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Preliminary communication

Intermediate: Cognitive phenotypes in bipolar disorder

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ABSTRACT

Background: Intermediate cognitive phenotypes (ICPs) are measurable and quantifiable states that may be objectively assessed in a standardized method, and can be integrated into association studies, including genetic, biochemical, clinical, and imaging based correlates. The present study used neuropsychological measures as ICPs, with factor scores in executive functioning, attention, memory, fine motor function, and emotion processing, similar to prior work in schizophrenia.

Methods: Healthy control subjects (HC, $n=34$) and euthymic (E, $n=66$), depressed (D, $n=43$), or hypomanic/mixed (HM, $n=13$) patients with bipolar disorder (BD) were assessed with neuropsychological tests. These were from eight domains consistent with previous literature; auditory memory, visual memory, processing speed with interference resolution, verbal fluency and processing speed, conceptual reasoning and set-shifting, inhibitory control, emotion processing, and fine motor dexterity.

Results: Of the eight factor scores, the HC group outperformed the E group in three (Processing Speed with Interference Resolution, Visual Memory, Fine Motor Dexterity), the D group in seven (all except Inhibitory Control), and the HM group in four (Inhibitory Control, Processing Speed with Interference Resolution, Fine Motor Dexterity, and Auditory Memory).

Limitations: The HM group was relatively small, thus effects of this phase of illness may have been underestimated. Effects of medication could not be fully controlled without a randomized, double-blind, placebo-controlled study.

Conclusions: Use of the factor scores can assist in determining ICPs for BD and related disorders, and may provide more specific targets for development of new treatments. We highlight strong ICPs (Processing Speed with Interference Resolution, Visual Memory, Fine Motor Dexterity) for further study, consistent with the existing literature.

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Cognitive dysfunction is a significant phenomenological dimension of many psychiatric illnesses, including bipolar disorder (BD). Difficulties in psychomotor speed, attention, executive function, memory, and fine motor skills have been extensively reported in BD, even in the euthymic state (Altshuler et al., 2004; Bora et al., 2009; Burdick et al., 2006; Martinez-Aran et al., 2004; Rubinsztein et al., 2000; van Gorp et al., 1998; Zubieta et al., 2001). Unfortunately, the specificity and potential genetic relevance of the cognitive dysfunction often observed in BD, schizophrenia (SCZ), major depressive disorder (MDD), and in some anxiety disorders (AD) is still of unclear significance. There are several genes that have been implicated in association studies of BD including COMT, BNDF, GRM3, CACNA1C, P2RX7GSK3, DAT, MAO-A, SCL6A4, and 5-HTTLPR, (Barnett et al., 2007; Burdick et al., 2007; Caldu et al., 2007; Donohoe et al., 2007; Ho et al., 2007; Lane et al., 2008; Meyer-Lindenberg et al., 2006; Pezawas et al., 2005; Pinheiro et al., 2007; Porteous et al., 2006; Rodriguez-Jimenez et al., 2006; Roffman et al., 2007; Tan et al., 2008); each of these genes individually contributes an odds ratio in the range of 1.2 to 1.4 (see Burmeister et al., Nature Reviews Genetics July 2008). As of yet, the data remain preliminary, with limited replication. However, it is

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anticipated that many of these genes will explain the susceptibility observed in psychiatric disorders, including BD, most likely as an additive effect: the expectation that any one given genetic variant will explain the genetic susceptibility for BD is all but abandoned. Importantly, as cognitive dysfunction is present in many, although not all, patients with MDD, BD, AD, and SCZ, cognitive dysfunction can only be considered one of several possible intermediate phenotypes, (Altshuler et al., 2004; Burdick et al., 2006; Langenecker et al., 2007; Martinez-Aran et al., 2004; McIntosh et al., 2005; Rubinsztein et al., 2000; Schretlen et al., 2007; van Gorp et al., 1998; Zubieta et al., 2001) each of which is likely to be driven by one or more genetic variants. A recent meta-analysis highlights the importance of neuropsychological variables in determining ICPs in BD (Bora et al., 2009).

