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Limited time-specific and longitudinal effects of depressive and manic symptoms on cognition in bipolar spectrum disorders

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Abstract

Objectives: Previous research suggests that cognitive performance worsens during manic and depressed states in bipolar disorder (BD). However, studies have often relied upon between-subject, cross-sectional analyses and smaller sample sizes. The current study examined the relationship between mood symptoms and cognition in a within-subject, longitudinal study with a large sample.

Methods: Seven hundred and seventy-three individuals with BD completed a neuropsychological battery and mood assessments at baseline and 1-year follow-up. The battery captured eight domains of cognition: fine motor dexterity, visual memory, auditory memory, emotion processing, and four aspects of executive functioning: verbal fluency and processing speed; conceptual reasoning and set shifting; processing speed with influence resolution; and inhibitory control. Structural equation modeling was conducted to examine the cross-sectional and longitudinal relationships between depressive symptoms, manic symptoms, and cognitive performance. Age and education were included as covariates. Eight models were run with the respective cognitive domains.

Results: Baseline mood positively predicted 1-year mood, and baseline cognition positively predicted 1-year cognition. Mood and cognition were generally not related for the eight cognitive domains. Baseline mania was predictive in one of eight baseline domains (conceptual reasoning and set shifting); baseline cognition predicted 1-year symptoms (inhibitory control—depression symptoms, visual memory—manic symptoms).

Conclusions: In a large community sample of patients with bipolar spectrum disorder, cognitive performance appears to be largely unrelated to depressive and manic symptoms, suggesting that cognitive dysfunction is stable in BD and is not dependent on mood state in BD. Future work could examine how treatment affects relationship between cognition and mood.

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Significant Outcomes: Cognitive dysfunction appears to be largely independent of mood symptoms in bipolar disorder.

Limitations: The sample was generally highly educated ($M = 15.22$), the majority of the subsample with elevated manic symptoms generally presented with concurrent depressive elevated symptoms, and the study did not stratify recruitment based on mood state.

KEYWORDS

bipolar disorder, cognition, depression, mania

1 | INTRODUCTION

Bipolar disorder (BD) is one of the top 10 leading causes of disability in the world.[1] Even during euthymic states, the disorder is associated with prolonged social, occupational, and everyday functional impairment,[2] and these dysfunctions significantly predict disability.[2] Importantly, neurocognitive performance is one of the strongest predictors of life functioning and subsequently disability in BD.[2,3]

Numerous studies have examined the relationship between cognition and short-term and long-term functional outcome in BD. Verbal memory predicted global functioning after a mood episode at 1-year and 4-year follow-ups,[4] and processing speed positively predicted global functioning 15 years after a manic episode.[5] Social functioning at 6-year follow-up is related to deficits in verbal memory, executive functioning, processing speed, and attention.[5,6] Furthermore, neurocognition is a predictor of vocational functioning and employment status in BD; the strongest elements being verbal memory, executive functioning, processing speed, attention, working memory, inhibition, and verbal learning.[5,6] We have previously shown that emotion processing and executive functioning predicted unemployment in a bipolar and healthy comparison sample.[7]

Cognitive abilities have been associated with mood symptoms, with the greater field of research focusing on cognitive dysfunction and mood symptoms in major depressive disorder (MDD). Cognition is impaired during an active depressive episode and then often rebounds during remission.[8] Compared with healthy controls, individuals with MDD present with deficits in working memory and sustained attention, particularly on tasks requiring greater effort.[9,10] Executive functioning is also more impaired in MDD individuals, particularly inhibition and verbal fluency,[11,12] but findings of executive dysfunction are not consistent across studies,[13] though a meta-analysis found overall support for impairments in executive functioning during depression.[14] Memory is impaired during depressive states of MDD; it negatively impacts the acquisition stage of memory resulting in poorer recall and recognition.[13,15] Emotion perception performance is also poorer during depression; depressed individuals demonstrate a negative response bias for sadness compared with healthy controls, such that they more frequently misperceive neutral, angry, or fearful faces as sad.[12,16] Psychomotor speed may be impacted during MDD, with some reporting deficits[17] but others not.[13] Fine motor functioning may be slowed, particularly in the melancholic subtype of depression.[18] Overall, the consensus is that cognition is compromised concomitantly with depressive symptoms in MDD, although the particular domain is not ubiquitous across all studies.

