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Association of clinical symptoms and neurocognitive performance in bipolar disorder: a longitudinal study

Olga C Chaves[a], **Lauren E Lombardo**[b], **Carrie E Bearden**[c,d], **Mary D Woolsey**[a], **David M Martinez**[a], **Jennifer A Barrett**[b], **Alexander L Miller**[e], **Dawn I Velligan**[e], and **David C Glahn**[b,f]

[a]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX

[b]Olin Neuropsychiatric Research Center, Institute of Living, Hartford, CT

[c]Semel Institute for Neuroscience and Human Behavior, University of California at Los Angeles

[d]Department of Psychology, UCLA, Los Angeles, CA

[e]Department of Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX

[f]Department of Psychiatry, Yale University, New Haven, CT, USA

Abstract

Objective—Despite evidence that individuals with bipolar disorder have neurocognitive impairment that persists during euthymia, the impact of changes in affective symptoms on cognitive function has not been well established. Here, we sought to determine whether specific neurocognitive functions are sensitive to mood changes in individuals with bipolar disorder assessed three months apart without changes in treatment regimen.

Methods—A total of 29 individuals with DSM-IV bipolar disorder and 30 healthy controls participated in the study. All participants received a comprehensive neuropsychological assessment and ratings of depressive [Hamilton Depression Rating Scale (HAMD)] and manic [Young Mania Rating Scale (YMRS)] symptoms at baseline and follow-up. Changes in symptoms over time were calculated and were examined in relation to changes in neurocognitive performance.

Results—At baseline, clinically stable but symptomatic patients were impaired on measures of speed of processing and attention. Over the three-month follow-up period, HAMD scores changed by 6 points on average [range: −10 to +18] and YMRS scores changed by 5.31 points on average [range −11 to +15]. Changes in depressive symptoms were correlated with poorer verbal fluency, while no relationship between manic symptoms and neuropsychological performance was detected.

Corresponding author: David C. Glahn, Ph.D., Olin Neuropsychiatry Research Center, Whitehall Research Building, Institute of Living, 200 Retreat Avenue, Hartford, CT 06106, USA, Fax: 860-545-7797, david.glahn@yale.edu.

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Conclusions—Individuals with bipolar disorder showed consistent impairment on speed of processing and attention over time, despite significant changes in mood.

Keywords

bipolar disorder; cognition; depression; mania; neuropsychology

Although studies have consistently found that individuals with bipolar disorder exhibit widespread neurocognitive dysfunction during acute episodes of mania (1) and depression (2), the discovery that these deficits endure during periods of euthymia raises the possibility that cognitive impairments may be associated with the core pathophysiology of the illness rather than being secondary to mood symptoms (3, 4). During euthymia, patients with bipolar disorder exhibit deficits in several cognitive domains, including executive function (5, 6), declarative memory (7–9), and sustained attention (10–12). Some cognitive deficits appear to be influenced by the same genes that predispose the illness (13), suggesting that cognitive impairment is closely linked to the etiology of bipolar disorder. Yet despite the potential trait-like qualities of cognitive impairments in bipolar disorder, performance on certain neurocognitive measures appears to vary with mood state. Indeed, Goldberg and colleagues (14) reported that while psychiatric symptoms in schizophrenia patients accounted for less than 5% of variance in neuropsychological testing, affective symptoms accounted for 30% of variance in individuals with bipolar disorder. While Martínez-Arán and colleagues (15) found that bipolar disorder patients were similarly impaired on measures of executive function and declarative memory, regardless of mood state, only the acutely ill subjects were impaired on measures of attention and processing speed. Further, Clark and Goodwin (16) found that while discrimination during an attention task is impaired in both depressed and manic patients, only manic patients make significantly more false positive errors. Together, these data suggest that while impairments in some cognitive domains may result from acute affective state, other neuropsychological deficits appear to be present regardless of symptom status.

