

## Original Article

## Differential executive functioning performance by phase of bipolar disorder

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**Objective:** This study examined the influence of illness phase on executive functioning performance using factor-derived cognitive scores in a cross-sectional design.

**Methods:** Healthy control (HC) subjects ( $n = 57$ ), and euthymic (E-BD) ( $n = 117$ ), depressed (D-BD) ( $n = 73$ ), and hypomanic/mixed (HM/M-BD) ( $n = 26$ ) patients with bipolar disorder (BD) were evaluated using executive functioning measures (Wisconsin Card Sorting Test, Trail Making Test–Parts A and B, Verbal Fluency, Parametric Go/No-Go, Stroop, and Digit Symbol) comprising Conceptual Reasoning and Set-Shifting (CRSS), Processing Speed with Interference Resolution (PSIR), Verbal Fluency and Processing Speed (VFPS), and Inhibitory Control (IC) factor scores.

**Results:** Two of the four executive functioning factors were significantly different between groups based upon phase of illness. The HM/M group was significantly worse than both of the other BD groups and the HC group in IC. The VFPS factor was sensitive to the active phase of BD, with the HM/M-BD and D-BD groups worse than HC. Extending our prior work, the PSIR factor, and now the CRSS factor were significantly worse in BD relative to HC, irrespective of phase of illness.

**Conclusions:** Phase of illness had differential cognitive profiles in executive functioning factors, even after considering and excluding the impact of clinical features, illness characteristics, medications, and demographics. Consolidating executive functioning tasks into reliable factor scores provides unique information to measure and define cognitive deficiencies throughout phases of BD, and to measure intermediate phenotypes in BD, and may aid in tracking and clarifying treatment focus.

Kelly A Ryan, Aaron C Vederman,  
E Michelle McFadden, Anne L  
Weldon, Masoud Kamali, Scott A  
Langenecker and Melvin G McInnis

Department of Psychiatry, University of Michigan,  
Ann Arbor, MI, USA

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Corresponding author:  
Kelly A Ryan, Ph.D.  
Department of Psychiatry  
University of Michigan  
2101 Commonwealth Boulevard, Suite C  
Ann Arbor  
MI 48105  
USA  
Fax: 734-936-9262  
E-mail: karyan@umich.edu

## Introduction

The literature on individuals with bipolar disorder (BD) has converged to show deficits in psychomotor speed, executive function, attention, memory, and fine motor skills (1, 2). Individuals in the active states of BD illness generally perform worse than healthy controls on neuropsychological tasks. The initial findings focused on the acute states of bipolar illness, but recent studies have shown that those in the euthymic state demonstrate persistent or trait-like cognitive deficits as compared to

healthy controls (3–7). Executive functioning (EF) impairments, however, are not universally found among the remitted BD patients in these studies (8–11), suggesting that EF skills may be more sensitive to fluctuations by phase of illness in BD.

There have been a limited number of studies demonstrating phase of illness effects in BD with regard to EF (7, 12–14). Small sample sizes or poorly represented BD groups, as well as the complexity and the multifactorial nature of the EF system may account for these differences and

the relative paucity of literature in this important area. For example, a small study demonstrated that remitted BD patients performed more accurately than manic BD patients on tasks of inhibitory control, response initiation/suppression, and verbal fluency (3). Other cross-sectional studies have found no differences when comparing remitted to manic or hypomanic states (7, 12, 14, 15) or remitted to depressed state (7, 12–15), but these were similarly limited by small sample sizes, a limited selection of EF measures, and failure to use convergent data methods like factor analysis.

In other contexts, factor analysis has been used to obtain reliable estimates of underlying cognitive constructs, which minimizes measurement error (2, 16, 17). This technique provides a stronger approach to measure and define cognitive abilities. Consolidating EF tasks into relevant factor scores is more likely to reflect the underlying latent variables present and can provide a greater understanding of particular deficits in BD. In addition, factors scores could be considered as intermediate phenotypes for BD, useful for genetic studies in BD. Cognitive dysfunction has been suggested to be a possible intermediate phenotype in BD (1, 2), with a recent meta-analysis underscoring the importance of neuropsychological variables in determining intermediate cognitive phenotypes in BD (1). According to Gottesman and Gould (18), a candidate intermediate phenotype should be associated with the illness and should be state-dependent, therefore manifesting in an affected individual whether or not the illness is in the active state. Furthermore, traditional neuropsychological tests often simultaneously measure multiple aspects of EF (19, 20) such as cognitive flexibility, set-shifting, planning, abstract thinking, rule acquisition, and response initiation and inhibition. It is also possible that use of factor scores may result in a better representation of the cognitive features present in phases of BD illness.