Within BD, decrements in cognition are consistently reported, notably dysfunction in attention, executive functioning, learning and memory, emotion perception, and psychomotor speed.[7,16,19–21] These reports primarily examine the euthymic state, consistent with cognitive dysfunction as an endophenotypic marker of BD.[22,23] Few studies have focused on cognition during active mood episodes, though reports that specifically address this question suggest cognitive deficits are more pronounced during depressive and manic/hypomanic mood states compared to euthymia,[24–26] in congruence with aforementioned research showing depression impacts cognition in unipolar depressed samples.[8–18] However, the analysis of the relationship between cognition and mood symptoms in BD has relied upon between-subject, cross-sectional comparisons and smaller samples sizes.

Based on the consistent findings of cognitive impairment in MDD depressed samples and the known relationship between cognition and life functioning in BD, it is crucial to examine cognition during mood states in BD while addressing previous research's limitations. By examining mood and cognition in BD in a longitudinal design, we can better understand how depression and mania impact cognition and subsequently functioning and disability in the disorder.

1.1 | Aims of the study

Thus, our study's objective was to examine the relationship between mood symptoms and cognition within BD in a large longitudinal study of BD and to address prior

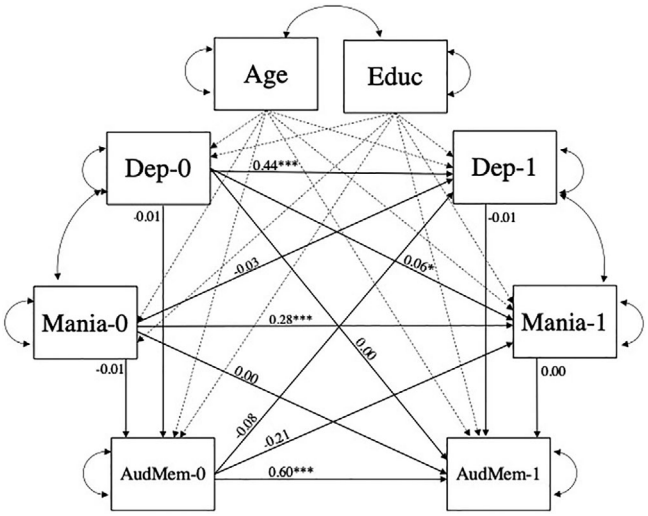

FIGURE 1 Results from Auditory Memory model with estimates for pathways of interest. Abbreviations: AudMem-0, baseline auditory memory; AudMem-1, 1-year auditory memory; Dep-0, baseline depression symptoms; Mania-0, baseline mania symptoms; Dep-1, 1-year depression symptoms; Mania-1, 1-year mania symptoms; Educ, education

research's limitations of between-subjects, cross-sectional designs and small sample sizes. In this study, we conducted structural equation modeling to examine three areas: (1a) do baseline symptoms of depression and mania predict baseline cognitive performance, (1b) do 1-year mood symptoms predict 1-year cognitive performance, (2) do mood symptoms at baseline predict cognitive performance at 1-year follow-up, and (3) does cognitive performance at baseline predict mood symptoms at 1-year follow-up (See Figure 1 for pathways). We hypothesized a positive relationship between mood across 1 year (i.e., higher mood symptoms at baseline predict higher mood symptoms at 1 year) and between cognition across 1 year (i.e., higher baseline cognitive performance predicts higher 1-year cognitive performance). We anticipated a negative relationship between mood and cognition, such that as mood symptoms increase, cognitive performance would decrease, both in cross-sectional and in longitudinal relationships.

2 | MATERIALS AND METHODS

2.1 | Study design

Participants were recruited for the Prechter Longitudinal Study of Bipolar Disorder,[22,27] a large naturalistic study of BD conducted at the University of Michigan—Ann Arbor (UM). The UM institutional review board approved the Prechter study, and recruitment occurred via advertisements in community mental health centers, an inpatient psychiatric unit, outpatient psychiatric clinics, at community outreach events, and on the internet. Individuals were excluded from the study if, at the time of study entry, they had a history of a diagnosis of schizophrenia, active substance dependence according to the DSM-IV-TR, or a history of neurological disease.

2.2 | Participants

At baseline, 1325 participants completed a diagnostic interview with an experienced clinician using the Diagnostic Interview for Genetics Studies (DIGS).[28] Diagnoses for participants were decided using a best estimates consensus model, with two MD/PhD clinicians independently evaluating the individual's psychiatric history based on information from the DIGS. For the present study, 552 subjects were excluded from present analyses because of being healthy controls or receiving a diagnosis other than BD. Thus, 773 participants diagnosed with BD (546 Bipolar I, 152 Bipolar II, and 75 Bipolar NOS) who were enrolled in the study from 2005 to 2018 and completed 1-year follow-up were included in the study. Participants' baseline age ranged from 18 to 84, with an average age of 39.57 ($SD = 13.61$), and their education ranged from 8 to 20 years, with a mean of 15.22 years ($SD = 2.19$). See Table 1 for means and SD and Appendix Table 1 for additional means and SD.

