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Research paper

Neurocognitive performance as an endophenotype for mood disorder subgroups

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ABSTRACT

Background: There is growing evidence that neurocognitive function may be an endophenotype for mood disorders. The goal of this study is to examine the specificity and familiality of neurocognitive functioning across the full range of mood disorder subgroups, including Bipolar I (BP-I), Bipolar II (BP-II), Major Depressive Disorders (MDD), and controls in a community-based family study.

Methods: A total of 310 participants from 137 families with mood spectrum disorders (n=151) and controls (n=159) completed the University of Pennsylvania's Computerized Neurocognitive Battery (CNB) that assessed the accuracy and speed of task performance across five domains. Mixed effects regression models tested association and familiality.

Results: Compared to those without mood disorders, participants with BP-I had increased accuracy in complex cognition, while participants with MDD were more accurate in emotion recognition. There was also a significant familial association for accuracy of complex cognition. Mood disorder subgroups did not differ in performance speed in any of the domains.

Limitations: The small number of BP-I cases, and family size limited the statistical power of these analyses, and the cross-sectional assessment of neurocognitive function precluded our ability to determine whether performance precedes or post dates onset of disorder.

Conclusions: This is one of the few community-based family studies of potential neurocognitive endophenotypes that includes the full range of mood disorder subgroups. There were few differences in neurocognitive function except enhanced accuracy in specific domains among those with BP-I and MDD. The differential findings across specific mood disorder subgroups substantiate their heterogeneity in other biologic and endophenotypic domains.

1. Introduction

Mood spectrum disorders, including Bipolar I disorder (BP-I), Bipolar II disorder (BP-II), and Major Depressive Disorder (MDD), are highly prevalent (Hasin and Grant, 2015; Kessler et al., 2007; Merikangas et al., 2007), and are a leading cause of disability worldwide (World Health Organization, 2008). There has been limited success in identifying either genetic factors or biologic markers for any of the major mood disorder subtypes (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Ripke et al., 2013). This failure has been attributed to the heterogeneity of mood disorder subtypes, pervasive comorbidity with other mental and physical conditions, and differential manifestations across the life span.

There is now a large body of research on neurocognitive function in mood disorders that has been subject to several reviews and meta-analyses (Burdick et al., 2014; Glahn et al., 2004, 2014; Porter et al., 2015). Most of this work focuses on performance outside of acute episodes (Arts et al., 2008; Bora et al., 2009; Bourne et al., 2013; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011; Robinson et al., 2006; Torres et al., 2007), whereas there are a few others that review neurocognition during in-episode (Kurtz and Gerraty, 2009) or first episode bipolar disorder (BPD) (Lee et al., 2014). Despite finding statistically significant differences between cases and controls, no obvious pattern of cognitive dysfunction in BPD has been shown,

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though there is some evidence to suggest impairment in verbal learning and memory during depressive episodes, and broader impairment during euthymia (Aminoff et al., 2013; Godard et al., 2011; Kurtz and Gerraty, 2009). As reviewed by Porter et al. (2015) a trend in decreasing effect sizes over time is evident; they attribute the inconsistent results to increasing sample sizes (smaller early negative studies may have been subject to publication bias), the exclusion of more impaired groups (to reduce heterogeneity) in more recent studies, and other methodologic differences among studies.

There are few studies of neurocognitive function attributable to the depressive component of BPD or MDD. Memory deficits have been proposed as a state marker for MDD, rather than a trait of people with MDD (Lee et al., 2012). Impairments in social cognition have also been reported in both MDD and BPD, specifically for facial emotional identification and differentiation, as reported in a meta-analysis (Kohler et al., 2011). Studies of the extent to which these measures reflect current state versus trait (Robinson et al., 2015; Van Rheenen and Rossell, 2014) or severity (Munkler et al., 2015) have been inconsistent. Among patients with depression, a recent meta-analysis showed impaired recognition of emotion for angry, disgusted, fearful, happy and surprised faces, but not sad faces (Dalili et al., 2015). This differs from the results of a study of euthymic BPD patients wherein accuracy deficits were found for fearful faces only (de Brito Ferreira Fernandes et al., 2016).

