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Factor analysis of temperament and personality traits in bipolar patients: Correlates with comorbidity and disorder severity

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ABSTRACT

Background: Temperament and personality traits have been suggested as endophenotypes for bipolar disorder based on several lines of evidence, including heritability. Previous work suggested an anxious-reactive factor identified across temperament and personality inventories that produced significant group discrimination and could potentially be useful in genetic analyses. We have attempted to further characterize this factor structure in a sample of bipolar patients.

Methods: A sample of 1195 subjects with bipolar I disorder was evaluated, all with complete data available. Dimension reduction across two inventories identified 18 factors explaining 39% of the variance.

Results: The two largest factors reflected affective instability and general anxiety/worry, respectively. Subsequent analyses of the clinical features associated with bipolar disorder revealed specificity for the factors in a predictable pattern. Cluster analysis of the factors identified a subgroup defined by a strong lack of general anxiety and low affective instability represented by the first two factors. The remaining subjects could be distinguished into two clusters by the presence of either more positive characteristics, including persistence/drive, spirituality, expressivity, and humor, or more negative characteristics of depression and anxiety.

Limitations: These analyses involved bipolar I subjects only and must be extended to other bipolar spectrum diagnoses, unaffected relatives, and individuals at risk.

Conclusions: These results suggest that temperament and personality measures access latent traits associated with important clinical features of bipolar disorder. By translating clinical variables into quantitative traits, we may identify subgroups of bipolar patients with distinct clinical profiles, thereby facilitating both individual treatment strategies and genetic analyses.

1. Introduction

Bipolar disorder (BD) is a severe mood disorder characterized by cycling between the emotional extremes of mania and major depression. Even the most severe form of BD, bipolar I, is common in the population, with a lifetime prevalence of approximately 1% (Goodwin and Jamison, 2007; Merikangas et al., 2011). Studies of BD face many challenges arising from the complex genetic architecture, as well as the inherent clinical heterogeneity. Current diagnostic systems primarily define BD using categorical clinical descriptors that inadequately capture the rich spectrum of bipolar symptomology, which is more consistent with a polygenic model and implies a continuous distribution of symptoms ranging from mild to severe. The historically high rate of misdiagnosis in BD highlights this need for alternative quantitative metrics that better capture the full range of bipolar symptomology (Altamura et al., 2015; Daigneault et al., 2015; Zimmerman et al., 2008).

As alternatives, temperament and other personality traits have been proposed as potential endophenotypes for BD (Savitz and Ramesar, 2006). Temperament refers to stable, innate aspects of one's disposition that can be measured quantitatively and that show continuous variation in the population (Goldsmith et al., 1987; von Zerssen and Akiskal, 1998). It has been suggested that temperament represents the most common expression of the genes underlying BD and that extreme variation in temperament is associated with an increased risk for illness (Akiskal, 2002; Akiskal and Pinto, 2000; Akiskal and Akiskal, 2005; Kelsoe, 2003). According to this model, temperament and personality mediate between upstream biological mechanisms and downstream

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clinical diagnosis and may better model the underlying genetic architecture of BD. As quantitative traits, temperament and other personality measures may also provide more sensitive predictors of specific aspects of bipolar symptomatology.

Studies have shown that traits related to emotional instability, hostility, novelty seeking, and anxiety are elevated in bipolar spectrum disorders, even in euthymia (Bagby et al., 1997; Evans et al., 2005; Nowakowska et al., 2005; Osher et al., 1996; Savitz et al., 2008a, 2008b). Other investigations have demonstrated the utility of temperament and personality traits for detecting genetic risk factors for BD (Alliey-Rodriguez et al., 2011; Greenwood et al., 2012, 2013a, 2013b; Savitz et al., 2008c), predicting risk for bipolar spectrum disorders (DeGeorge et al., 2014), and discriminating those with BD or other mood disorders from healthy controls (Akiskal et al., 1977; Cassano et al., 1992; Evans et al., 2005; Harley et al., 2011; Kesebir et al., 2005; Loftus et al., 2008; Mendlowicz et al., 2005; Young et al., 1995). For these investigations, the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire (TEMPS-A) has been used to evaluate lifelong, milder aspects of bipolar symptomatology according to five temperaments: hyperthymic, dysthymic, cyclothymic, irritable, and anxious (Akiskal et al., 2005a, 2005b). The Temperament and Character Inventory (TCI) has also been used to evaluate personality according to four temperament domains (novelty seeking, harm avoidance, reward dependence, and persistence) and three character domains (self-directedness, cooperativeness, and self-transcendence) (Cloninger et al., 1993). One study of BD patients, their family members, and healthy controls identified an anxious-reactive factor across these two inventories that produced significant group discrimination across mood states and genetic risk categories, suggesting potential utility for genetic analyses (Evans et al., 2005).