2.3 | Protocol

Participants completed a neuropsychological test battery at baseline and 1-year follow-up, which were administered by trained research associates and supervised by the study's neuropsychologists. The neuropsychological battery included the tests: the California Verbal Learning Test-II (CVLT-II),[29] Rey-Osterrieth Complex Figure Test (RCFT),[30] Purdue Pegboard,[31] Emotion Perception Test (EPT),[32] Facial Emotion Perception Test (FEPT),[33] Trail Making Test (TMT),[34] Digit Symbol Test (DST),[35] Stroop Color-Word Test (SCWT),[36] Controlled Oral Word Association (COWA),[37] Parametric Go/No Go Test (GNG),[38] and the Wisconsin Card Sort Test (WCST),[39] The Wechsler Abbreviated Scale of Intelligence (WASI),[40] was used to estimate overall intelligence.

In accordance with our previous research,[22] principal axis factor analysis was utilized to reduce the tests to fewer variables. In this process, scores on negative scales (e.g., response time) were inverted so that a lower factor score reflects worse performance. Next, a confirmatory factor analysis was computed, resulting in eight latent

TABLE 1 Summary of baseline correlations and 1-year correlations, means, and standard deviations for depression symptoms, mania symptoms, and cognitive domains

	1	2	3	4	5	6	7	8	9	10	11	12	*M*	*SD*
1. HDRS	–	0.34***	−0.11**	−0.07	−0.10*	−0.11*	−0.09*	−0.09*	−0.04	−0.08	0.05	−0.18***	8.52	5.93
2. YMRS	0.38***	–	−0.04	−0.08	−0.06	0.00	0.01	0.04	0.05	−0.02	−0.04	−0.12**	3.13	3.70
3. FM	−0.10**	−0.05	–	0.34***	0.32***	0.57***	0.32***	0.61***	0.41***	0.52***	−0.49***	0.03	−0.17	0.86
4. VM	−0.08*	−0.06	0.32***	–	0.46***	0.39***	0.32***	0.39***	0.30***	0.49***	−0.29***	0.80	−0.09	0.97
5. AM	−0.08*	−0.05	0.29***	0.43***	–	0.43***	0.33***	0.36***	0.30***	0.49***	−0.22***	0.13**	−0.05	0.89
6. VFPS	−0.11**	−0.02	0.58***	0.40***	0.43***	–	0.50***	0.78***	0.58***	0.64***	−0.36***	0.15***	−0.12	0.68
7. CRSS	−0.08*	−0.11**	0.34***	0.33***	0.38***	0.44***	–	0.46***	0.33***	0.51***	0.21***	0.15***	−0.05	0.70
8. PSIR	−0.07	−0.02	0.59***	0.44***	0.42***	0.79***	0.43***	–	0.67***	0.60***	−0.49***	0.02	−0.13	0.70
9. IC	−0.05	−0.03	0.37***	0.24***	0.27***	0.51***	0.28***	0.61***	–	0.48***	−0.32***	−0.36	0.01	0.69
10. EP	−0.08*	−0.05	0.51***	0.47***	0.47***	0.60***	0.48***	0.59***	0.43***	–	−0.46***	0.05	−0.06	0.80
11. Age	−0.01	−0.03	−0.43***	−0.36***	−0.22***	−0.31***	−0.26***	−0.45***	−0.30***	−0.50***	–	–	–	–
12. Educ	−0.16***	−0.11**	0.09*	0.07	0.12***	0.18***	0.09*	0.07	−0.00	0.07	0.23***	–	–	–
M	9.52	3.61	−0.13	−0.11	−0.06	−0.09	−0.03	−0.12	−0.10	−0.01	39.57	15.22	–	–
SD	6.27	4.03	0.85	0.96	0.91	0.69	0.76	0.69	0.69	0.80	13.61	2.19	–	–

Note: Correlations for baseline data are presented below the diagonal, and correlations for 1-year follow-up data are presented above the diagonal. Means and standard deviations for baseline are presented in the vertical columns, and means and standard deviations for 1-year are presented in the horizontal rows.