Several studies have examined neurocognitive function in extended families of people with BPD to determine whether neurocognitive function may comprise a trait marker, or a potential endophenotype that may be a closer reflection of underlying genetic and biologic risk factors for BPD (Bearden and Freimer, 2006). Evidence for endophenotypes require that the putative measure: (1) discriminate between cases and controls; (2) reflect trait versus state markers; (3) demonstrate familial aggregation; and (4) discriminate between unaffected relatives of cases versus controls (Gottesman and Gould, 2003). There is also compelling evidence that neurocognitive function may be an endophenotype for mood disorders (Bearden et al., 2006; Bora et al., 2009; Fears et al., 2014; Glahn et al., 2004, 2014; Raust et al., 2014). Identifying endophenotypes may assist in reducing the heterogeneity of mood disorders, which may inform treatment efficacy, risk prediction, and the identification of genetic variability (Balanza-Martinez et al., 2008; Fears et al., 2014). The two major sources of data on neurocognitive factors as potential endophenotypes for mood disorders are family and twin studies that assess patients and their affected and unaffected relatives (Arts et al., 2008; Balanza-Martinez et al., 2008; Bora et al., 2009; Clark et al., 2005a, 2005b; Fears et al., 2014), and offspring of parents with mood disorders (Klimes-Dougan et al., 2006; Maziade et al., 2009). Neurocognitive endophenotypes have also been examined in large samples of extended pedigrees of probands with BPD (Fears et al., 2014; Glahn et al., 2010; Pagani et al., 2016) or with MDD (Glahn et al., 2012). These studies have discriminated genetic and environmental components of cognitive factors and their association with BPD (Georgiades et al., 2016). Neurocognitive domains that have been shown to have substantial heritability in these studies include: processing speed, verbal working memory, long-term memory, and verbal fluency (Fears et al., 2014).

Most participants in studies of neurocognitive endophenotypes for mood disorder subgroups have been recruited in clinical settings that represent the most severe cases (Bora et al., 2009; Volkert et al., 2016), often during the acute phase of mood disorders that may be complicated by affective state and medication use (Burdick et al., 2014; de Brito Ferreira Fernandes et al., 2016; Georgiades et al., 2016; Glahn et al., 2010; Lee et al., 2014; Xu et al., 2012). Associations found in these studies differ by source of the samples, mood disorder subgroups (Godard et al., 2011), clinical characteristics including current state (Martinez-Aran et al., 2004), medication use, psychotic features, severity, consequences (Jaeger et al., 2006; Martinez-Aran et al., 2007; Ruggero et al., 2007) or precursors of the disorder (Pavuluri et al., 2006), as well as substantial differences in the measures and domains assessed (Porter et al., 2015). To date, the most compelling evidence supports memory and attention as neurocognitive endophenotypes for BPD (Bora et al., 2009; Cardenas et al., 2016; Olvet et al., 2013).

The goal of this study is to examine neurocognitive function in a community-based family study of the full range of mood disorder subgroups outside of acute episodes in order to tap potential trait measures. Specifically, the two major aims of these analyses are: (1) to investigate the associations between neurocognitive function with specific mood disorder subgroups including BP-I, BP-II, and MDD compared to those without mood disorders; and (2) to examine the familial correlations in neurocognitive function.

2. Methods

2.1. Sample

The sample were participants in the National Institute of Mental Health (NIMH) Family Study of Affective Spectrum Disorders, a large community-based family study of probands assessed for the full range of mood disorders. The subsample in these analyses includes 310 participants: 119 probands, and 191 relatives (151 first-degree) who reside in the greater Washington, D.C. area and underwent evaluation at the National Institutes of Health (NIH) Clinical Center. The procedures for the study are described in detail in Merikangas et al. (2014). Briefly, standard family study methodology was employed including direct interviews of probands and relatives by experienced clinicians, with systematic enumeration of relatives, including children and spouses, and blind assessment of relatives (Weissman et al., 1986). Aside from diagnostic interviews, a subset of local probands and relatives had a comprehensive evaluation including physical examination, neuroimaging, and neurocognitive testing. Probands were recruited from a survey of the local community, and enriched through volunteers and referrals from the NIH Clinical Center. The only inclusion criteria for this phenomenological family study were the ability to speak English, availability to participate in the study, and consent to contact at least two living first-degree relatives; therefore, those without the cognitive ability to understand consent procedures and to comprehend the interview were not included in the study. Among the enrolled probands, 73% had at least one first-degree adult relative with a diagnostic interview, and 71% of the first-degree relatives who were alive and could be located were enrolled in the study.

2.2. Diagnostic assessment

Mood spectrum diagnoses (BP-I, BP-II, and MDD) were based on direct semi-structured diagnostic interview and family history reports, using the NIMH Family Study Diagnostic Interview for Affective Spectrum Disorders, which is an extension of the Schedule for Affective Disorders and Schizophrenia (SADS)/Diagnostic Interview for Genetic Studies (DIGS) (Merikangas et al., 1998a, 1998b). This interview ascertains diagnostic criteria for current and lifetime DSM-IV-TR disorders. Inter-rater reliability was excellent (intraclass coefficients are 0.87 or above for all major diagnostic categories) (Merikangas et al., 2014) and the interview detected all cases of mood disorders derived from structured clinical interview for DSM-IV interviews on the inpatient unit of the NIH Clinical Center. Best estimate diagnoses for this study were based on all available information by a team of experienced clinicians (psychologists and psychiatrists). Controls could have no lifetime history of mood disorders.

2.3. Neurocognitive assessment

The University of Pennsylvania Computerized Neurocognitive