#### Aims of the study

The aims of the present study were to segregate those EF processes related to trait risk for BD—or intermediate phenotypes—from those EF processes that are influenced specifically by different acute phases of the illness. Likewise, it is possible that those factors that represent intermediate phenotypes would exhibit an additional degree of dysfunction in active phases of illness. The factor scores that were used represent underlying cognitive constructs representative of distinct aspects of EF based upon our prior work (2). We predicted that all BD patients would

perform more poorly than healthy controls on all EF factors. Additionally, we predicted that those individuals in the manic/hypomanic/mixed state would demonstrate poorer inhibitory control relative to healthy controls and relative to those individuals in the depressed and euthymic states. Those in the depressed phase of BD are expected to perform worse than other BD groups and healthy controls on EF tasks that have a timed or contain a processing speed component.

## Materials and methods

### Subjects

All participants were recruited into a longitudinal study of BD with the goal of gathering phenotypic data and biological material for the Prechter Bipolar Repository at the University of Michigan (Ann Arbor, MI, USA). Participants included in the study were 216 individuals with confirmed BD (187 with bipolar I disorder and 29 with bipolar II disorder) and 57 healthy controls (HC). One hundred and twenty-two of these BD subjects were reported in our prior study (2) and we have added an additional 94 participants with BD and 23 healthy controls for the present study. Notably, the prior study had a very small number of subjects in the hypomanic/mixed group ( $n = 13$ ), preventing well-powered comparisons of the type conducted herein. Recruitment of participants occurred through advertisements on the web and in the newspaper, an outpatient specialty psychiatric clinic, and an inpatient psychiatric unit. All participants underwent an evaluation using the Diagnostic Interview for Genetic Studies (DIGS) (21), neuropsychological testing, psychiatric symptom questionnaires, Hamilton Depression Rating–17 item version (HDRS-17) (22), and Young Mania Rating Scale (YMRS) (23). A best estimate process by at least three of the authors was used to confirm diagnoses. Participants were excluded if they had active substance use at the time of the evaluation or neurological disease. The HDRS-17 and YMRS were used to determine mood state at the time of administration of the neuropsychological tests. Of the 216 BD patients assessed, 117 were assessed when euthymic ( $\text{HDRS-17} < 8$  and  $\text{YMRS} < 8$ ), 73 when depressed ( $\text{HDRS-17} \geq 8$  and  $\text{YMRS} < 8$ ), and 26 when manic, hypomanic or mixed ( $\text{YMARS} \geq 8$ ) (see Table 1). The manic/hypomanic ( $n = 18$ ) and mixed ( $n = 8$ , also had  $\text{HDRS-17} > 8$ ) groups were combined into one group to increase statistical power.

## Executive functioning and bipolar disorder

Table 1. Demographic and clinical variables for bipolar disorder (BD) and healthy control groups

