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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 familiarity 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 familiarity.

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 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

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among those with BP-I and MDD. The differential findings across specific mood disorder subgroups substantiate their heterogeneity in other biologic and endophenotypic domains.

Keywords

Bipolar disorder; mood disorders; endophenotypes; neurocognition; community-based family study; Penn CNB

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; Glahn et al., 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, 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 fewer 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 Rhee 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; Glahn et al., 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; Clark et al., 2005b; Fears et al., 2014), and more recently, 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.

METHODS

Sample

The sample were participants in the National Institute of Mental Health (NIMH) Family Study of Affective Spectrum Disorders, a large community-based controlled 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.

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 based on the Schedule for Affective Disorders and Schizophrenia (SADS)/Diagnostic Interview for Genetic Studies (DIGS) (Merikangas et al., 1998a; Merikangas et al., 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.

Neurocognitive Assessment

The University of Pennsylvania Computerized Neuropsychological Test Battery (CNB) (Gur et al., 2010) was used to measure accuracy and response time of neurocognitive function across fifteen tasks in five domains. This battery was selected because it included the major

domains that have been tested in previous studies of mood disorders, especially in children (Pavuluri et al., 2006; Schenkel et al., 2007), the availability of comparative data across the age spectrum of relevance to this family study, the computerized administration procedures, and ongoing collaboration between the NIMH and the University of Pennsylvania Neuropsychiatry research program where the CNB was developed. The domains are: (1) complex cognition (2 tasks measuring visuospatial and verbal reasoning); (2) executive function (2 tasks measuring working memory and abstraction and mental flexibility); (3) episodic memory (4 tasks measuring verbal memory and learning, facial memory, and memory of shapes); (4) social cognition (1 task measuring emotion recognition); and (5) sensorimotor ability (2 tasks measuring sensorimotor speed and motor praxis). The CNB is administered in a private room by a trained research technician. The battery takes approximately one hour to complete, and is well tolerated by study participants. Systematic validation procedures of the CNB were run for each participant, and specific tasks judged to be non-valid were excluded from these analyses. That is, data were excluded at the task level such that if a participant had some valid and some non-valid tasks, only the non-valid tasks for that participant were excluded. Tasks can be marked invalid due to deviation from standard administration techniques, environmental disruption, or lack of participant effort. Participants were euthymic at the time of assessment. Task standardization and construct validation are described by Gur et al. (Gur et al., 2010). The tasks, described in detail (Gur et al., 2012; Gur et al., 2010; Moore et al., 2015) are briefly summarized below:

Complex Cognition

The Short Penn Verbal Reasoning Test (SPVRT) measures language-mediated complex cognition ability. The task involves a series of analogy problems patterned after Educational Testing Service factor-referenced test kit.

The Penn Line Orientation Test (PLOT) measures the complex reasoning domain of visuospatial ability. The participant is shown two lines on the computer screen that differ in length and orientation, and must press a button to rotate one of the lines until its orientation (angle relative to a horizontal line) is the same as the other (non-rotating) line.

Executive Function

The Penn Conditional Exclusion Test (PCET; (Kurtz et al., 2004a; Kurtz et al., 2004b)) measures the executive functions of abstraction and mental flexibility, which are critical for effective problem solving. It assesses the ability to derive principles and concepts from feedback, as well as the ability to detect and adjust to changing rules. The PCET uses the “odd man out” paradigm, in which participants determine which object in a group does not belong. The exclusion rule can be based on the shape or configuration of the objects, the size of the objects, or the thickness of the lines outlining the objects. The participant is given feedback (“correct” or “incorrect”) after each response, and the test-administration program automatically changes the exclusion rule after ten consecutively correct responses (without informing the participant). The participant must then use the feedback to determine what the new exclusion rule is, and after ten consecutively correct responses, the rule is changed again.