Intermediate cognitive phenotypes (ICP) have the distinct advantage of being dimensional and can be assessed across all clinically defined phenotypes as well as in healthy unaffected control individuals. Only a few studies have used ICPs in BD, although ours and several other large studies are underway (Antila et al., 2007; Osher and Bersudsky, 2007; Palo et al., 2007; Rybakowski et al., 2003; Savitz et al., 2005; Zalla et al., 2004). We quantified possible ICPs for BD using factor analysis to obtain more reliable estimates of underlying cognitive constructs in the participants, minimizing measurement error and consistent with prior convention (Bleiberg et al., 2000; Langenecker et al., 2007; Rund et al., 2006). These factor scores included visual and verbal learning and memory, psychomotor speed and dexterity, emotion processing, inhibitory control, processing speed with interference resolution, verbal fluency and processing speed, and conceptual reasoning and set-shifting. We hypothesized that individuals with BD would perform statistically more poorly than HCs in these factors. We further hypothesized that cognitive decrements will exist in all states of BD, yet be exacerbated in the active phases of the illness (Clark and Goodwin, 2004; Gruber et al., 2007; Martinez-Aran et al., 2004; McIntosh et al., 2005). Finally, we evaluated medications and clinical features that may reflect the severity of the illness to study the effect of these factors on the ICPs for BD (Altshuler et al., 2004; Honig et al., 1999; MacQueen et al., 2004; Martinez-Aran et al., 2004). Importantly, we make no argument that cognitive decrements in BD are unique intermediate phenotypes for BD, as the extant literature would not support such a contention. Rather, we assert that ICPs are one of several critical factors in complex polygenetically determined illnesses like BD. These ICPs have the advantage of being objectively measured and have a reasonable likelihood of specificity of a genetic or biological basis based upon preliminary work by others, much more so than the traditional DSM-IV defined phenotypes.

1. Methods

Subjects were recruited to participate in a naturalistic longitudinal study of bipolar disorder with the goal of gathering phenotypic information and biological material for the Prechter Bipolar Repository at the University of Michigan. One hundred, twenty-two individuals with confirmed Bipolar I ($n=104$), Bipolar II ($n=12$), schizoaffective bipolar disorder ($n=5$), or bipolar disorder NOS ($n=1$), and 34 healthy controls participated in the present study. Recruitment of subjects occurred through an outpatient specialty psychiatry clinic, an inpatient psychiatric unit, and advertisements on the web and in the newspaper. The evaluation included a Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), neuropsychological testing, life event and symptom questionnaires, Hamilton Depression Rating, Young Mania Rating, and blood draw for genetics. A best estimate process by at least three of the authors (SAL, EFHS, MGM) was used to determine diagnoses. HDRS and YMRS were used to determine mood state at the time of administration of the neuropsychological tests. Table 1 illustrates demographic and clinical data for the participants in the study, with YMRS and HDRS cut-offs for euthymic, depressed, and hypomanic/mixed phase of the illness.

Table 1
Demographic information for bipolar and healthy control groups.

	(Euthymic BD, $n=66$)		(Depressed BD, $n=43$)		(Hypomanic/ mixed BD, $n=13$)		Healthy controls ($n=34$)	
	M	SD	*M*	SD	*M*	SD	*M*	SD
Age	40.48	12.39	39.12	12.03	36.15	12.73	36.85	16.60
Education [a]	15.72	2.19	14.65	2.34	14.38	2.43	16.00	2.51
Gender								
Females	43		29		7		22	
Males	23		14		6		12	
Wechsler Abbreviated Scale of Intelligence (WASI) [b]	110.62	12.18	108.19	12.74	108.51	9.23	115.07	11.83
Hamilton Rating Scale for Depression [c]	4.36	2.90	14.72	3.90	9.38	5.16	1.74	2.06
Young Mania Rating Scale [d]	1.44	2.04	1.54	1.84	12.61	4.03	0.22	0.59
Number of hospitalizations – psychiatric	2.92	3.49	3.77	5.96	2.92	2.75	NA	
Mania age at onset	23.35	8.88	24.86	10.70	21.90	11.55	NA	
Mania – number of episodes [e]	7.62	9.92	6.46	5.34	24.40	27.47	NA	
Depression – age at onset	22.02	20.67	20.63	11.53	20.31	13.07	NA	
Depression – number of episodes	21.31	59.29	17.26	25.99	24.54	25.60	NA	
Hypomania – age at onset	23.39	11.24	22.79	12.45	19.64	10.39	NA	
Hypomania number of episodes	25.24	44.10	50.25	78.15	52.45	81.49	NA	

[a] HC, EBD>DBD.
[b] Not significant, after covarying for significant differences in education ($F(3,149)=2.59$, $p=.06$). Cut-offs are HDRS>9.
[c] (with DBD>HMBD>EBD>HC) and YMARS>7.
[d] (HMBD>EBD, DBD>HC) for depression and hypomania, respectively.
[e] HMBD had more manic episodes compared to EBD and DBD groups.