Abbreviations: AM, auditory memory; CRSS, conceptual reasoning with set shifting; EP, emotion processing; Educ, education; HDRS, Hamilton Depression Rating Scale; FM, fine motor; IC, inhibitory control; PSIR, processing speed with influence resolution; VM, visual memory; VFPS, verbal fluency with processing speed; YMRS, Young Mania Rating Scale.

***$p < 0.001$. **$p < 0.01$. *$p < 0.05$.

factors: fine motor dexterity, visual memory, auditory memory, emotion processing, and four factors of executive functioning: verbal fluency and processing speed (VFPS); conceptual reasoning and set shifting (CRSS); processing speed with influence resolution (PSIR); and inhibitory control. See Appendix Table 2 for specific test scores that are included in each domain and Appendix Table 3 for specific test score means and SD.

During the neuropsychological testing, mood was assessed using the Structured Interview Guide for the Hamilton Depression Rating Scale (HDRS),[41] and the Young Mania Rating Scale (YMRS).[42] HDRS is a 17-item assessment with potential scores ranging from 0 to 50, representing overall symptom severity for depression over the past week. YMRS is an 11-item structured interview and rating with scores ranging from 0 to 60, representing manic/hypomanic symptoms over the past week. See Table 1 for baseline and 1-year HDRS and YMRS scores.

2.4 | Data analysis

Analyses were performed in R[43] using the package, OpenMx.[44] For this study, structural equation modeling was utilized to examine the relationship between mood symptoms and cognitive performance at baseline and at 1-year follow-up. We used structural equation modeling, which offers benefits over other longitudinal statistical modeling, including ability to correlate errors in measurement related to each variable over time and account for missing data. We ran eight main models, one for each of the cognitive factors of interest. We focused our investigation to three main hypotheses: (1) mood symptoms (depression and mania) negatively predict contemporaneous cognitive performance (i.e., baseline mood predicts baseline cognition and 1-year mood predicts 1-year cognition), (2) mood symptoms at baseline negatively predict cognitive performance at 1-year follow-up, and (3) cognitive performance at baseline negatively predicts mood symptoms at 1-year follow-up. Our models specified direct paths from: baseline mood to baseline cognition, 1-year mood to 1-year cognition, and baseline mood and cognition to 1-year mood and cognition. Baseline age and education were included as covariates, with direct pathways from age and education to baseline mood and cognition and to 1-year mood and cognition (See Figure 1).

To determine the significance of each path, we utilized likelihood ratio testing, which involves rerunning each model with the specific path of interest removed from the model and then comparing the relative fit of the new model to the original model. If the fit of the new model decreases (as measured by χ^2), then the removed pathway is significant. Because of the intercorrelations between the parameters of this study's models and the nested nature of the data, likelihood ratio tests of significance offer more accurate p values for paths than standard errors methods.

To examine the absolute model fit, comparative fit index (CFI) and root mean squared error of approximation (RMSEA) were calculated. These indices of fit examine how the conducted model compares to saturated (best possible model fit) and independence models (worst possible model fit). CFI ranges from 0 to 1, and a finding greater than 0.90 is considered good fit for the conducted model. For RMSEA, a finding less than 0.05 is considered good fit, less than 0.08 is acceptable fit, and greater than 0.10 is poor fit.

3 | RESULTS

3.1 | Bivariate analyses

See Tables 1 and 2 for correlation tables with our included variables: baseline depression, baseline mania, baseline cognitive domains, 1-year depression, 1-year mania, 1-year cognitive domains, baseline age, and baseline education. In general, HDRS and YMRS scores across baseline and 1-year were weakly to moderately correlated (r ranged from 0.13 to 0.47), and cognitive domains were weakly to strongly associated with other baseline and 1-year cognitive domains (r ranged from 0.22 to 0.82).

3.2 | Structural equation modeling

Figure 1 presents the structural equation modeling for the pathways of interest for auditory memory, and Table 3 presents the results for the auditory memory model, including the estimates and standard errors for the regressions, variances, covariances, and means of each variable. Table 3 also shows results of the likelihood ratio tests, which examine the significance of each pathway of interest by removing the pathway and comparing the fit of the model with the removed path to the base model. The findings in Table 3 suggest that, within the auditory memory model, baseline depression positively predicted 1-year depressive symptoms ($\beta = 0.44$, SE $= 0.04$, $\chi^2 = 115.97$, $p < 0.001$) and 1-year manic symptoms ($\beta = 0.06$, SE $= 0.03$, $\chi^2 = 5.53$, $p = 0.02$). Similarly, baseline mania predicted 1-year mania ($\beta = 0.28$, SE $= 0.04$, $\chi^2 = 40.50$, $p < 0.001$), such that higher baseline mania predicts higher 1-year mania. Baseline auditory memory also positively predicted 1-year auditory memory