The Penn Letter N-Back Test measures working memory, the ability to keep and refresh goal-related information. Participants attend to a continual series of letters that flash on the screen (one at a time) and press the spacebar according to three different rules (called the 0-back, 1-back, and 2-back). During the 2-back condition, which is analyzed in this study, he/she must press the spacebar when the letter on the screen is the same as the letter before the previous letter (i.e. 2 letters back).

Episodic memory

The Penn Word Memory Test (PWMT) measures episodic memory for verbal material. In the first part of this test, participants are shown 20 words (for one second each) that they will be asked to identify later. During the recognition phase, participants are shown a series (one at a time) of 40 words, 20 of which are the stimuli they were asked to memorize, and the other 20 are distractors (matched for frequency of use, length, imageability and concreteness). For each word, the participant must decide whether he/she has seen the word in the memorization phase on a four-choice scale (“definitely not,” “probably not,” “probably yes,” or “definitely yes”).

The Penn Facial Memory Test (PFMT) measures episodic memory for faces. The task is identical to the Penn Word Memory Test (above), except that the participant is asked to memorize faces instead of words. PFMT distractor faces are matched for age, ethnicity, and gender.

The Short Visual Object Learning Test (SVOLT) measures episodic memory for shapes. The task is nearly identical to the PWMT and PFMT, except that the participant is asked to memorize 10 Euclidean shapes instead of 20 words or faces.

The Penn List Learning Task (PLLT) is a measure of verbal learning and verbal memory. This test is modeled after the Hopkins Verbal Learning Test (HVLT) (Benedict et al., 1998). It is composed of immediate recall, short delay recall, short delay cued recall, long delay recall and long delay cued recall sessions. The participant listens to a series of 16 words read by the test administrator, and is asked to repeat as many of the items as possible, in any order. The PLLT can be scored based on the number of correct responses (excluding perseverations), number of perseverations, intrusions, semantic cluster, expected semantic cluster, chance-adjusted semantic clusters, serial clusters, expected serial clusters and chance-adjusted serial clusters for each block. This test is not timed, and only accuracy is recorded.

Social Cognition

The Penn Emotion Identification Test (ER40) measures the social cognition domain of emotion identification, specifically the ability to decode and correctly identify facial expressions of emotion. Participants are shown 40 faces (one at a time), and determine whether the emotion expressed by the actor’s face is happiness, sadness, anger, fear, or none at all. There are four female and four male faces for each emotion.

Sensorimotor Processing

The Motor Praxis task (MP) requires moving the mouse and clicking as quickly as possible on a green square that disappears after the click. The square changes location and gets increasingly small. Since it is rare for participants to miss a target, no accuracy score is calculated and the median response time is used as the main dependent measure. An un-speeded version of this task is administered at the beginning of the session to assure the participant has sufficient skills in moving and clicking the mouse.

The Computerized Finger Tapping Test (CTAP) measures motor speed by how quickly the participant can press the spacebar using only the index finger. After a practice trial with each hand, the test presents five trials for the dominant hand alternating with five trials for the non-dominant hand. In each, the participant is asked to tap the spacebar repeatedly for 10 seconds when the green “GO” screen is presented. The computer records the number of taps.

The sensorimotor tasks were not included in the analyses presented here, but were instead used to demonstrate an ability to complete the other computerized tasks.

Statistical analyses

Raw accuracy and response time values were z-transformed to their standard equivalents based on means and standard deviations for the entire sample. Z-scores for response time were multiplied by -1 to produce speed values. Domain scores for accuracy and speed are simply a z-scored average of the z-scored values for the tasks in that domain. In all instances higher scores reflect better performance, and the value represents the number of standard deviations the group differs from the mean. Crude models comparing participants with mood disorders and controls without mood disorders were completed via t-tests. Mixed effects regression models comparing participants with mood disorders to those without (including relatives), controlling for the participant’s age and sex, were completed via proc MIXED in SAS 9.3 (SAS Institute Inc.); the models include random intercepts to account for the within family correlation. Models also controlling for current psychotropic medication use (defined as use of Lithium, anticonvulsants, antidepressants, or anxiolytics within the last 30 days) were completed, but were not significantly associated with any of the CNB measures, so we did not control for the medication use in the models presented here (analytic results available upon request). Task familiarity was evaluated using mixed effects regression. Again, the models include random intercepts to account for the within family correlation; all models controlled for age and sex of the participants.