	Euthymic BD (n = 117)	Depressed BD (n = 73)	Hypomanic/mixed BD (n = 26)	Healthy controls (n = 57)	F	p-value
Age, mean (SD)	38.19 (12.14)	40.32 (11.96)	38.76 (13.19)	35.52 (14.75)	1.47	0.22
Education, mean (SD)	15.48 (2.07)	15.00 (2.35)	14.68 (2.16)	15.88 (2.43)	2.52	0.06
Gender, % female <sup>a</sup>	43.1	38.6	52.0	43.6		0.71
WASI vocabulary scaled score, mean (SD)	12.61 (2.79)	12.22 (2.95)	11.43 (2.45)	12.75 (3.07)	1.42	0.24
HRDS-17, mean (SD) <sup>b</sup>	4.56 (3.18)	13.86 (3.33)	12.27 (6.63)	1.38 (1.87)	183.97	< 0.001
YMRS, mean (SD) <sup>c</sup>	1.59 (1.93)	2.21 (2.02)	12.44 (5.61)	0.26 (0.78)	168.11	< 0.001
Years ill, mean (SD)	28.81 (13.49)	32.87 (14.82)	26.86 (14.37)	NA	2.33	0.10
No. psychiatric hospitalizations, mean (SD)	3.03 (3.49)	3.56 (6.40)	3.20 (2.94)	NA	0.15	0.86
History of psychosis, (%) <sup>a</sup>	64.0	60.9	56.5			0.77
Average no. episodes/years ill, mean (SD)	4.56 (16.30)	8.30 (33.70)	4.74 (5.40)	NA	0.58	0.56
Mania (age at onset), mean (SD)	22.90 (17.84)	22.10 (13.09)	17.96 (11.37)	NA	0.96	0.39
Mania (no. episodes), mean (SD) <sup>d</sup>	7.01 (14.40)	6.28 (11.37)	24.28 (37.47)	NA	10.67	< 0.001
Depression (age at onset), mean (SD)	19.08 (10.13)	18.42 (10.32)	18.31 (9.98)	NA	0.20	0.82
Depression (no. episodes), mean (SD) <sup>e</sup>	16.66 (45.56)	33.84 (59.06)	40.88 (46.62)	NA	3.93	0.02
Hypomania (age at onset), mean (SD)	14.72 (14.15)	13.49 (12.03)	18.88 (12.36)	NA	1.55	0.21
Hypomania (no. episodes), mean (SD) <sup>d</sup>	13.88 (30.34)	19.64 (40.36)	52.52 (73.99)	NA	12.68	< 0.001

BD = bipolar disorder; D-BD = depressed bipolar disorder; E-BD = euthymic bipolar disorder; HDRS-17 = Hamilton Depression Rating Scale-17 item version; HC = healthy controls; HM/M-BD = hypomanic or mixed bipolar disorder; NA = not applicable; SD = standard deviation; WASI = Wechsler Adult Scale of Intelligence; YMRS = Young Mania Rating Scale.

<sup>a</sup>Chi-square test.

<sup>b</sup>HC < E-BD < HM/M-BD < D-BD.

<sup>c</sup>HM/M-BD > E-BD, D-BD > HC.

<sup>d</sup>HM/M-BD > E-BD, D-BD.

<sup>e</sup>HM/M-BD > E-BD.

### Neuropsychological assessment

A battery of neuropsychological tasks measuring components of EF were administered: the Wisconsin Card Sorting Test (24), the Stroop Color and Word Test (25), the FAS verbal fluency task of the Controlled Oral Word Association Test, and Animal Fluency (26), Digit Symbol from the Wechsler Adult Intelligence Scale-III (WAIS-III) (27), the Trail Making Test-Parts A and B (28), and the Parametric Go/No-Go task (29). Standard data reduction techniques (principal axis factor analysis) were used to collapse the EF tasks with oblique rotation and were used as the factor scores for subsequent analyses. All scores with negative

scale properties were inverted; as a result, lower factor scores reflect poorer performance. A confirmatory factor analysis was computed with the above variables, consistent with our prior study (2). The four factors were Verbal Fluency and Processing Speed (VFPS), Conceptual Reasoning and Set-Shifting (CRSS), Processing Speed with Interference Resolution (PSIR), and Inhibitory Control (IC). Variables that load on the factors and reliability of the factor scores (adjusted alpha) are reported in Table 2, similar to our previous report. In addition to the above tasks, the Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence was compared as a methodological control for premorbid ability (30).

Table 2. Main effects for executive functioning factor scores in bipolar disorder and healthy control participants