TABLE 2 Summary of baseline-1-year correlations for depression symptoms, mania symptoms, and cognitive domains

	1	2	3	4	5	6	7	8	9	10
1. HDRS	**0.47*** **	**0.22*** **	−0.04	−0.05	−0.07	−0.08	−0.04	−0.10	−0.05	−0.01
2. YMRS	**0.13*** *	**0.35*** **	0.00	0.01	−0.05	−0.02	−0.08	−0.03	−0.02	−0.05
3. FM	**−0.12*** *	−0.07	**0.78*** **	**0.32*** **	**0.28*** **	**0.50*** **	**0.31*** **	**0.53*** **	**0.37*** **	**0.45*** **
4. VM	**−0.14*** *	**−0.12*** *	**0.29*** **	**0.59*** **	**0.39*** **	**0.37*** **	**0.30*** **	**0.35*** **	**0.22*** **	**0.41*** **
5. AM	−0.09*	**−0.09*** *	**0.25*** **	**0.35*** **	**0.64*** **	**0.37*** **	**0.27*** **	**0.31*** **	**0.23*** **	**0.41*** **
6. VFPS	**−0.10*** *	−0.03	**0.52*** **	**0.39*** **	**0.42*** **	**0.82*** **	**0.42*** **	**0.67*** **	**0.51*** **	**0.55*** **
7. CRSS	−0.09	−0.06	**0.32*** **	**0.29*** **	**0.32*** **	**0.39*** **	**0.57*** **	**0.36*** **	**0.24*** **	**0.42*** **
8. PSIR	−0.07	−0.01	**0.56*** **	**0.42*** **	**0.42*** **	**0.71*** **	**0.44*** **	**0.80*** **	**0.57*** **	**0.54*** **
9. IC	0.07	0.03	**0.34*** **	**0.23*** **	**0.27*** **	**0.43*** **	**0.25*** **	**0.50*** **	**0.59*** **	**0.35*** **
10. EP	−0.06	−0.04	**0.49*** **	**0.48*** **	**0.42*** **	**0.53*** **	**0.44*** **	**0.55*** **	**0.43*** **	**0.76*** **

Note: Baseline data are presented in the columns, and 1 year are presented in the rows. Bolded values represent test-retest reliability over time.
Abbreviations: AM, auditory memory; CRSS, conceptual reasoning with set shifting; EP, emotion processing; FM, fine motor; HDRS Hamilton Depression Rating Scale; IC, inhibitory control; PSIR, processing speed with influence resolution; VM, visual memory; VFPS, verbal fluency with processing speed; YMRS, Young Mania Rating Scale.
Note: $^{**}p < 0.01$. $^{***}p < 0.001$. $^{*}p < 0.0$.

($\beta = 0.60$, SE $= 0.03$, $\chi^2 = 386.52$, $p < 0.001$). Mood symptoms and auditory memory did not appear to be related, as baseline mood did not predict baseline or 1-year auditory memory. Furthermore, baseline cognition did not predict 1-year mood.

This pattern of significant findings persisted across all examined cognitive domains. Specifically, baseline mood predicted 1-year mood and baseline cognition predicted 1-year cognition. In contrast with our hypotheses, mood symptoms did not predict cognitive performance in any of the cognitive models, with the following exception: baseline mania was significantly related to baseline CRSS ($\beta = -0.02$, SE $= 0.01$, $\chi^2 = 6.78$, $p = 0.01$, see Table 4). Similarly, baseline cognition did not predict 1-year mood symptoms in any of the models, with two exceptions: higher baseline visual memory significantly predicted lower manic symptoms at 1-year follow-up ($\beta = -0.34$, SE $= 0.17$, $\chi^2 = 4.09$, $p = 0.04$, see Appendix Table 4) and higher baseline inhibitory control significantly predicted higher depressive symptoms at 1-year follow-up ($\beta = 0.87$, SE $= 0.34$, $\chi^2 = 6.42$, $p = 0.01$, see Appendix Table 5). See Appendix Tables 6–9 for detailed results from the fine motor dexterity, VFPS, PSIR, and emotion processing models, respectively.