Medications were coded for presence of psychopharmacological treatment (89.8% were currently taking medication at the time of data collection) for BD, including lithium ($n=41$, Mean=848.02 mg, SD=425.48), mood stabilizers ($n=56$, e.g., divalproex sodium $n=22$, Mean=1250.0 mg, SD=10.66, lamotrigine $n=20$, Mean=211.25 mg, SD=140.13), antipsychotics ($n=46$, e.g., quetiapine $n=17$, Mean=160.23 mg, SD=244.78, aripiprazole $n=10$, Mean=260.00 mg, SD=197.99, risperidone $n=8$, Mean=42.50 mg, SD=45.96), sedatives/tranquilizers ($n=27$, e.g., clonazepam $n=11$, Mean=113.20 mg, SD=297.26, trazadone $n=7$, Mean=85.71 mg, SD=50.61), antidepressants ($n=55$, e.g., bupropion $n=20$, Mean=374.90 mg, SD=235.64), thyroid medications ($n=22$, e.g., levothyroxine $n=13$, Mean=161 mg, SD=257.96), and stimulants ($n=7$). The effects of these medications were assessed in a specific set of analyses listed in the Results section below for hypothesis four.

Neuropsychological tests focused heavily upon areas known to be adversely affected in BD, including memory, attention and executive functioning, psychomotor speed, and emotion

Table 2
Main effects for analyses of key cognitive factor scores (CS) in bipolar disorder.

CS, factor analysis and reliability (alpha)	Test	Factor loading	Group effect	Posthoc difference
Memory				
(Auditory, alpha $r=0.83$)	California Verbal Learning Test-II		$F(3, 152)=3.95$, $p=0.01$,	HC>D, HM
	Total Learning Five Trials	0.90	$n^2=0.072$	E>D
	Short Delay Free Recall	0.94		
	Short Delay Cued Recall	0.95		
	Long Delay Free Recall	0.95		
	Long Delay Cued Recall	0.96		
	CVLT-II, recognition hits	0.72		
(Visual, alpha $r=0.79$)	Rey–Osterrieth Complex Figure Test		$F(3, 152)=3.43$, $p=0.019$,	HC>E, D
	Immediate recall	0.96	$n^2=0.063$	
	Delayed recall	0.96		
	Recognition	0.53		
Motor				
Fine Motor Dexterity (alpha $r=0.92$)	Purdue Pegboard		$F(3, 152)=10.09$, $p<10e\text{-}5$,	HC>E, D, HM
	Dominant	0.91	$n^2=0.166$	E>D
	Non-dominant	0.94		
	Bimanual	0.94		
Emotion Processing				
Emotion Processing (alpha $r=0.67$)	Emotion Perception Test		$F(3, 152)=1.01$, $p=0.146$,	HC>D
	Errors (inverted)	0.78	$n^2=0.035$	
	Facial Emotion Perception Test			
	Accuracy	0.80		
	Facial Emotion Perception Test			
	Response Time (inverted)	0.74		
Executive Function				
Verbal Fluency and Processing Speed (alpha $r=0.82$)	Phonemic Fluency	0.55	$F(3, 152)=3.56$, $p=0.016$,	HC, E>D
	Category Fluency	0.41	$n^2=0.066$	
	Digit Symbol	0.58		
	Stroop Color Word Test (SCWT)			
	Stroop Word Condition T	0.96		
	Stroop Color Condition T	0.84		
	Trail Making Test (TMT)			
	Form B	0.36		
Conceptual Reasoning and Set-Shifting (alpha $r=0.79$)	Wisconsin Card Sort Test		$F(3, 152)=2.75$, $p=0.045$,	HC>D
	Correct^	0.95	$n^2=0.052$	
	Perseverative errors (inverted)^	0.95		
	Parametric Go/No-Go (PGNG)			
	Mean accuracy for target trials	0.51		
Processing Speed with Interference Resolution (alpha $r=0.67$)	TMT		$F(3, 152)=11.66$, $p<10e\text{-}6$,	HC>E, D, HM
	Form A	0.63	$n^2=0.186$	
	Form B	0.44		
	Digit symbol	0.32		
	SCWT			
	Interference T	0.72		
	PGNG			
	Mean target response time (inverted)	0.75		
Inhibitory Control (na)	PGNG		$F(3, 152)=2.65$, $p=0.05$,	HC>HM
	Mean target response time (inverted)	−0.33	$n^2=0.05$	
	PGNG			
	Mean accuracy for inhibitory trials	0.89		
Sum of all regressed factors ($n=8$)	Factors 1–8	NA	$F(3, 152)=10.68$, $p<10e\text{-}5$,	HC>E, D, HM
			$n^2=0.174$	E>D
Sum of all significant factors only ($n=7$)	Factors 1–3, 4–8		$F(3, 152)=12.35$, $p<10e\text{-}6$,	HC>E, D, HM
			$n^2=0.196$	E>D