Factor analysis and reliability (alpha)	Test	Factor loading	Group effect	Post-hoc difference			
Verbal Fluency and Processing Speed <sup>a</sup>	Phonemic Fluency	0.49	$F(3,269) = 3.05,$ $p = 0.02$	HC > D, HM/M			
	Category Fluency	0.42					
	Digit Symbol	0.46					
	Stroop Color Word Test						
	Word Condition T	0.89					
	Color Condition T	0.75					
Conceptual Reasoning and Set-Shifting <sup>b</sup>	Wisconsin Card Sort Test		$F(3,269) = 6.63,$ $p = 0.01$	HC > E, D, HM/M			
	Correct	0.96					
	Perseverative errors (inverted)						
	Parametric Go/No-Go	0.89					
	Mean accuracy for target trials	0.47					
Processing Speed With Interference Resolution <sup>c</sup>	Trail Making Test		$F(3,269) = 6.70,$ $p = 0.00005$	HC > E, D, HM/M			
	Part A	0.63					
	Part B	0.69					
	Digit Symbol	0.42					
	Stroop Color Word Test						
	Interference T	0.72					
	Parametric Go/No-Go						
	Mean target response time (inverted)	0.67					
	Inhibitory Control <sup>d</sup>	Parametric Go/No-Go				$F(3,269) = 3.31,$ $p = 0.02$	HC > HM/M D, E > HM/M
		Mean accuracy for inhibitory trials			0.95		

D = depressed; E = euthymic; HC = healthy controls; HM/M = hypomanic or mixed.

<sup>a</sup>Alpha  $r = 0.80$ .

<sup>b</sup>Alpha  $r = 0.79$ .

<sup>c</sup>Alpha  $r = 0.76$ .

<sup>d</sup>Not applicable.

#### Clinical variables

Specific clinical data points were extracted from the DIGS interview to study the relationships between factor scores and clinical indices of severity. These variables, listed in Table 1, include the historical number of psychiatric hospitalizations, age at onset of first episode, summation of number of depressive and manic episodes, lifetime presence of psychosis, chronicity of affective symptoms, years since first episode, and mean number of episodes per year the individual was ill (i.e., mean number of manic and depressive divided by number of years

since first episode). These clinical variables were chosen based upon prior literature demonstrating that these factors have a potential impact upon cognitive functioning. There were no significant differences between BD groups and HC for age:  $F(2,207) = 0.662, p = 0.517$ ; education:  $F(2,207) = 1.979, p = 0.141$ ; or gender:  $\chi^2(2, n = 211) = 1.38, p = 0.502$ . There were no significant differences between BD groups for number of hospitalizations, lifetime presence of psychosis, number of episodes per year that the individual was ill, or age of onset of depression, mania, or hypomania (see Table 1).

Statistical analyses

Our hypotheses of overall EF impairment in BD, and of phase-specific effects in BD were both assessed with a 4 \* 4 multivariate analysis of variance (MANOVA). The four groups were healthy controls (HC), currently depressed bipolar disorder (D-BD), euthymic bipolar disorder (E-BD), and hypomanic or mixed (HM/M-BD). The four factors of EF used were derived by principal axis confirmatory factor analysis and oblique rotation. In addition, other multivariate analyses were run to evaluate the contributions, and potentially confounding influence of clinical, medication, and demographic variables.

Individuals with BD were taking a range of medications from a broad range of classes. To address the impact of medications on factor scores between our BD groups, we examined the influence of medications in two ways. First, MANOVAs were used with binary yes/no response options for each of the five categories of medication (antidepressant, mood stabilizer, antipsychotic, sedative/anxiolytic, and stimulant) as the independent variables and the factor scores as the dependent variables. Secondly, we adopted a protocol often seen in the literature to assess total medication load. Antidepressant, anxiolytic, mood stabilizer, and antipsychotic medications were coded as absent = 0, low = 1, or high = 2 based on previously employed methods to convert each medication to a standardized dose (31–33) Antipsychotics were converted into chlorpromazine dose equivalents (34). Following Hassel et al.'s (31) methodology we generated a composite

measure of total medication load by summing all individual medication codes for each individual medication within categories for each BD participant. Analysis of variance was used to compare the four groups on total medication loading.

Results

Comparison of EF factor scores by group

A MANOVA was computed with the four EF factor scores as dependent variables and the four groups as independent variables. Results showed that there was a significant group effect,  $F(12,804) = 3.05, p < 0.0001$ ; the HC group outperformed the E-BD on two of the four EF factors (PSIR and CRSS), the D-BD on three out of the four EF factors (PSIR, CRSS, and VFPS), and the HM/M-BD group on four out of the four EF factors (PSIR, CRSS, VFPS, and IC) (Fig. 1). The E-BD performed similarly to the D-BD group on all factors while both groups outperformed the HM/M-BD group on IC. These differences are shown in Table 2 (with factor score/reliability) and illustrated in Figure 1. Although the sample sizes for the hypomanic–manic ( $n = 18$ ) and mixed ( $n = 8$ ) BD patients were small, there were no significant differences between these two groups for any of the factor scores in a follow-up, two group by four factor MANOVA,  $F(4, 21) = 0.805, p = 0.535$ . There were also no differences between the two subgroups of the HM/M-BD group on demographic or clinical variables, suggesting that these groups were appropriate to combine for analyses into one group (HM/M-BD).