RESULTS

A total of 310 participants from 137 families are included in the analyses presented here (216 adults, 94 children). Of the 137 families, 80 had two or more family members who completed the neurocognitive assessment (253 participants), and 57 families had only one family member who completed the assessment. For the analyses of Aim 1 on the specificity of mood disorder subgroups, probands and relatives who met lifetime criteria for BP-I, BP-II and MDD were considered “cases” and those with a history of no mood, anxiety, behavior, or substance use disorders were “controls”. Analyses were repeated with the inclusion of

probands and relatives with non-mood disorders (i.e., anxiety, substance, behavior without mood disorders), and similar results emerged. Therefore, we combined the Other/None groups for these analyses. The distribution of demographic and clinical characteristics of the mood disorder diagnostic subgroups is shown in Table 1; the mean age of the sample is 36.6 years, the sample is 40% male, and primarily Caucasian (71.2%). 70.9% of the mood disorder participants had received mental health treatment (BP-I 96.0%; BP-II 64.7%; MDD 66.3%). About half the adult (n=196) sample (50.5%) had some college education or completed college (BP-I 33.3%; BP-II 54.6%; MDD 51.5%; Other/None 53.7%), and a high proportion (43.3%) had completed education beyond college (BP-I 50.0%; BP-II 36.4%; MDD 42.4%; Other/None 43.9%). 8% of the cases had a history of psychotic symptoms (data not shown). The distributions of the CNB sample and the total sample did not differ by sex or mood disorder subgroups; however, the CNB sample included a greater proportion of young people than the total sample.

The results for the mixed effects regressions are shown in Table 2; note that, because composite scores are z-scores the beta coefficients can be interpreted as standardized betas. After controlling for the effects of the participant's sex and age, the only statistically significant association was found for the complex cognition domain accuracy among BP-I participants ($\beta=0.5567$, $p=0.02$). There was moderately greater accuracy on the social cognition domain among those with MDD ($\beta=0.2493$, $p=0.05$). No statistically significant differences were found for accuracy in the other domains (executive function, episodic memory), nor for speed in any of the domains. Complex cognition domain accuracy was the only domain with a statistically significant familial association ($\beta=0.3318$, $\beta=0.03$). The means and twice the standard error for domain accuracy and speed are shown in Figure 1. Here we show that, among the mood disorder subgroups and controls, BP-I participants had the greatest variability in performance across neurocognitive domains. BP-I also performed more accurately on the complex cognition domain, and MDD participants performed more accurately on the social cognition domain. Note that some groups show negative means in Figure 1, and yet have positive coefficients in the regression model; this is due to adjusting for age and sex.

In order to determine which task in the complex cognition domain was driving the association with BP-I, Penn Line Orientation Test (PLOT) and short Penn Verbal Reasoning Test (SPVRT) accuracy were examined in more detail (Table 3). Here we found that the complex cognition association was being driven by PLOT performance among BP-I participants ($\beta=0.5834$, $\beta=0.01$). There was also an association found between PLOT and MDD ($\beta=0.2881$, $\beta=0.04$), and the task demonstrated significant familiarity ($\beta=0.3653$, $\beta=0.01$). The means and twice the standard error for PLOT and SPVRT accuracy are shown in Figure 2, where we can see that BP-I participants perform better on this task, followed by MDD. BP-II and control participants performed similarly to one another.