processing. Due to the large number of dependent variables in the neuropsychological tests, standard data reduction techniques were used to reduce the tests using conceptually and theoretically categorized variables (Bilder et al., 2002; Bleiberg et al., 2000; Langenecker et al., 2007; Rund et al., 2006). First, all scores with negative scale properties (lower numbers reflect better performance) were inverted. Second, five separate factor analyses were conducted based upon existing knowledge of factor structures. The first four factor analyses were confirmatory factors analyses, with variables entered based upon construct and theoretical knowledge of the tests employed. For example, five subtests scores of the California Verbal Learning Test were entered into a factor analysis (Auditory Memory factor, Aud. Mem.), and an obtained factor score was derived based upon Bartlett's regression. There were three variables entered into a Visual Memory (Vis. Mem.) factor from the Rey–Osterrieth Complex Figure Test. There was a fine motor dexterity factor (FMD) based upon three subtest scores from the Purdue Pegboard test. Finally, there was an emotion processing factor score (EP) derived from one score from the Emotion Perception test and the two scores from the Facial Emotion Perception test. The last factor analysis was computed and resulted in four factors, including tests of attention, fluency, psychomotor speed, conceptual reasoning, and inhibitory control (these are listed in Table 2). The tests entered into this factor analysis were Stroop Color Word Test, Phonemic and Category Fluency, Wisconsin Card Sort Test, Parametric Go/No-Go Test, Digit Symbol, and Trail Making Test. These factors were Verbal Fluency and Processing Speed (VFPS), Conceptual Reasoning and Set-Shifting (CRSS), Processing Speed with Interference Resolution (PSIR), and Inhibitory Control (IC). Reliability of the factor scores (adjusted alpha) are reported in Table 2.

Specific clinical datapoints were extracted from the DIGS interview to study the relationships between cognitive decrements and clinical indices of severity and a specific set of correlations of these relationships are also reported. These variables, listed in Table 3, include the historical number of psychiatric hospitalizations, age at onset of first episode, summation of number of depressive and manic episodes, presence/chronicity of psychosis, chronicity of affective symptoms, general impact of illness on functioning, years since first episode, and mean number of episodes per year the individual was ill (i.e., number of manic and depressive episodes divided by number of years since first episode).

Statistical analyses were computed using a MANOVA to compare the factor scores of the four groups (healthy control — HC, euthymic bipolar disorder — E, Depressed phase Bipolar Disorder — D, and Hypomanic/Mixed bipolar disorder — HM). Posthoc analyses were completed as appropriate. A MANCOVA was also completed with the effects of different medication classes, using phase of illness as a covariate with the eight factor scores and posthoc analyses as appropriate. Finally, correlations were computed between factor scores and clinical variables in the entire BD sample. The reported correlations were computed with the E-BD group only, but they were nearly identical in significance compared to those computed with the entire BD sample.

2. Results

2.1. ICPs in bipolar disorder

MANOVA was computed with the eight factor scores as dependent variables and the four groups as independent variables. There was a significant group effect, ($F_{24,441} = 2.54$, $p < 0.0001$, $n^2 = 0.122$), with the HC group outperforming the E-BD group in 3 of 8 factors and the D-BD group for 7 of 8 factors, and the HM-BD group in 4 of 8 factors. These differences are notated in Table 2 and illustrated in Fig. 1. As a control analysis to clarify the specificity of cognitive decrements in BD, the Vocabulary subtest from the Wechsler Adult Intelligence Scale ($F_{3,\ 147} = 2.47$, $p = 0.064$, $n^2 = 0.048$) and Synonym Knowledge task ($F_{3,\ 147} = 1.71$, $p = 0.169$, $n^2 = 0.034$) were compared between groups with neither results being significant. Results for individual tests are presented in a Supplementary Table. Because individual tests are more affected by error variance, factor scores were used.

2.2. Relationship of cognitive factor scores to clinical variables

Correlations were computed between indices of clinical severity, such as number of psychiatric hospitalizations, years of illness, total number of manic or depressive episodes, etc. and cognitive factor scores. Initially, we performed these correlations with the E group only to avoid confounding effects of depression and mania symptoms upon cognitive function. We also computed them with the active-phase BD participants and the correlations were virtually identical in significance. Nonetheless,

Table 3
Relationships of cognitive factors with clinical indices.