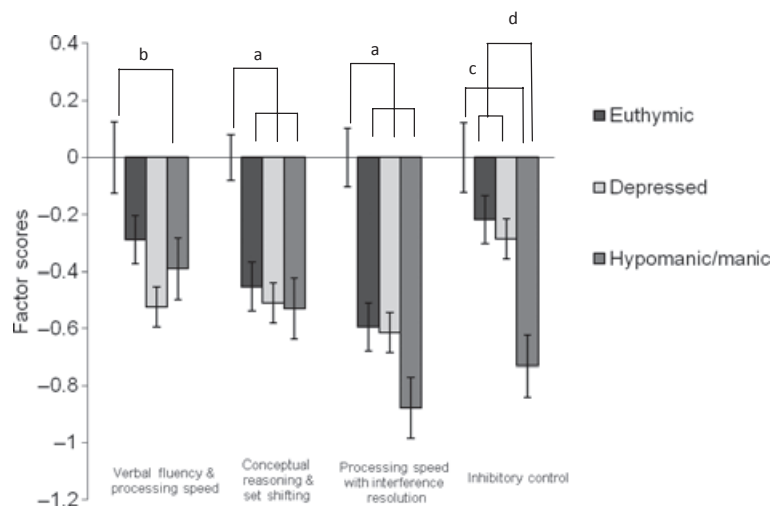


Fig. 1. Phase of illness by executive function factor score. Factor scores were re-adjusted based on healthy control values being set to zero. <sup>a</sup>Healthy controls performed significantly better than all bipolar disorder groups. <sup>b</sup>Healthy controls performed significantly better than active phase bipolar disorder groups. <sup>c</sup>Healthy controls performed better than the hypomanic/mixed group. <sup>d</sup>The hypomanic/mixed group performed significantly worse than the depressed and euthymic bipolar disorder groups.

## Clinical variables by phase of BD illness

There were no significant differences between BD groups (E, D, and HM/M) on MANOVA for most clinical variables and illness severity, such as number of inpatient psychiatric hospitalizations, age of onset, number of years ill, chronicity of psychosis, chronicity of affective symptoms, or total number of depressive and manic episodes per year ill (Table 1). The HM-M BD showed significantly more lifetime manic and hypomanic episodes than E-BD and D-BD,  $F(6,400) = 5.72$ ,  $p < 0.001$ .

We took steps to rule out this illness severity (episodes) marker as a confound driving particular effects in targeted post-hoc analyses as appropriate (when the HM-M BD group was significantly different from any other BD group). To verify specific phase of illness effects, we matched subgroups of the E-BD, D-BD and HM/M-BD groups based on number of manic and hypomanic episodes, and an additional post-hoc analysis was conducted. MANOVA results continued to show a significant group effect,  $F(12,573) = 3.29$ ,  $p = 0.0001$ ; the HC group outperformed the E-BD on three of the four EF factors (PSIR, CRSS, and VFPS), the D-BD on three out of the four EF factors (PSIR, CRSS, and VFPS), and the HM/M-BD group on three out of the four EF factors (PSIR, CRSS, and IC). In this specific post-hoc analysis, the E-BD performed similarly to the D-BD group on all factors and the E-BD and D-BD groups still outperformed the HM/M-BD group on IC ( $p < 0.05$ ).

There were no significant differences between all four groups on the vocabulary subtest of the WASI,  $F(3) = 1.42$ ,  $p = 0.238$ , a traditionally defined 'hold' test that would be expected not to change based upon scar or burden effects of illness (35). The lack of difference on both the vocabulary subtest and in years of formal education between groups suggests that they were well matched in premorbid ability.