DISCUSSION

Summary

We found few differences in neurocognitive function among people with mood disorders in this large community-based family study of the full spectrum of mood disorders. Among the

domains examined, enhanced accuracy of complex cognition, specifically visuospatial ability, was the only domain associated with BP-I disorder, and complex cognition accuracy also showed a significant familial association. There was also a moderate association between MDD and better social cognition accuracy, while there were no statistically significant associations for BP-II. Confirming earlier reports, we did not find differences in speed of neurocognitive performance in any of the domains (Daban et al., 2012). The specificity in differences in cognitive functioning across the three mood disorder subgroups demonstrates the heterogeneity of mood disorders that has been shown in other domains including biological markers (Glaus et al., 2014; Thase, 2014), structural and functional neuroimaging (Zhang et al., 2016), and treatment response (Karyotaki et al., 2016).

Previous studies have demonstrated poorer performance in line orientation and other tests of visuospatial processing between BPD patients and controls (Frantom et al., 2008; Georgiades et al., 2016; Torres et al., 2010). Our finding of enhanced performance may be attributable to the non-clinical sources of our sample and the euthymic state of the majority of probands and relatives. The significant familial association for visuospatial ability confirms the recent finding of substantial heritability of visuospatial learning in a twin-family study of a clinical sample of BPD (Georgiades et al., 2016). This finding is also notable given that males tend to outperform females on the PLOT (Gur et al., 2012; Moore et al., 2016), yet the BP-I group still outperforms the controls even though they are only 28% male (versus 47% male in controls). The association with BPD as well as its familial association suggests that visuospatial ability may be a potential endophenotype for BPD (Swagerman et al., 2016). Unfortunately, our sample size was too small to permit testing of the endophenotype criterion of differences in this domain among the unaffected relatives of probands with BPD. The association between BPD and the line orientation task may also provide insight into the neural pathways underlying bipolar disorder because this task activates right temporo-parietal regions (Gur et al., 2000; Gur et al., 2010; Tranel et al., 2009). There is extensive evidence that right hemispheric activation is associated with negative affect (Borod, 1993; Davidson, 1993; Sackeim et al., 1982).

The theory of impaired emotion recognition aligns with cognitive theories of depression, wherein people with impairment in this domain are more likely to have difficulty interpreting social stimuli and therefore interacting in social situations. The association between MDD and enhanced social cognition, as measured by an emotion recognition task, is contrary to theory and meta-analytic results suggesting that emotion recognition is typically impaired in depression (Dalili et al., 2015; Demenescu et al., 2010; Kohler et al., 2011). This effect does appear to be moderated by clinical state or symptom severity (Munkler et al., 2015) and medication use. For example, fluoxetine administration has been shown to inhibit emotion recognition (Capitao et al., 2015). In addition, previous research offers conflicting information about which specific emotions are impaired (Bourke et al., 2010; Dalili et al., 2015), or how much emotional intensity was required to identify a difference (Munkler et al., 2015).

Correlates of Cognitive Function in BPD

The enhanced function in some of the domains in our sample differs from the deficits that characterize most earlier work on BPD (Bauer et al., 2016; Cardenas et al., 2016; Lee et al., 2014; Sharma et al., 2016), and may reflect findings from earlier studies that people with BPD may actually have superior functioning in some cognitive domains, and higher IQ, school performance, and social functioning prior to onset of BPD (Demjaha et al., 2012), even in childhood (Cannon et al., 2002; Koenen et al., 2009; MacCabe et al., 2010). Of particular relevance to our study, the line orientation task has been shown to index greater functional life skills performance (for basic financial tasks) (Allen et al., 2015), so our finding of greater accuracy in visuospatial function could actually have broader functional implications. It has been postulated that some genes may increase susceptibility to mania and also lead to superior intellectual performance, while the same genes may have altered cognitive function due to some neurodevelopmental insult, which could lead to more impaired presentation in those patients with psychotic symptoms (Demjaha et al., 2012).