	1	2	3	4	5	6	7	8	9
Number of psychiatric hospitalizations	−0.40**	−0.30*	−0.14	−0.28*	−0.26*	−0.18	0.04	−0.20	−0.38**
Age at onset	−0.02	0.09	0.07	0.09	0.17	−0.17	0.16	−0.12	0.04
Total depressive and manic episodes	−0.09	0.02	−0.05	−0.01	0.06	−0.02	0.10	0.07	0.02
Chronicity of psychosis	−0.09	0.07	−0.15	−0.27	0.03	−0.18	0.11	−0.13	−0.11
Chronicity of affective symptoms	−0.07	−0.17	−0.26	0.05	−0.01	−0.06	0.27	−0.04	−0.07
General impact of illness on functioning	0.13	−0.18	0.09	−0.05	0.18	−0.17	0.05	−0.09	−0.03
Number of years of illness [a]	−0.07	−0.30*	−0.33**	−0.01	−0.23	−0.46**	0.41**	−0.38**	−0.31**
Episodes/years ill	−0.01	0.28*	0.08	−0.02	0.16	0.27*	−0.10	0.24	0.22

1 = Auditory Memory, 2 = Visual Memory, 3 = Fine Motor Dexterity, 4 = Verbal Fluency and Processing Speed, 5 = Conceptual Reasoning and Set-Shifting, 6 = Processing Speed with Interference Resolution, 7 = Inhibitory Control, 8 = Emotion Processing, 9 = Sum of All Factor Scores.

[a] Effects remain if age is covaried in partial correlations.

* $p < 0.05$.

** $p < 0.01$.

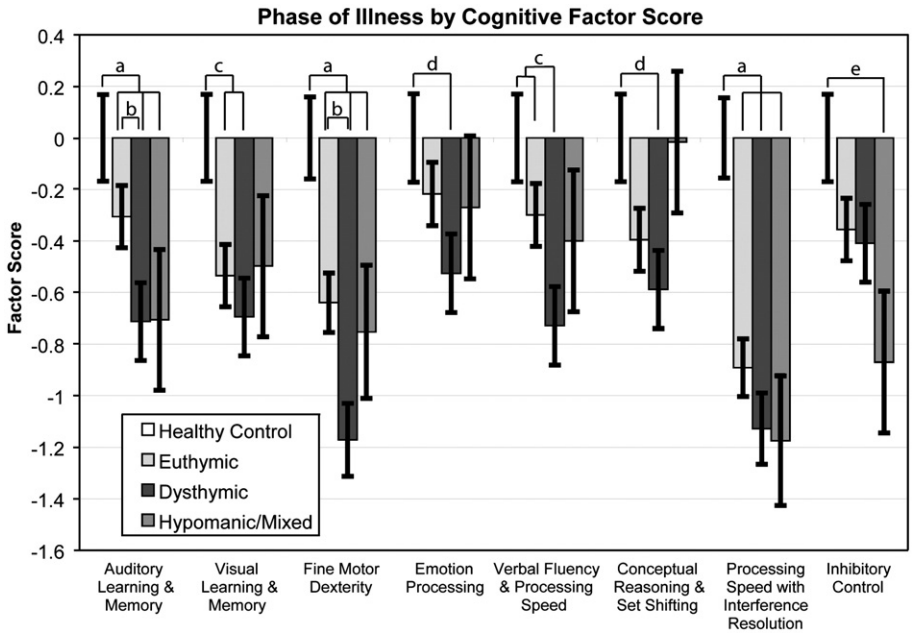


Fig. 1. [a] Healthy Control group performed significantly better than all the Bipolar participant groups. [b] Euthymic bipolar group performed significantly better than the Depressed group. [c] Healthy Control group performed better than the Euthymic and Depressed bipolar participant groups. [d] The Healthy Control group performed better than the Depressed bipolar group. [e] The Healthy Control group performed better than the Hypomanic/Mixed bipolar group.

consistent with standard convention, we report correlations with the E-BD group only. As there were a large number of correlations computed, these analyses should be considered exploratory in nature and no multiple comparison correction was applied. The most robust correlations with cognitive function were with number of psychiatric hospitalizations (4 of 8 factor scores were significant), and number of years of illness (5 of 8 factor scores). Number of psychiatric hospitalizations ($r=-0.38$, $p=0.0018$) and number of years of illness ($r=-0.31$, $p=0.013$) were also significantly correlated with the sum of all 8 factor scores. Table 3 includes correlations computed for each cognitive factor score with clinical variables of interest. Fig. 2, includes a scatterplot of the number of psychiatric hospitalizations by the sum of all factor scores (panel A) and a scatterplot of years since onset of illness by the PSIR factor (panel B).

