective temperaments when viewed as a categorical measure (e.g. Kesebir et al., 2005) and to have higher scores on measures that assess for such temperaments (Aguiar Ferreira et al., 2012; Evans et al., 2005; Gandotra et al., 2011; Mendlowicz et al., 2005; Savitz et al., 2008a).

Several studies support the familial aggregation of affective temperaments among relatives of BPD patients (Akiskal et al., 1985;

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Evans et al., 2005; Gandotra et al., 2011; Kesebir et al., 2005; Mendlowicz et al., 2005; Savitz et al., 2008b; Vázquez et al., 2008). However, although many studies have reported significantly increased affective temperaments among patients compared to controls, studies involving relatives have yielded less consistent results. One study to date has demonstrated a gradient, consistent with the heritability of risk for bipolar disorders, with BPD patients having the highest rates of cyclothymic temperament, followed by their unaffected relatives, and then by unrelated healthy controls (Mendlowicz et al., 2005). Several other studies have not found any differences in cyclothymic temperament between unaffected relatives and controls (Aguiar Ferreira et al., 2012; Evans et al., 2005) but have reported elevations in patients compared to relatives (Savitz et al., 2008b). Another study of healthy relatives of patients with BPD reported elevations in affective temperaments among the relatives compared to controls for the dysthymic, cyclothymic, irritable, and anxious temperaments but reported null results for the hyperthymic temperament (Vázquez et al., 2008). The directionality of findings for the hyperthymic temperament has also been inconsistent, with some studies finding that patients and relatives have elevated levels of hyperthymia compared to controls (Gandotra et al., 2011; Kesebir et al., 2005), other studies reporting that controls are elevated on this subscale (Evans et al., 2005), and several studies reporting no significant differences in hyperthymia between patients, relatives, and controls (Mendlowicz et al., 2005) or between relatives and controls (Aguiar Ferreira et al., 2012; Vázquez et al., 2008).

One possible reason for the discrepancies between the findings is the inclusion of parents and offspring, in addition to siblings, in the samples of first degree relatives. The inclusion of parents allows for the possibility that some of the included relatives did not contribute hereditary risk for BPD to the proband. The inclusion of offspring may be problematic in that some young adults may themselves go on to develop BPD but may be too young to have developed the full phenotype. As the majority of patients have developed the disorder by age 25, and siblings tend to develop the disorder at around the same age as probands (Bellivier et al., 2003), restricting unaffected first-degree relatives to siblings past the age of 25 and approximately the same age or older than the age of illness onset in their affected sibling may be the most powerful design from which to examine the endophenotypic nature of temperamental traits.

Another temperamental aspect that may be related to risk for BPD is schizotypy, a personality type marked by odd, irritable, socially isolated, and hypersensitive behaviors (e.g. Raine, 1991). There is some evidence that schizotypy ratings are elevated in patients as well as in their healthy relatives (Kendler et al., 1995) compared to controls, indicating a relationship with genetic risk. Schizotypy may also be thought of as psychosis proneness, as several lines of evidence suggest that individuals who rate high on schizotypy are at increased risk for developing psychosis (Claridge et al., 1996). Given that approximately 50–70% of patients with BPD I exhibit psychotic symptoms during mood episodes (Goodwin and Jamison, 2007), it would be expected that patients with BPD are elevated on this trait. Indeed, limited data suggest that BPD patients score higher than healthy controls on measures of schizotypy (Rossi and Daneluzzo, 2002) although replication of these results is required. Given these data, psychosis proneness may be a candidate endophenotype for BPD. To date, however, there have been few studies of this trait in family members of BPD patients. In one study of unaffected relatives of patients with BPD and schizophrenia, psychosis proneness scores did not differ between the two groups (Schürhoff et al., 2005). Furthermore, psychosis proneness was found to be elevated in relatives of BPD patients with psychosis compared to relatives of BPD patients without psychosis (Schürhoff et al., 2005). In order to examine the endophenotypic status of this trait, however, an examination of patients, relatives, and controls is required.

In the present study, we aimed to further clarify the relationship between affective temperamental traits, psychosis proneness, and the genetic susceptibility for bipolar disorder by examining patients with BPD and their unaffected siblings and comparing them with unrelated healthy controls. We hypothesized that affective temperament and psychosis proneness would demonstrate a gradient, such that levels of each were highest in patients, intermediate in unaffected siblings, and lowest in healthy controls. We also expected that affective temperament and psychosis proneness would be strongly correlated within each of the three groups. Finally, we expected that unaffected siblings of probands with psychosis would have elevated levels of psychosis proneness compared to siblings of probands without psychosis.

2. Methods

2.1. Sample

Fifty-five sibling pairs discordant for Bipolar Disorder participated in the study, along with 113 healthy control participants. Of the 55 patients with BPD who participated in the study, 47 were diagnosed with Bipolar I Disorder, 5 were diagnosed with Bipolar II Disorder, and the remaining 3 patients were diagnosed with Bipolar Disorder NOS as determined using the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 1994). None of the patients were related to one another and all were clinically stable outpatients at the time of the assessment. Patients who expressed an interest in the study were asked to contact their unaffected siblings who might also be interested in participating; these unaffected siblings then contacted the study team. Siblings were at least 25 years of age and were at least two years older than the age of onset in their affected sibling. In addition, unaffected siblings were free from any major Axis I mood or psychotic disorder as determined by the SCID. Eight of the siblings were diagnosed with Depressive Disorder NOS and an additional three subjects in the unaffected sibling group were diagnosed with an anxiety disorder. All healthy volunteers were free from any current or lifetime Axis I diagnoses, as determined by the SCID-NP, and did not have any first degree relatives with any Axis I disorder. A diagnostic consensus conference involving psychologists and psychiatrists reviewed the SCID interview for each participant to confirm the diagnosis of Bipolar Disorder in patients and to screen for Axis I disorders in unaffected siblings and healthy controls. All participants denied substance abuse or dependence in the three months prior to their participation. All procedures were approved by the local IRB and written informed consent was obtained from all participants.

2.2. Measures

Temperament was assessed using the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego, Auto-questionnaire version (TEMPS-A) (Akiskal et al., 2005). This self-report questionnaire consists of true/false items relating to how one generally acts and assesses five empirically-derived affective temperaments thought to confer vulnerability to mood disorders: cyclothymic (i.e. tendency to have abrupt changes in mood as well as exaggerated mood states), dysthymic, irritable, hyperthymic (i.e. tendency toward extraversion, expansive mood, cheerfulness, etc.), and anxious.

Psychosis proneness was assessed in all participants using the Schizotypal Personality Questionnaire (Raine, 1991). This self-report questionnaire assesses three main factors associated with schizotypy: (1) the cognitive-perceptual deficits factor is