## Medication effects on EF factor scores in BD

The effects of medication may have confounded the results of the study, as those in the active state of illness or with more severe illness might be expected to be prescribed more medications and there might be variable adherence with medication by phase of illness. Each medication effect on the four factor scores was assessed in a MANCOVA/MANOVA, with binary yes/no response options for each of the five categories of medication (antidepressant, mood stabilizer, antipsychotic, sedative/anxiolytic, and

stimulant) used as the independent variables. HDRS-17, YMRS, age of illness onset, number of years ill, and number of inpatient psychiatric hospitalizations were initially entered as covariates in the model. For four out of the five classes of medications, there were no significant covariate effects on the four EF factors. Therefore, results from MANOVAs only are reported. There were no differences in EF factor performance among individuals taking the following classes of medications: mood stabilizer:  $F(4,202) = 0.91$ ,  $p = 0.46$ ; antidepressant:  $F(4,202) = 0.23$ ,  $p = 0.92$ ; sedative/anxiolytic:  $F(4,202) = 0.69$ ,  $p = 0.62$ ; or stimulant:  $F(4,202) = 0.54$ ,  $p = 0.71$ . The sole significant medication effect upon the EF factors was for treatment with antipsychotics,  $F(4,202) = 2.87$ ,  $p = 0.02$ . Those taking this class of medications had worse performance on the VFPS factor,  $F(1,205) = 9.87$ ,  $p = 0.002$ ; however, those taking antipsychotic medications tend to have a history of a greater number of inpatient hospitalizations, suggesting that disease severity may have contributed to this EF performance difference, similar to prior work (36). Among types of mood stabilizers, lithium has been associated with cognitive side effects, such as mental slowing. In this study, there were no differences in performance in individuals taking lithium compared to those taking some other mood stabilizer,  $F(4,140) = 1.75$ ,  $p = 0.14$  for the four factor scores.

Additionally, a correlational analysis was used to examine the relationship between the four EF factor scores and total medication loadings for all BD participants. Total medication loading was not correlated with the VFPS ( $r = -0.14$ ,  $p = 0.17$ ), CRSS ( $r = -0.01$ ,  $p = 0.89$ ), PSIR ( $r = -0.11$ ,  $p = 0.26$ ), or IC ( $r = -0.09$ ,  $p = 0.39$ ) factors. There also were no differences in total medication loading between the three BD groups,  $F(2) = 2.31$ ,  $p = 0.10$ .

## Relationship of EF factor scores with clinical variables

Bivariate correlations between EF factor scores and clinical variables for all BD patients as well as just the E-BD group are shown in Table 3. These are provided to better characterize the subgroups of BD participants and for comparison with other studies, not as additional, hypothesis-driven comparisons. Among all BD patients, number of inpatient hospitalizations was negatively associated with three out of the four factor scores (VFPS,  $r = -0.26$ ; CRSS,  $r = -0.37$ ; and PSIR,  $r = -0.20$ ), number of years ill was significantly associated with three factors scores (VFPS,  $r = -0.20$ ; CRSS,  $r = -0.23$ ; and PSIR,  $r = -0.32$ ), the

Table 3. Relationship of executive function factors with clinical variables

	Verbal Fluency and Processing Speed <sup>a</sup>	Conceptual Reasoning and Set-Shifting <sup>a</sup>	Processing Speed With Interference Resolution <sup>a</sup>	Inhibitory Control <sup>a</sup>
No. psychiatric hospitalizations	-0.26 <sup>c</sup> (-0.35 <sup>c</sup> )	-0.37 <sup>c</sup> (-0.39 <sup>c</sup> )	-0.20 <sup>d</sup> (-0.24 <sup>d</sup> )	-0.03 (-0.02)
Age at onset	0.12 (0.06)	0.01 (-0.04)	-0.17 <sup>d</sup> (-0.22 <sup>d</sup> )	0.03 (0.19 <sup>d</sup> )
Total depressive episodes	-0.06 (0.05)	-0.10 (0.05)	-0.10 (0.03)	0.05 (0.14)
Total hypomania/mixed episodes <sup>b</sup>	0.80 (-0.05)	-0.15 <sup>d</sup> (-0.10)	-0.16 <sup>d</sup> (-0.15)	-0.13 (0.08)
Chronicity of psychosis	-0.13 (-0.15)	-0.05 (-0.06)	-0.05 (-0.20)	-0.01 (0.04)
Chronicity of affective symptoms	0.02 (0.02)	-0.04 (-0.04)	-0.08 (-0.06)	-0.06 (-0.14)
No. years of illness	-0.20 <sup>c</sup> (-0.09)	-0.23 <sup>c</sup> (-0.21 <sup>d</sup> )	-0.32 <sup>c</sup> (-0.32 <sup>c</sup> )	0.08 (0.03)
No. episodes/years ill	-0.10 (-0.16)	0.07 (0.09)	0.002 (-0.04)	-0.06 (-0.02)
Hamilton Depression Rating Scale	-0.14 <sup>d</sup> (-0.01)	-0.01 (0.14)	-0.07 (-0.08)	-0.03 (0.01)
Young Mania Rating Scale	0.01 (-0.13)	0.01 (0.06)	-0.07 (-0.11)	-0.15 <sup>d</sup> (-0.11)
Total medication load	-0.14 (0.17)	-0.01 (0.89)	-0.11 (0.26)	-0.09 (0.39)