2.3. Medication effects on cognitive factor scores in BD

Each medication effect was assessed in a MANCOVA, with binary yes/no response options for each of the seven categories

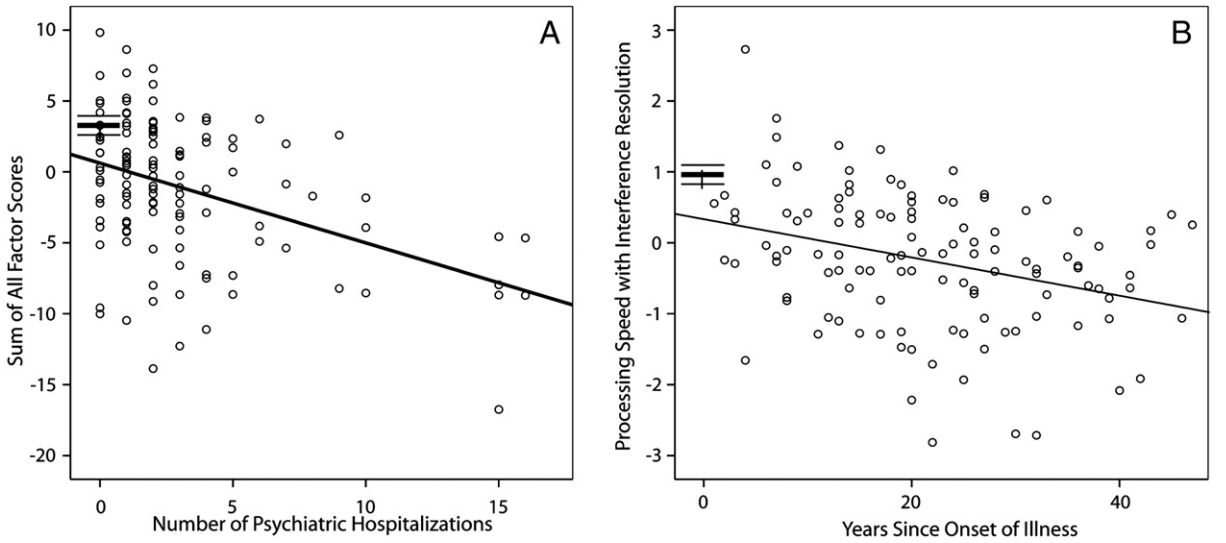


Fig. 2. Panel A. Scatterplot and regression line of total number of psychiatric hospitalizations by the Sum of All Factor Scores. Mean of the control group (+/− SEM) is shown on the left of the scatterplot. Panel B. Scatterplot of the number of years since onset of illness by Processing Speed with Interference Resolution. Mean of the control group (+/− SEM) is shown on the left of the scatterplot.

of medication and each of the eight factor scores. To avoid effects already known to significantly impact cognitive functioning, the analyses were run both with and without age at onset, years of illness, number of psychiatric hospitalizations, and YMRS and HDRS scores as covariates. This resulted in no substantive differences in any analyses. Thus we report effects for the MANOVA analyses only. The only MANOVA that achieved significance, of the seven medication classes, was that for treatment with antipsychotics ($F_{8,86}=2.17$, $p=0.036$, $n^2=0.149$), with worse performance in those taking this class of medications in VerM ($F_{1,106}=6.69$, $p=0.011$, $n^2=0.059$), FMD ($F_{1,106}=8.86$, $p=0.004$, $n^2=0.077$), VFPS ($F_{1,106}=7.90$, $p=0.006$, $n^2=0.069$), and EP ($F_{1,106}=4.25$, $p=0.042$, $n^2=0.039$) factor scores. The MANOVAs for lithium ($F_{8,100}=0.81$, $p=0.60$, $n^2=0.061$), mood stabilizer ($F_{8,99}=0.87$, $p=0.54$, $n^2=0.066$), sedative/anxiolytic ($F_{8,100}=1.58$, $p=0.14$, $n^2=0.112$), antidepressant ($F_{8,99}=0.80$, $p=0.61$, $n^2=0.060$), thyroid ($F_{8,99}=1.42$, $p=0.20$, $n^2=0.103$), and stimulant ($F_{8,99}=1.20$, $p=0.31$, $n^2=0.088$) medications did not reach significance.