Several studies have demonstrated that impaired neurocognitive performance among those with BPD could be attributable to correlates or consequences of the disorder. Antipsychotic medications that are commonly prescribed for BPD can impact cognitive function (especially psychomotor speed and sustained attention) (Bora et al., 2009). Neurocognitive function may also be attributable to the subset of BPD with psychotic features (Hill et al., 2013). Indeed, several authors have suggested that similar to genetic and other biologic findings (Lichtenstein et al., 2009), BPD with psychotic features is more closely affiliated with schizophrenia (Tondo et al., 2016). These and other correlates of cognitive performance have been increasingly used to identify subtypes of BPD (Volkert et al., 2016).

Numerous studies have also examined the influence of current clinical state on cognitive performance in mood disorders (Bourne et al., 2013; Porter et al., 2015), with greater impairment among more severe and acute cases (Munkler et al., 2015). Several recent studies have controlled for clinical state and shown that some of the findings dissipate after controlling for state. For example, Georgiades et al. (2016) showed that the association between working memory and BPD dissipated after control for current affective symptoms, whereas the association with visuospatial learning persisted after such control.

Strengths and Limitations

There are some limitations that should be considered when interpreting this work. Notably, the relatively small number of probands in the BP-I group diminished our statistical power and ability to control for comorbid conditions. Likewise, the small family size (typically 1 or 2 family members per proband) limited our ability to calculate heritability. In addition, we could not test all of the criteria for endophenotypes because we did not have sufficient numbers of unaffected relatives of cases and controls. The cross-sectional assessment of neurocognitive function also precluded determining whether performance differences precede or post date onset of disorder. Finally, the large number of cognitive tests led to multiple statistical comparisons. In order to reduce the number of comparisons, we collapsed across tasks and focused on the four major domains, and then only presented specific tasks within the domains on which the case and control groups exhibited significant differences.

Similar to previous studies of neurocognitive functioning in mood disorders, we did not apply a multiple testing procedure because these analyses were based on a priori hypotheses regarding the higher order domains.

Strengths of this study include the community-based sampling across a broad age range, which extends the generalizability of the findings beyond clinical samples that have been the basis of most prior neurocognitive research. However, at the same time, the broad age range is also a limitation because of limited power to compare the findings in age-specific subgroups. In addition, our study included sufficient sample sizes of each of the mood disorder subgroups, which enabled us to examine their specificity in neurocognitive performance. The euthymic status of our participants is an additional strength, as evaluating persons out of episodes gives a more naturalistic assessment of their basal cognitive function.

Future directions

Future studies in additional family-based samples are necessary to replicate these findings, and enable the comparison of unaffected relatives of cases and controls. Given the large number of statistical tests used here, employing classification methods such as latent variable and machine learning approaches to reduce data complexity may lead to more robust associations. Further, the examination of biologic and neural correlates of visuospatial ability as potential endophenotype for BP-I, as well as whether cognitive function differences are associated with other potential endophenotypes such as structural neuroimaging findings, temperamental factors, psychophysiological measures, and objective measures of sleep and activity would be potential next steps.

Conclusions

In general, there were few neurocognitive deficits in this large community-based sample of the mood disorder spectrum. In fact, the only significant findings were enhanced accuracy of visuospatial ability and familiarity among those with BP-I, and more accurate emotional recognition among those with MDD. The differential findings across specific mood disorder subgroups demonstrate the heterogeneity of these conditions that should be evaluated in future studies.