To assess fully the relationship between affective symptoms and cognitive functioning, serial neuropsychological assessments on the same individuals are needed (17). However, very few within-subject longitudinal studies have been conducted in bipolar disorder patients, and most of these involve a pharmacological treatment (4, 15), making it difficult to determine whether cognitive changes are due to treatment effects or are secondary to changes in severity of mood symptoms. In addition, few studies to date have included healthy comparison subjects, making it difficult to determine whether observed cognitive changes over time are more than would be expected as a function of practice effects (18). Here, we administered a neuropsychological battery to subjects at baseline and at a follow-up session approximately three months later. Participants included individuals with bipolar disorder recruited from community mental health centers in San Antonio, TX, and demographically matched healthy volunteers. Although patients displayed a range of mood symptomatology at both assessments, all were clinically stable outpatients living either independently or with family members, and did not experience changes in medication status over the assessment interval. Based on prior work, we hypothesized that specific cognitive measures, such as attention, will be sensitive to mood fluctuations in individuals with

bipolar disorder, while performance on tests assessing executive functioning and declarative memory will remain stable over time.

Methods

Participants

A total of 29 outpatients with bipolar disorder (22 type I and 7 type II) and 30 healthy comparison subjects participated in the study. Groups were matched for gender (16 versus 15 females, $\chi^2 = 0.72$, p = 0.4, respectively) and parental education (12.22 ± 2.3 versus 12.50 ± 3.3 years, $t = -0.336$, p = 0.716). However, bipolar disorder patients were older (39.76 ± 12.4 versus 32.10 ± 8.8 years, $t = 2.74$, p = 0.008) and had a lower level of education than comparison subjects (13.24 ± 2.3 versus 16.10 ± 2.6 years, $t = -4.54$, $p = 3.0 \times 10^{-5}$). For this reason, all case–control comparisons were adjusted for age and education. The ethnic composition of the two groups did not differ (p = 0.25), and was representative of the San Antonio metropolitan area. Patients were recruited from the University of Texas Health Science Center San Antonio (UTHSCSA) outpatient clinics and community mental health facilities. All participants provided written informed consent for the study, as approved by the institutional review board at UTHSCSA. Inclusion criteria for patients were (i) a diagnosis of bipolar I or II disorder, as determined by the Structured Clinical Interview for DSM-IV (19); (ii) no current comorbid Axis I disorder [with the exception of anxiety disorders, given the high rates of comorbidity between the two illnesses (20)]; (iii) no alcohol or drug abuse / dependence within the past six months; and (iv) no history of a medical or neurological condition that might affect cognitive function. One patient severely decompensated during the three-month period and was excluded from all analyses. Healthy comparison subjects were recruited through advertisements in the community, according to the same exclusion criteria used for patients. In addition, control participants had no history of Axis I disorder based on structured interview.

Assessment procedure

All subjects participated in an initial assessment and a follow-up assessment approximately three months apart (average 3.07 ± 0.28 months). The initial visit included a structured clinical interview conducted by master's- or Ph.D.-level research staff who had been trained to a high level of diagnostic reliability ($\kappa > 0.80$). Subjects completed a neuropsychological battery and clinical symptom assessment on both occasions. Affective symptomatology at the time of assessment was determined with the 21-item Hamilton Depression Rating Scale (HAMD) (21) and the 12-item Young Mania Rating Scale (YMRS) (22).

Neuropsychological evaluation

Each subject received the South Texas Assessment of Neurocognition (STAN) (23), a 90-min neuropsychological evaluation consisting of standard and computerized measures. Tests included in this battery were selected based on evidence of sensitivity to bipolar disorder and minimal effects of language / culture. The STAN taps a wide range of cognitive domains, including *speed of processing* [Letter and Semantic Fluency (24), Digit-Symbol Coding (25), Trail Making Test-part A (24)]; *attention* [Identical Pairs Continuous Performance Test (IP-CPT) (26), Digit Span Forward (25)]; *executive functioning and*

working memory [Digit Span Backward (25), Digit Sequencing Task (25), Penn Conditional Exclusion Test (PCET) (27), Trail Making Test-part B (24)]; and *declarative memory* [California Verbal Learning Test (CVLT) (28), Digit-Symbol Recall (25)]. Neuropsychological measures were administered in a fixed order by psychometricians. Alternate forms of memory and executive test were used at follow-up.

Hypothesis testing

Statistical analyses addressed the following predictions:

1. In healthy subjects, neuropsychological performance will remain stable over time.
2. Patients with bipolar disorder will be impaired on measures of attention, processing speed, executive functioning, and declarative memory, relative to healthy controls at baseline.
3. Among individuals with bipolar disorder, changes in affective symptoms over time will influence performance on attentional measures, but will not affect performance on tests of executive function and declarative memory.