4 | DISCUSSION

Our results that mood symptoms at baseline predicted mood symptoms at 1-year follow-up is consistent with our previous report that found the likelihood of future mood states to be dependent on both the chronicity and duration of past mood states.[45] Furthermore, cognitive performance at baseline predicted cognitive performance at 1-year follow-up, consistent with findings that cognition is stable over the course of a year, in both healthy controls and in bipolar disorder.[46,47]

In contrast with our hypotheses that mood symptoms and cognition would be related, our findings indicate that neither baseline nor 1-year mood symptoms predicted fine motor, visual and auditory memory, emotion processing, executive functioning at baseline or 1-year follow-up. Similarly, baseline mood did not predict 1-year cognitive abilities, and baseline cognition did not predict 1-year mood. This suggests that cognitive functioning in bipolar disorder is state-independent and is not significantly impacted by mood symptoms. Thus, cognitive performance does not change during euthymic, depressed, and manic states. As previous research has consistently found cognitive deficits in individuals with bipolar disorder compared with healthy controls,[21,26,47] our results, in combination with these studies, suggest that these cognitive deficits likely remain regardless of phase of illness. Thus, cognitive dysfunction is likely either a trait effect in bipolar disorder or a consequence of the disorder, which aligns with previous conceptualizations of cognition across the life span in mood disorders.[48] Future studies that evaluate at-risk populations and follow them through illness onset and multiple episodes will be able to dissociate whether these stable cognitive deficits are trait effects or consequences.

The current findings are in contrast with prior research that suggests cognitive performance changes during depressed and manic states. This discrepancy is potentially related to differences in statistical methods. First, our study included a large sample of over 750

TABLE 3 Results from the Auditory Memory model and likelihood ratio tests

	Estimate	Standard Error	χ^2	CFI	RMSEA	*p*
Regressions						
Dep-0 to Dep-1	0.44	0.04	115.97	0.85	0.39	<0.001***
Dep-0 to Man-1	0.06	0.03	5.53	1.00	0.08	0.02*
Dep-0 to AM-0	−0.01	0.01	1.14	1.00	0.01	0.29
Dep-0 to AM-1	0	0.01	0.12	1.00	0.00	0.73
Man-0 to Dep-1	−0.03	0.06	0.29	1.00	0.00	0.59
Man-0 to Man-1	0.28	0.04	40.50	0.95	0.23	<0.001***
Man-0 to AM-0	−0.01	0.01	0.36	1.00	0.00	0.55
Man-0 to AM-1	0	0.01	0.04	1.00	0.00	0.85
Dep-1 to AM-1	−0.01	0.01	0.95	1.00	0.00	0.33
Man-1 to AM-1	0	0.01	0.04	1.00	0.00	0.85
AM-0 to Dep-1	−0.08	0.25	0.10	1.00	0.00	0.75
AM-0 to Man-1	−0.21	0.17	1.58	1.00	0.03	0.21
AM-0 to AM-1	0.6	0.03	386.52	0.67	0.50	<0.001***
Age to Dep-0	0.01	0.02	–	–	–	–
Age to Man-0	0	0.01	–	–	–	–
Age to Dep-1	0.03	0.02	–	–	–	–
Age to Man-1	−0.01	0.01	–	–	–	–
Age to AM-0	−0.02	0	–	–	–	–
Age to AM-1	−0.01	0	–	–	–	–
Educ to Dep-0	−0.47	0.11	–	–	–	–
Educ to Man-0	−0.23	0.07	–	–	–	–
Educ to Dep-1	−0.38	0.11	–	–	–	–
Educ to Man-1	−0.11	0.07	–	–	–	–
Educ to AM-0	0.07	0.02	–	–	–	–
Educ to AM-1	0.03	0.01	–	–	–	–
Covariances						
Dep-0 and Man-0	9	1.03	–	–	–	–
Dep-1 and Man-1	5.14	0.79	–	–	–	–
Age and Educ	6.86	1.11	–	–	–	–
Variances						
Dep-0	38.29	2	–	–	–	–
Man-0	15.9	0.89	–	–	–	–
Dep-1	26.52	1.6	–	–	–	–
Man-1	11.72	0.72	–	–	–	–
AM-0	0.76	0.04	–	–	–	–
AM-1	0.45	0.03	–	–	–	–
Age	185.05	9.53				
Educ	4.78	0.25				
Means						
Dep-0	16.09	1.63	–	–	–	–
Man-0	7.04	1.12	–	–	–	–
Dep-1	9.12	1.68	–	–	–	–

TABLE 3 (Continued)

	Estimate	Standard Error	χ^2	CFI	RMSEA	*p*
Man-1	3.56	1.13	–	–	–	–
AM-0	−0.38	0.25	–	–	–	–
AM-1	−0.18	0.23	–	–	–	–
Age	39.56	0.5	–	–	–	–
Educ	15.22	0.08	–	–	–	–