In further posthoc analyses, the patients prescribed antipsychotic (AP+) medications were compared to those not taking antipsychotic (AP−) medications. The AP+ group had over twice as many psychiatric hospitalizations ($M=4.80$, SD=6.22) compared to the AP- group ($M=2.07$, SD=2.02, $t_{105}=-2.87$, $p=0.006$). The two groups did not differ for age of onset for mania ($t_{101}=0.28$, $p=0.78$) or depression ($t_{102}=-0.48$, $p=0.63$). The groups also did not differ in number of manic ($t_{93}=-0.81$, $p=0.42$) or depressive ($t_{105}=-0.37$, $p=0.71$) episodes, nor did they differ in age at onset ($t_{98}=0.07$, $p=0.95$), cumulative number of episodes ($t(105)=-0.29$, $p=0.77$), years since onset of illness ($t_{97}=0.18$, $p=0.86$), HDRS ($t_{105}=-1.56$, $p=0.12$), YMRS ($t_{102}=0.51$, $p=0.61$), age ($t_{104}=0.31$, $p=0.76$), or years of formal education ($t_{104}=0.83$, $p=0.41$).

4. Discussion

The present study characterizes ICPs for BD at the factor score, or domain, level. We computed eight factor scores, including visual and auditory memory, fine motor skill, emotion processing, and four within the broad rubric of executive functions. The four executive function factors included verbal fluency and processing speed, processing speed with interference resolution, conceptual reasoning and set-shifting, and inhibitory control. We also showed that cognitive dysfunction, particularly in psychomotor and executive functioning substrates, may well identify an underlying intermediate cognitive phenotype for a subset of individuals who have developed BD. Consolidation of neuropsychological assessments into factor scores is a strong approach to measuring and defining the underlying phenotype for studies of genetic risks for BD and related disorders as it reduces error in measurement, is easier to conceptualize as a cognitive construct, and is more likely to reflect the underlying latent variable that could be considered as a candidate ICP. We replicated prior studies showing dysfunction for memory, attention, executive functioning, and fine motor skill in BD, even in the euthymic state using these more reliable measurements (McIntosh et al., 2005; Nehra et al., 2006; Thompson et al., 2005; Zubieta et al., 2001).

4.1. ICPs for further evaluation in bipolar disorder

There were three factor scores identified as potential markers for an intermediate cognitive phenotype for BD. The Processing Speed and Interference Resolution is a promising factor score. It is a combination of the Trail Making Test, Parametric Go/No-Go task, WAIS Digit Symbol subtest, and Stroop Color Word Interference score. This finding is very similar to other studies where significant difficulties with processing speed, interference resolution, or set-shifting are present in all phases of BD and is similar to a factor reported in the schizophrenia literature accounting for 11% of the variance in COMT polymorphism (Altshuler et al., 2004; Balanza-Martinez et al., 2005; Bilder et al., 2002; Borkowska and Rybakowski, 2001; Kieseppa et al., 2005; Robinson et al., 2006). The relationship of this variable to indices of disease severity and duration further enhance the value of ICPs. We also found significant decrements in the Fine Motor factor score, including fine motor dexterity and speed in the euthymic state of BD, which may serve as an excellent intermediate phenotype for BD. This area is less well studied in BD, but initial reports clearly suggest a decrement in motor skills (Ferrier et al., 2004; Nehra et al., 2006). The visual memory factor score was also different between the euthymic BD and HC groups (Martinez-Aran et al., 2004; Pirkola et al., 2005; Rubinsztein et al., 2000).

Unlike previous studies, some with smaller samples, we did not demonstrate decreased verbal learning and memory ability in the euthymic BD group compared to the HC group (Ferrier et al., 2004; Gruber et al., 2007; MacQueen and Young, 2003; Nehra et al., 2006; Thompson et al., 2007; van Gorp et al., 1998). As might be expected though, both BD groups in the active phase of the illness performed more poorly on this factor relative to the HC group. Our cut-offs in determining euthymic BD were more conservative relative to previous studies in an attempt to refine the ICP irrespective of phase manifestations of the illness. This might explain why we did not observe a significant difference in verbal learning and memory between the euthymic bipolar disorder group and the HC group, but did observe such decrements in the depressed bipolar disorder group. This may also be due to the higher level of education in the E-BD group (average of 15.7 years of education), or the result of using a factor score wherein learning, recall and recognition are collapsed across all variables. Whereas high reliability can be obtained with use of factor scores (alpha $r>0.8$), there may some relative loss of specificity for the comparison of BD and the HC group in this instance.

4.2. State affects of illness on possible ICPs

We present one of the few studies to demonstrate executive functioning measures that dissociate based upon the hypomanic or mixed states. Lower scores in inhibitory control for the HM group, but not for the E or D bipolar groups indicate increased impulsivity in our hypomanic/mixed group. This may reflect decreased ability to appropriately regulate behavior during hypomanic phases of illness in the context of some areas of non-affected performance. This observation provides some ecological validity of the measures employed, as increases in impulsivity are considered prototypic of hypomanic and manic states.