In the present study, we explore the utility of latent temperament and personality traits in defining clinical profiles within the context of BD. By combining items across domains from these instruments, we aim to identify quantitative traits that may serve as indices for key features of illness and help refine the clinical heterogeneity associated with BD.

2. Methods

2.1. Subject ascertainment

A sample of 1195 unrelated patients with bipolar I disorder were selected from the Bipolar Genome Study (BiGS). All were of European Ancestry and derived originally from those collected as part of Wave 5 by the National Institute of Mental Health Genetics Initiative for Bipolar Disorder at 11 sites across the US. All subjects were assessed using the Diagnostic Interview for Genetic Studies (DIGS), which was combined with family informant data and medical records to arrive at best-estimate diagnoses according to DSM-IV criteria (Nurnberger et al., 1994). Detailed demographic and clinical information was available for each subject from the DIGS interview, including overall functioning as measured by the Global Assessment of Functioning (GAF). Written informed consent was obtained for all subjects according to the local institutional review boards.

2.2. Phenotypes

The TEMPS-A and TCI-125 were administered at the time of the clinical interview, and only subjects with complete data across both instruments were selected for analysis. The TEMPS-A includes a total of 109 self-rated true/false questions (110 for women) measuring subclinical affective traits and has been shown to have very good reliability, internal consistency, and stability over time (Akiskal et al., 2005a, 1998; Kawamura et al., 2010; Perugi et al., 2012; Placidi et al., 1998a, 1998b), as well as significant heritability in BD families (Greenwood et al., 2013a; Savitz et al., 2008c). The TCI-125 (125-question version) is a self-administered true/false questionnaire that evaluates personality according to a psychobiological model with demonstrated reliability, internal consistency, stability over time, and heritability in both BD families and the general population (Cloninger et al., 1993; Greenwood et al., 2013a; Heath et al., 1994; Keller et al., 2005; Savitz et al., 2008c). The Wender-Utah Rating Scale (WURS) was administered to evaluate childhood features of attention-deficit disorder in three factors related to oppositional/defiant behavior, inattention and resultant problems in school, and mood features of depression and anxiety (Ward et al., 1993). The Lifetime History of Aggression (LHA) scale was also administered to evaluate total aggression according to factors related to aggression, antisocial behavior, and self-directed aggression (Coccaro et al., 1997). The majority of subjects (77%) were euthymic at the time of assessment.

2.3. Statistical analyses

Dimension reduction was performed on the combined 235 items from the TEMPS-A and TCI-125 via exploratory factor analysis. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.93 and the significance of Bartlett's test of sphericity was < 0.001. A variety of tests and criteria were used to best determine the number of relevant factors, including Kaiser's criterion, the scree plot elbow rule, 50% variance explained cutoff, an *a priori* hypothesis of a ten factor structure (Evans et al., 2005), and parallel analysis. Ultimately, the 18-factor structure proposed by parallel analysis was chosen, as the factor solution exhibited minimal complex loadings, and each factor described a cohesive, distinct trait. Furthermore, parallel analysis has been shown to be more accurate in determining the optimal number of factors relative to both Kaiser's criterion and the scree plot test (Franklin et al., 1995). Bivariate correlations were performed between all factor pairs and confirmed their independence with negligible correlations ($r < 0.001$). The factors were then subjected to Varimax rotation and standardization. Cronbach's alpha (α) was used to evaluate the internal consistency of the factors, which was generally quite high, with only four factors having an $\alpha < 0.7$.

To validate the factor structure, we explored the relationship of each factor to clinical features of BD. Correlations of the factors with quantitative variables were evaluated using Pearson's *r*, and independent samples *t*-tests were used to assess the relationship of the factors to categorical variables. Effect sizes were calculated using Cohen's *d* for factors demonstrating significant differences. We hypothesized that each factor would produce a unique and specific pattern of association across clinical descriptors. A p value threshold of 0.003 was applied to represent a 5% probability of a false positive across the 18 independent factors.

Cluster analytic methods were applied to the 18 factors to identify subgroups of patients with more similar profiles. Subjects were first subjected to hierarchical clustering via Ward's method according to their factor scores to determine a preliminary number of clusters. Results of these initial analyses suggested 2, 3, or 6 cluster structures. Further analysis with a two-step cluster procedure using the Bayesian information criterion confirmed a 3-cluster structure. K-means clustering was then performed with 3 subgroups (k=3) to generate a final cluster solution in the 18-variable space of the factors. Comparison of the k-means cluster solution with the 3-group hierarchical cluster solution suggested good agreement ($p < 0.001$). To allow for visualization of the subgroups, multivariate discriminant analysis was performed to summarize the variation among factors that maximally separated the subgroups identified by k-means clustering. Analysis of variance was used to compare the factors across cluster groups. All analyses were carried out in SPSS v. 20. (IBM, Armonk, NY).

3. Results

The 18 identified factors comprised 162 items and explained 39% of