Statistical analyses were performed with SPSS 17.0. Neuropsychological variables were tested for assumptions of normalcy (Shapiro-Wilk test, $p < 0.01$), and those variables that did not conform to normal distributions were log transformed (specifically, CPT a').

To assess the test–retest reliability of the neuropsychological tests employed (Hypothesis 1), we examined performance by healthy subjects over time. Specifically, Spearman's rho correlation coefficients were calculated for each measure between the initial and follow-up assessments. In addition, a difference score was determined for each measure across assessments (initial test – follow-up) and one-sample Student *t*-tests were calculated to determine whether change in performance differed significantly from 0. A measure was considered to have good test–retest reliability if: (i) the Time 1 and Time 2 scores were significantly correlated, as indicated by a significant Pearson correlation ($p < 0.01$), and (ii) the *t*-test was not significant ($p > 0.10$), indicating stability of performance over time. To test Hypotheses 2 and 3, a between-group repeated-measures MANOVA, covarying for change scores on the HAMD and YMRS (initial test – follow-up) and demographic variables (age and education) was performed. Within this analysis framework, the relationship between mood symptomatology and neuropsychological performance over the three-month interval was examined as a within-subject effect of the symptom change score over time. False discovery rate (FDR) methods were used to correct for multiple comparisons (FDR < 0.05), and effect sizes (partial eta squared) were calculated for each analysis.

Results

Establishing test–retest reliability

In healthy subjects, initial and follow-up performance scores were highly correlated for virtually every measure (see Table 1). However, the number of perseverative errors (Spearman's rho 0.34, $p = 0.08$) on the PCET was not significantly correlated over time, suggesting that initial performance was not a good predictor of subsequent performance.

While performance on most measures did not significantly differ between assessments, healthy subjects performed significantly better on the Digit-Symbol Coding task (t =2.21, p = 0.04), PCET number correct (t = 3.92, p = 5.5×10^{-4}), and Trails-B (t = −2.24, p = 0.03) on the follow-up compared to the initial assessment, suggesting learning and / or practice effects on these tests.

Effects of diagnosis

As can be seen in Table 2, after covarying for age and education, individuals with bipolar disorder showed baseline cognitive deficits relative to healthy control subjects in speed of processing (Digit-Symbol Coding, Trails-A) and attention (IP-CPT) measures, with large to very large effect sizes. In addition, patients with bipolar disorder were impaired at baseline on measures of declarative memory (CVLT total Recall, Recognition). However, these differences did not survive correction for multiple comparisons (see Table 2).

Effect of mood symptoms on neuropsychological measures

The average HAMD and YMRS scores at baseline were 18.62 ± 7.0 [range: 4–31] and 11.76 ± 6.8 [range: 1–26], respectively, in the patient sample. On average, these symptom ratings were similar at the three-month follow-up assessment, although there was a trend toward increase in depressive symptomatology, on average (HAMD: 21.24 ± 7.7 [1–36], paired t-test = −1.857, p = 0.07; YMRS: 11.21 ± 6.7 [2–24], paired t-test = 0.457, p = 0.654). Although the mean affective state of the full sample did not differ between intake and follow-up, symptom levels of individual patients did change considerably. Indeed, the range of change scores for depressive symptoms was −10 to +18 (average 2.62 ± 7.6; absolute value of change scores: 6.41 ± 4.63 [0–18]), suggesting considerable within-individual variation. Similarly, manic symptom change scores ranged from −11 to +15 (average −0.55 ± 6.5; absolute value: 5.31 ± 3.95 [0–15]).

Results of the between-group repeated-measures MANOVA examining the interaction between change in neuropsychological performance and symptom change scores indicated that change in verbal letter fluency performance was significantly correlated with change in depressive symptoms, such that as depressive symptoms increased, verbal fluency performance decreased (see Table 2). Similar trends were seen for Digit Span Forward and CVLT Delayed Recall and Recognition. However, these effects did not withstand correction for multiple comparisons. No significant relationship between manic symptoms and neuropsychological performance over time was detected.