<sup>a</sup>The values in parentheses are correlations between the clinical variables within the euthymic bipolar disorder group only.

<sup>b</sup>Sample matched on no. hypomanic/mixed episodes.

<sup>c</sup> $p < 0.01$ .

<sup>d</sup> $p < 0.05$ .

HRDS was significantly associated with one factor (VFPS,  $r = -0.14$ ), and the YMRS was significantly associated with one factor (IC,  $r = -0.15$ ). Number of hypomanic/mixed episodes was significantly associated with two factors (CRSS,  $r = -0.15$ ; and PSIR,  $r = -0.16$ ). Age of onset of any mood episode was negatively associated with PSIR ( $r = -0.17$ ). None of the other clinical variables were significantly related to the factor scores ( $p > 0.05$ ).

**Discussion**

Cognitive intermediate phenotypes for BD

There are general EF impairments observed in active and euthymic phases of BD, as well as specific EF impairments related to the two active phases of BD evaluated here. All BD patients performed worse than healthy controls on tasks of PSIR and CRSS. This suggests that executive tasks that comprise a set-shifting or interference resolution component are weaker among BD patients, regardless of mood state, and are potentially strong intermediate phenotypes in BD. There are additional, more modest effects based upon years of illness, number of hospitalizations, and current phase of illness above and beyond what could be

considered the intermediate phenotype component for these set-shifting and interference resolution factors. Nonetheless, there is sufficient evidence, from our work and in the literature, that these are intermediate phenotypes worthy of further, careful investigation (1).

Furthermore, individuals in the remitted state performed similarly to, often only slightly and non-significantly better than, those who were currently depressed or hypomanic/mixed on factors assessing VFPS, PSIR, and the conceptual reasoning with set-shifting, suggesting that these deficiencies may be chronic, trait-like deficiencies in BD. These factor scores use combinations of the Wisconsin Card Sorting Test, Trail Making Test, Stroop Color Word Test, Digit Symbol, and Parametric Go/No-Go test, similar to findings in other studies that showed worse performance in BD as compared to healthy controls (1, 2). Furthermore, our findings confirm and extend PSIR as a potential intermediate phenotype. This factor was identified as a potential marker in our previous work using a smaller sample of our participants. Here we show with greater specificity that three EF factors have trait-like characteristics for intermediate phenotype consideration, beyond the one factor from the previous study.

Non-specific executive dysfunction in both active phases of BD

Patients in the two active mood states performed similarly on most EF factors except for inhibitory control. The factor where both active groups, but not the remitted group, underperformed relative to the healthy control group was the VFPS factor. As seen in Figure 1, however, the relative magnitude of the difference between the remitted BD group and the hypomanic/mixed group or the depressed group was relatively small. This suggests that the VFPS factor may be a relatively weak intermediate cognitive phenotype, with a very modest trait-like effect, and more marked phase effects.