These findings appear to be in contrast to a recent meta-analysis that suggested that inhibitory control deficits may be reflective of a trait-like cognitive endophenotype in BD (Bora et al., 2009). There is an important distinction to be made between the use of response inhibition as described by Bora et al. (2009), compared to the interference resolution with processing speed and inhibitory control used herein. The Stroop Color Word test includes response inhibition, but the primary dependent variable used is time, so speed of resolution of the interfering color and word processing streams is critical (Langenecker et al., 2004; Persson and Reuter-Lorenz, 2008). This aligns well with the other factors on the processing speed with interference resolution factor, PGNG response time and TMT time. All include the speed at which one can flexibly modulate contents of working memory or resolve conflicting stimuli from multiple sources and this may be a critical identifying ICP in BD that exists irrespective of phase of illness, as we demonstrate herein. Herein we are able to distinguish between speed of interference resolution, affected in all states of illness, and success in inhibitory control, affected only in the hypmanic/mixed state.

We also demonstrate phase effects of the illness for depression, similar to previous studies (Gruber et al., 2007; Martinez-Aran et al., 2004). Specifically, decreases in verbal learning and memory, verbal fluency and processing speed and fine motor function were observed in the depressed phase of the illness when compared to the euthymic phase of the illness. In addition, the depressed BD group exhibited poorer performance compared to the HC group in emotion processing, visual memory, conceptual reasoning and set-shifting, and processing speed with interference resolution. In sum, the depressed BD group profile looks very similar to the profile observed in MDD (Burt et al., 1995; Rogers et al., 2004). The extent of cognitive decrements in the depressed BD group might be considered suggestive of global cognitive dysfunction, though several analyses and non-significant factors discount this possibility. The depressed group did not differ from the HC group in synonym knowledge, an estimate of premorbid vocabulary and knowledge. And while vocabulary scaled scores from the WASI subtest were slightly lower for the depressed group, this effect was not significant after controlling for the lower level of education in the depressed group relative to the HC group. Finally, the presence of some specific areas of cognitive decrements in the euthymic phase of BD suggests that some aspects of dysfunction are trait features and some are state features, imferring a definite specificity of factor scores of cognitive decrements in BD.

5. Limitations

Limitations include slight (but non-significant) differences between the D-BD and HM-BD groups and the HC and E-BD groups in years of formal education. Nonetheless, the effects reported in the present study were directed primarily toward comparisons between E-BD and HC groups (where education and IQ were equivalent), in which three of eight factor scores were lower in the E-BD group compared to the HC group. In fact, the mean age of onset of illness for BD was slightly younger in the D-BD and HM-BD groups (age 20) and these initial episodes may have interfered with completion of educational studies for a sizeable proportion of these individuals. As is typical for every large scale study of BD, we were unable to control for effects of medication in this naturalistic design. Nonetheless, we did not show any adverse effects of most medication classes, with the exception being that those treated with antipsychotic medication performed more poorly than those not taking medications from this class. However, we discovered that those taking antipsychotic medications had nearly twice as many inpatient hospitalizations, suggesting that there was an underlying factor of disease severity that may account for the increased number of hospitalizations, need for therapeutic use of antipsychotic medication, and underlying greater cognitive dysfunction.

In summary, our results support pursuing ICPs for BD and related disorders. Like several large studies of euthymic BD patients, we show cognitive decrements in executive functioning, fine motor dexterity and visual memory, but not verbal memory. We show additional decrements in the depressed and hypomanic states, with a differential pattern for each. Further, we show differential severity linkages between years of illness and number of psychiatric hospitalizations and potentially therapeutic need for or benefit from treatment with antipsychotic medications. Of note is a critical need to distinguish between the relative presence of cognitive decrements in BD, the severity of such decrements, and the specificity of such decrements in future studies, with important additional considerations for phase of illness and medication status (Bora et al., 2009). We contend that it is unlikely that there will be great specificity in the decrements that are present in BD, SCZ, and MDD, particularly when general cognitive constructs are studied with standard neuropsychological probes. Identification of more disease-specific ICPs will require very detailed design characteristics and may not be feasible. Clearly cognitive decrements of this nature do not appear to occur in BD alone. We and others argue that there may be common ICPs for BD and related disorders that can be pursued in future studies of phenotypes with subsequent integration of genetic data. As a result there could be an expectation of earlier identification and preventative or ameliorative treatment, or development of specific targets for novel treatments. ICPs are measurable, reliable and easy to assess, and we have identified 3 factor scores of priority including Processing Speed and Interference Resolution, Fine Motor, and Visual Memory that are worthy of further pursuit.

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Conflict of interest

There are no disclosures to report for any authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jad.2009.08.018.

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