Discussion

Our results indicate three key findings. Specifically, we found: (i) relatively good test–retest reliability in healthy controls across the majority of neuropsychological measures, with the exception of PCET (executive functioning); (ii) deficits of moderate to large effect in bipolar disorder patients relative to controls on measures of speed of processing and attention; and (iii) relatively small effects of changes in mood symptoms over time on neurocognitive performance change within the bipolar disorder group. While variation in mood symptomatology did influence a single processing speed measure (verbal fluency), most

neurocognitive measures were not significantly influenced by variation in affective symptoms over a three-month period. Our findings may be limited by our relatively small sample size (see below) and / or by the restricted range of symptom change occurring within clinically stable patients. Indeed, it is possible that more dramatic changes in depressive or manic symptoms could have more profound effects on cognitive processing. Nonetheless, large ($\eta^2 > 0.14$) and moderate ($\eta^2 > 0.06$) effect sizes were found for the influences of depressive symptoms on speed of processing, attentional, and declarative memory performance (see Table 2). Similarly, changes in manic symptoms were associated with moderate effect sizes on processing speed measures, although these results did not withstand multiple comparison correction. Together, these data suggest that while variation in affective symptoms does contribute to neuropsychological performance at some level, the effects of mood state do not fully explain neurocognitive deficits in bipolar disorder.

A strength of the current study is the inclusion of a healthy comparison sample that allows for assessment of the stability of the neuropsychological measures over time (18). Healthy subjects performed better on three neuropsychological tests at follow-up compared to baseline (Digit-Symbol Coding, PCET, and Trails-B), suggesting significant learning effects on these measures. Similarly, bipolar disorder patients showed learning effects on these measures (data not shown), and without a comparison sample, these changes could be erroneously ascribed to treatment or changes in psychiatric symptoms (18). Consistent with several previous studies, individuals with bipolar disorder were impaired on measures of processing speed and attention, and trended toward impairment on a test of declarative memory (29).

Limitations of this study include differences in age between the patient and control groups and the use of psychotropic medications among virtually all bipolar disorder patients. However, these factors were only relevant for the case-control analyses, where our findings were generally consistent with previous reports (29). The relatively modest sample size likely limited power to detect significant baseline group differences on memory and executive measures. Nevertheless, the effect sizes for these measures were in the moderate-to-large range. Our patient sample included patients with both type I (n = 22) and type II (n = 7) bipolar disorder. However, bipolar type was not significant when included as a covariate in statistical models. While results from the present study improve our understanding of the relationship between affective symptoms and cognition in bipolar disorder, additional within-subject longitudinal studies that can dissociate additional clinical and psychosocial factors are warranted. Findings suggesting that neuropsychological dysfunction is relatively independent of affective symptom variation in bipolar disorder imply that bipolar disorder patients could benefit from therapeutic interventions designed to enhance or augment cognition.

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Table 1

Test–retest reliability for neuropsychological data in healthy subjects (n = 30)

Neuropsychological measure	Baseline mean (SD)	Follow-up mean (SD)	Correlation[a]	Change score[b]
Speed of processing				
Letter Fluency	42.93 (11.4)	45.59 (11.6)	0.78, 2.8×10^{-6}	1.38, 0.18
Semantic Fluency	48.52 (8.6)	46.15 (9.1)	0.71, 4.8×10^{-5}	−0.33, 0.74
Digit-Symbol Coding	55.67 (11.5)	58.61 (15.4)	0.89, 1.8×10^{-10}	2.21, 0.04
Trail Making Test A[c]	25.17 (8.0)	24.36 (9.6)	0.47, 0.012	−0.48, 0.64
Attention				
IP-CPT Hits	44.53 (3.5)	44.64 (4.4)	0.79, 6.6×10^{-7}	0.46, 0.65
IP-CPT False Alarms	1.83 (2.0)	2.18 (2.1)	0.40, 0.038	0.63, 0.54
IP-CPT a′	0.97 (0.1)	0.97 (0.0)	0.81, 1.4×10^{-7}	0.35, 0.73
Digit Span Forward	8.77 (2.0)	8.52 (1.8)	0.58, 9.8×10^{-4}	−0.89, 0.38
Executive functioning				
Digit Span Backward	6.57 (2.5)	6.83 (2.7)	0.67, 6.7×10^{-5}	0.36, 0.72
Digit Sequencing	20.27 (4.6)	20.52 (4.5)	0.66, 9.7×10^{-5}	0.22, 0.83
PCET Correct	45.83 (7.7)	52.62 (10.7)	0.42, 0.024	3.92, 5.5×10^{-4}
PCET Categories	2.14 (0.5)	2.90 (1.1)	0.42, 0.025	3.78, 8.0×10^{-4}
PCET Perseverative Errors	14.31 (4.6)	10.45 (5.6)	0.34, 0.075	−3.58, 1.3×10^{-3}
Trail Making Test B[c]	59.97 (31.1)	51.61 (26.5)	0.50, 0.007	−2.24, 0.03
Declarative memory				
CVLT Learning Recall	50.77 (9.7)	53.03 (9.8)	0.81, 1.3×10^{-7}	2.00, 0.06
CVLT Semantic Clustering	1.74 (2.2)	1.85 (2.3)	0.65, 1.5×10^{-4}	0.49, 0.63
CVLT Long-Delayed Recall	11.90 (3.4)	12.61 (2.5)	0.75, 7.8×10^{-4}	1.17, 0.25
CVLT Recognition a′	0.96 (0.1)	0.97 (0.1)	0.64, 2.7×10^{-4}	1.30, 0.21