Note: The regressions present the pathway from one variable to another (e.g., Dep-0 to Dep-1: regression from baseline depression to 1-year depression). Covariances present the covariance between two variables (e.g., Dep-0 and Man-0: covariance between baseline depression and baseline mania). CFI and RMSEA represent the fit of the comparative model when the respective pathway is removed to conduct likelihood ratio testing.
Abbreviations: AM-0, baseline auditory memory; AM-1, 1-year auditory memory; Dep-0, baseline depression; Dep-1, 1-year depression; Educ, education; Man-O, baseline mania, Man-1, 1-year mania.
Note: $^{**}p < 0.01$. $^{***}p < 0.001$. $^{*}p < 0.05$.

individuals, in contrast to previous studies that include 50 or fewer subjects with elevated depressed or manic symptoms. Additionally, SEM analyses allow for simultaneous cross-sectional and longitudinal examination, thus allowing for both between-subject and within-subject comparisons (therefore a more sensitive analytic technique). Additionally, mood symptoms were kept as continuous variables rather than creating binary, categorical mood state variables.

Cognitive performance predicts disability and functional impairment in BD,[2,3] and prolonged dysfunction persists in the disorder after symptoms remit.[2] Our findings that cognitive performance remains unchanged and stable regardless of phase of illness may help explain why difficulties in functioning persist in BD. This has implications for clinical treatment of BD; improving everyday or life functioning for individuals may necessitate directly addressing cognitive difficulties in addition to mood symptoms (e.g., cognition focused neuromodulation).[49] It could also inform how we understand the application of the Americans with Disabilities Act for individuals with BD and have significant ramifications for neuropsychological evaluations for identification of occupational disability. As these results suggest that cognitive difficulties do not resolve with mood resolution, long-term disability or reasonable accommodations within the workplace may be warranted.

This study had some limitations. The participants in the current study had an average of 15.22 years of schooling. As education is a protective factor against cognitive decline,[2,50] it may also mitigate the impact of mood symptoms on cognition. Thus, future research may want to focus specifically on a bipolar sample with lower educational attainment to determine whether the relationship between mood and cognition is different in individuals with lower education. Additionally, of the individuals with a clinically elevated level of manic symptoms (generally defined as YMRS ≥6), the majority also endorsed clinically elevated depression (HDRS ≥7). For example, at baseline, 145 individuals received a score of 6 or greater on YMRS, suggesting a hypomanic or manic state in the last week. Of those, only 30 subjects (21%) received less than a 7 on HDRS. In contrast, at baseline, 457 people were above the HDRS clinical cutoff for depression, and 308 (67%) of them had YMRS scores below the cutoff. Overall, this suggests that our sample had a large subsample of individuals with only elevated depressive symptoms and a large subsample of individuals with concurrent depressive and manic symptoms. However, we did not have as many individuals with isolated elevated manic symptoms, which limited our ability to examine the effect on cognition of elevated manic symptoms without concurrent depression symptoms. We also did not systematically recruit individuals to be in different within-subject mood states, so it is possible that we incidentally evaluated participants in the same mood state both times. Nonetheless, we still did not generally see between-subject links between cognition and mood. We also did not systematically evaluate for the effects of medication, as this was not a controlled, blinded, clinical trial. Types of treatments, adherence by participants, and effectiveness of a given medication regime for anyone participant were not evaluated. A future study with a controlled medication trial or multiple arms could evaluate the potential interactive effects of medication, mood, and cognition in BD.

Future research would benefit from examining how other clinical factors (e.g., medication, rapid cycling, and comorbidities) impact the relationship between cognition and mood. In addition, individuals with BD with lower educational attainment may yield different results and thus be an important future analysis. Finally, as we continue to enroll more participants in the Prechter Longitudinal Study, the opportunity to examine more individuals with heightened manic symptoms without elevated depressive symptoms may emerge.