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HIGHLIGHTS

- Community-based family study examining neurocognition across mood disorder subgroups
- No differences in performance speed in any of the domains assessed
- Greater accuracy of complex cognition for BP-I vs. those without mood disorders (visuospatial)
- Familial association for accuracy in the complex cognition domain (visuospatial)
- Visuospatial ability may comprise a potential endophenotype for bipolar disorder

Figure 1.
Domain Accuracy and Speed

Figure 2.
Complex Cognition Domain Accuracy

Table 1Demographic and Clinical Characteristics by Mood Disorder Subgroups¹

	All	BP-I	BP-II	MDD	Other/None
N	310	25	34	92	159
Sex (% male)	40.0	28.0	47.1	29.4	46.5
Age (years)					
mean	36.6	42	36.5	41.2	33.2
range	(7.0–84.0)	(14.0–63.0)	(13.0–72.0)	(7.0–79.0)	(7.0–84.0)
Age Groups (%¹, n)					
7–17 years	93	4.0 (1)	14.7 (5)	22.8 (21)	41.5 (66)
18–44 years	101	56.0 (14)	47.1 (16)	30.4 (28)	27.0 (43)
45–65 years	93	40.0 (10)	29.4 (10)	39.1 (36)	23.3 (37)
65 and older	23	0 (0)	8.8 (3)	7.7 (7)	8.2 (13)
Education² (%¹, n)					
12 year or less	6.2 (12)	16.7 (4)	9.1 (2)	6.1 (4)	2.4 (2)
13–16 years	50.5 (98)	33.3 (8)	54.6 (12)	51.5 (34)	53.7 (44)
Greater than 16 years	43.3 (84)	50.0 (12)	36.4 (8)	42.4 (28)	43.9 (36)
Treatment for mood Disorder³ (%¹) Medication Use (%¹, n)	70.9	96.0	64.7	66.3	NA
Anti-depressant	15.1 (45)	50.0 (12)	14.7 (5)	21.7 (20)	5.4 (8)
Mood stabilizer	2.6 (8)	16.0 (4)	2.94 (1)	1.1 (1)	1.3 (2)

¹ Probands and Relatives with and without Mood Disorders² Only for participants 21 and older (n=194)³ Only for BP-I, BP-II, and MDD groups

Table 2

Regression Coefficients and p-values from mixed effect regression models of Mood Disorder Subgroups on Accuracy, Speed, and Familiarity of CNB Domains

Domain	Disorder	Accuracy			Speed			Familiarity	
		BP-I	BP-II	MDD	BP-I	BP-II	MDD	Accuracy	Speed
Complex Cognition	Estimate p-value	0.5567	0.1797	0.2174	-0.0703	-0.1029	-0.0655	0.3318	0.0239
		0.02 *	0.34	0.13	0.76	0.59	0.65	0.03 *	0.90
Executive Function	Estimate p-value	0.0890	0.3386	0.1909	-0.1992	0.1759	0.0781	-0.0338	0.0756
		0.70	0.09	0.19	0.36	0.33	0.57	0.79	0.45
Memory	Estimate p-value	0.0108	0.1322	0.0944	-0.3152	0.2302	0.1245	0.0624	-0.0353
		0.96	0.50	0.51	0.16	0.22	0.36	0.45	0.83
Social Cognition	Estimate p-value	0.1470	0.0564	0.2493	0.0173	0.1699	-0.0146	-0.1127	0.3464
		0.47	0.75	0.05	0.93	0.33	0.91	0.14	0.11

All models are adjusted for the age and sex of the participant, with other/none as the reference group. The familiarity models also include the proband's performance on the same CNB measure.

* Indicates statistical significance at $\alpha < 0.05$

Table 3

Regression Coefficients and p-values from models of Mood Disorder Subgroups of Accuracy of Complex Cognition Domain Subtests

Accuracy	Penn Line Orientation Test Correct Responses		Short Penn Verbal Reasoning Test Correct Responses	
	Estimate	p-value	Estimate	p-value
BP-I	0.5834	0.01 *	0.3867	0.09
BP-II	0.1260	0.50	0.2315	0.22
MDD	0.2881	0.04 *	0.1301	0.35
Familiarity	0.3653	0.01 *	0.2480	0.06

All models are adjusted for the age and sex of the participant, with other/none as the reference group. The familiarity models also include the proband's performance on the same CNB measure.

* Indicates statistical significance at $\alpha < 0.05$