IP-CPT = Identical Pairs Continuous Performance Test; PCET = Penn Conditional Exclusion Test; CVLT = California Verbal Learning Test.

[a] Within-subject Spearman's rho and two-tailed p-value for initial and follow-up performance.

[b] One-sample *t*-test value for Time 1–Time 2 change and two-tailed p-value.

[c] As these variables represent time (in seconds), higher scores on these measures indicate worse performance. For all other variables, higher scores indicate better performance.

Table 2

Neuropsychological performance differences and interaction of affective symptom change over three months

Neuropsychological measure	Between-group differences			Depressive symptoms[a]			Manic symptoms[b]		
	F	Significance	Partial η^2	*F*	Significance	Partial η^2	*F*	Significance	Partial η^2
Speed of processing									
Letter Fluency	1.93	0.17	0.04	**13.97**	**5.4×10^{-4}**	0.25	0.02	0.90	0.00
Semantic Fluency	0.72	0.40	0.02	0.05	0.82	0.00	0.47	0.50	0.01
Digit-Symbol Coding	**17.19**	**1.5×10^{-4}**	0.29	2.92	0.10	0.06	4.68	0.04	0.10
Trail Making Test A	**19.53**	**6.6×10^{-5}**	0.31	0.39	0.54	0.01	3.69	0.06	0.08
Attention									
IP-CPT Hits	**7.22**	**0.01**	0.14	3.01	0.09	0.07	0.58	0.45	0.01
IP-CPT False Alarms	**6.73**	**1.3×10^{-3}**	0.14	2.77	0.10	0.06	1.45	0.24	0.03
IP-CPT a′	**9.45**	**3.6×10^{-3}**	0.18	1.39	0.24	0.03	1.38	0.25	0.03
Digit Span Forward	0.06	0.81	0.00	4.61	0.04	0.10	0.14	0.71	0.00
Executive functioning									
Digit Span Backward	2.44	0.13	0.05	0.00	0.99	0.00	0.17	0.68	0
Digit Sequencing	3.23	0.08	0.07	0.04	0.84	0.00	1.06	0.31	0.02
PCET Correct	1.96	0.17	0.04	1.03	0.32	0.02	1.84	0.18	0.04
PCET Categories	1.34	0.25	0.03	0.00	0.99	0.00	1.01	0.32	0.02
PCET Perseverative Errors	3.07	0.09	0.07	0.55	0.46	0.01	1.32	0.26	0.03
Trail Making Test B	2.91	0.10	0.06	0.53	0.47	0.01	1.80	0.19	0.04
Declarative memory									
CVLT Learning Recall	4.85	0.03	0.10	0.97	0.33	0.02	0.28	0.60	0.01
CVLT Semantic Clustering	0.53	0.47	0.01	1.70	0.20	0.04	0.83	0.37	0.02
CVLT Long-Delayed Recall	2.78	0.10	0.06	5.10	0.03	0.11	0.50	0.49	0.01
CVLT Recognition a′	4.06	0.05	0.09	7.67	0.01	0.15	0.70	0.41	0.02

IP-CPT = Identical Pairs Continuous Performance Test; PCET = Penn Conditional Exclusion Test; CVLT = California Verbal Learning Test.

Variables in **bold** are significant when controlling for multiple comparisons (false discovery rate < 0.05).

[a] Interaction between depressive symptoms (Hamilton Depression Rating Scale change score) and neuropsychological performance change over time.

[b] Interaction between manic symptoms (Young Mania Rating Scale change score) and neuropsychological performance change over time.