TABLE 4 Results from the CRSS model and likelihood ratio tests

	Estimate	Standard Error	χ^2	CFI	RMSEA	*p*
Regressions						
Dep-0 to Dep-1	0.44	0.04	116.13	0.90	0.39	<0.001***
Dep-0 to Man-1	0.06	0.03	6.06	1.00	0.08	0.01*
Dep-0 to CRSS-0	0	0	2.24	1.00	0.01	0.33
Dep-0 to CRSS-1	0	0	1.60	1.00	0.03	0.21
Man-0 to Dep-1	−0.04	0.07	0.27	1.00	0.00	0.60
Man-0 to Man-1	0.28	0.04	41.15	0.96	0.23	<0.001***
Man-0 to CRSS-0	−0.02	0.01	6.78	1.00	0.09	0.01*
Man-0 to CRSS-1	0	0.01	0.49	1.00	0.00	0.49
Dep-1 to CRSS-1	−0.01	0	0.44	1.00	0.00	0.51
Man-1 to CRSS-1	0.01	0.01	3.30	1.00	0.05	0.07
CRSS-0 to Dep-1	−0.18	0.33	0.01	1.00	0.00	0.91
CRSS-0 to Man-1	0	0.22	0.44	1.00	0.00	0.50
CRSS-0 to CRSS-1	0.51	0.04	371.37	0.67	0.69	<0.001***
Age to Dep-0	0.01	0.02	–	–	–	–
Age to Man-0	0	0.01	–	–	–	–
Age to Dep-1	0.03	0.02	–	–	–	–
Age to Man-1	0	0.01	–	–	–	–
Age to CRSS-0	−0.02	0	–	–	–	–
Age to CRSS-1	−0.01	0	–	–	–	–
Educ to Dep-0	−0.47	0.11	–	–	–	–
Educ to Man-0	−0.23	0.07	–	–	–	–
Educ to Dep-1	−0.38	0.11	–	–	–	–
Educ to Man-1	−0.13	0.07	–	–	–	–
Educ to CRSS-0	0.05	0.01	–	–	–	–
Educ to CRSS-1	0.04	0.01	–	–	–	–
Covariances						
Dep-0 and Man-0	8.98	1.02	–	–	–	–
Dep-1 and Man-1	5.17	0.79	–	–	–	–
Age and Educ	6.86	1.11	–	–	–	–
Variances						
Dep-0	38.29	2	–	–	–	–
Man-0	15.9	0.89	–	–	–	–
Dep-1	26.51	1.6	–	–	–	–
Man-1	11.76	0.72	–	–	–	–
CRSS-0	0.5	0.03	–	–	–	–
CRSS-1	0.31	0.02	–	–	–	–
Age	185.05	9.53				
Educ	4.77	0.25				
Means						
Dep-0	16.08	1.63	–	–	–	–
Man-0	7.05	1.12	–	–	–	–
Dep-1	9.17	1.68	–	–	–	–

TABLE 4 (Continued)

	Estimate	Standard Error	χ^2	CFI	RMSEA	*p*
Man-1	3.62	1.13	–	–	–	–
CRSS-0	−0.05	0.2	–	–	–	–
CRSS-1	−0.46	0.19	–	–	–	–
Age	39.56	0.5	–	–	–	–
Educ	15.22	0.08	–	–	–	–

Note: The regressions present the pathway from one variable to another (e.g. Dep-0 to Dep-1: regression from baseline depression to 1-year depression). Covariances present the covariance between two variables (e.g. Dep-0 and M-0: covariance between baseline depression and baseline mania). CFI and RMSEA represent the fit of the comparative model when the respective pathway is removed to conduct likelihood ratio testing.
Abbreviations: CRSS-0, baseline conceptual reasoning with set shifting; CRSS-1, 1-year conceptual reasoning with set shifting; Dep-0, baseline depression; Dep-1, 1-year depression; Man-O, baseline mania, Man-1, 1-year mania, Educ, education.
Note: $^{**}p < 0.01$. $^{***}p < 0.001$. $^{*}p < 0.05$.

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CONFLICT OF INTEREST

Ms. Easter, Dr. Estabrook, Dr. Ryan, and Dr. Marshall have no competing interests to report. Dr. Langenecker received grants from the National Institutes of Health and is a consultant for Otsuka Pharmaceuticals and EPI-Q unrelated to this work. Dr. McInnis has consulted with Otsuka and Janssen Pharmaceuticals and has received research support from Janssen Pharmaceuticals.

AUTHOR CONTRIBUTIONS

Melvin McInnis and Scott Langenecker designed the larger longitudinal study of bipolar disorder, and Melvin McInnis procured the overall funding for the project. Rebecca Easter, Kelly Ryan, David Marshall, Scott Langenecker, and Melvin McInnis all contributed significantly to the implementation of the study, including data collection. Rebecca Easter conducted main statistical analyses, created tables and figures, and wrote the first and subsequent drafts of the manuscript. Ryne Estabrook contributed to data analysis plans. All authors contributed to manuscript review and have approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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