Specific executive dysfunction for inhibitory control in the hypomanic and mixed phase of BD

Individuals in the hypomanic/mixed group had worse inhibitory control as compared to the depressed and euthymic patients, a novel and well-powered finding within the context of groups matched on clinical, demographic, premorbid and treatment characteristics. This is consistent with the notion that those in a hypomanic/mixed state have greater difficulties regulating behavior. One of the key diagnostic features of the manic state is difficulty with impulse control, and the present findings confirm and specify the nature of this relationship. These findings significantly extend our prior pilot findings in which only the healthy controls outperformed the hypomanic/mixed group on inhibitory control. In the present study, those in the hypomanic/mixed phase underperformed relative to matched depressed and euthymic groups. These findings would appear similar to those of the pilot study by Dixon et al. (4), who reported that individuals in the manic phase performed worse on inhibitory control than individuals in the remitted phase. The study of Dixon and colleagues was confounded by significant differences in education, premorbid ability, anti-psychotic doses, degree of thought disorder by phase of illness, and presence of mixed symptoms in the depressed and manic samples, which made it difficult to be confident about the results. In contrast, the present study clarifies and extends this pilot study with a larger group and adds several important qualifiers. Here, we show phase-specific impairments in the hypomania/mixed group for inhibitory control relative to the depressed and euthymic groups. Our euthymic and depressed groups have negligible manic symptoms, and the inhibitory control-specific results are

the same when groups are matched on all of the clinical and demographic features of interest. In addition, we show that it is a specific effect related to inhibitory control, whereas other effects are related to active phase of illness (VFPS), or presence of illness (conceptual reasoning with set shifting, and PSIR), more generally.

Treatment implications of inhibitory control dysfunction in hypomanic/mixed states

The capacity to measure current levels of and changes in EF performance can have important clinical implications. First, EF changes may coincide with or predate phase shifts in illness and can aid in self- and clinician-identification with subsequent treatment modification. For example, it is possible that changes in inhibitory control occur early in the hypomanic phase, before full-blown mania has emerged. The increased interpersonal, vocational, and legal ramifications of the manic phase of illness might be avoided with early identification and treatment modification.

In addition, specific knowledge of intra-patient fluctuation in EF can aid in redefining treatment focus and disease management. A differential pattern of executive dysfunction in a phase-specific manner in BD suggests that multiple tests are needed to fully characterize and understand EF. Thus treatment uses for diagnostic purposes, such as traditional clinical neuropsychological evaluation, may need several EF tasks to be administered to fully assess pertinent subdomains. In contrast, to develop tools to track impulsivity, for example, a much more limited subset could be used for repeated assessment in clinical settings.

### Limitations

One specific limitation for this study in comparing groups by current phase of illness was the inclusion of a relatively small hypomanic/mixed group, in comparison to the large euthymic BD and depressed BD groups. Important effects for this group in comparison to other groups may have been missed. A larger hypomanic/mixed BD group should be recruited in order to demonstrate significant differences more clearly. Another important limitation of the study is the cross-sectional design, which prevents examination of intra-individual differences in EF over time. It is difficult to speculate whether the pattern of executive dysfunction by phase of BD illness will change as individuals shift from one phase to another phase. Future studies could investigate this by using a



longitudinal design, a specific aim of the Prechter Longitudinal Study of BD. As is common among most naturalistic studies of this kind, it is difficult to control for the effects of medication, treatment adherence, and treatment optimization. However, we did not show substantial adverse effects of most medication classes, with the exception that those being treated with antipsychotic medications performed more poorly than those not taking antipsychotic medications. When using a protocol often seen in the literature to assess total medication load in patients with BD, we found no difference between our three BD groups based upon medication load, and medication load was not related to the EF factor scores.

### Conclusion

Prior studies of EF in BD have primarily focused on comparing individuals in one or two phases of the BD illness to healthy controls or have focused on only comparing depressed to euthymic, manic to euthymic, or manic to depressed using very small sample sizes and poorly represented BD groups. A particular strength of the present study was the inclusion of a well-representative, well-characterized, and large sample of BD individuals and a large healthy comparison group. In summary, EF factors appear to have promise as intermediate cognitive phenotypes marking trait risk for illness in the PSIR and CRSS factors. In addition, there are two factors that are moderated by phase of illness. Specifically, VFPS appears to worsen in the depressed and hypomanic/mixed phase of illness. In contrast, IC worsens in the manic phase of illness with similar performance on the factor between the depressed and remitted patients. These factor scores may aid in tracking EF across phase of BD illness, which may one day be objectively helpful in tracking a patient's risk for mania.

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