Neurocognitive Functioning in Patients With Bipolar I Disorder Recently Recovered From a First Manic Episode

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Objective: Although cognitive impairment is an important clinical feature of bipolar disorder, it is unknown whether deficits are present at illness onset. The purpose of this study was to determine whether neuropsychological impairments are present in clinically stable patients with bipolar disorder shortly after resolution of their first manic episode.

Method: Within a large university medical center, 45 recently diagnosed (*DSM-IV-TR*) patients with bipolar disorder type I were evaluated after resolution of their first manic episode, along with 25 matched healthy comparison subjects. Participants were administered a neuropsychological battery evaluating 5 broad cognitive domains, including verbal/premorbid intellectual functioning, learning/memory, spatial/nonverbal reasoning, attention/processing speed, and executive function. Data were collected from July 2004 to August 2007.

Results: Relative to controls, patients showed broad impairments in learning/memory, spatial/nonverbal reasoning, executive function, and some aspects of attention (all $P < .01$). Specifically, deficits were evident on tests assessing sustained attention, attentional and mental set shifting, spatial working memory, nonverbal reasoning, and verbal learning and recall (all $P < .01$). Cognitive impairments in patients could not be fully attributed to substance abuse, medication status, or residual mood symptoms.

Conclusions: Results indicate that core neuropsychological deficits in sustained attention, learning and recall, spatial/nonverbal reasoning, and several aspects of executive function are present at illness onset. Cognitive deficits in bipolar disorder are, thus, most likely not exclusively attributable to progressive decline associated with increased illness burden, cumulative treatment effects, or chronicity of illness. These findings may provide etiologic clues into the illness and identify clinical targets for early treatment.

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Patients with bipolar disorder show broad cognitive impairments in sustained attention, memory, and executive functioning not only during acute mood episodes but also during euthymic periods.[1,2] These cognitive deficits persist even after controlling for potential confounds, including residual mood symptoms and medication variables.[3] Thus, cognitive impairment is often characterized as trait features of the illness.[4,5] Little, however, is known about the presence or nature of cognitive impairment at the time of illness onset, nor its evolution throughout the course of illness. Such knowledge could provide important insights into the etiology of bipolar disorder, as well as identify relevant clinical targets for early medical and psychosocial intervention. The presence of neuropsychological impairment early in the course of illness could signal expression of genetic vulnerability, abnormal neurodevelopmental processes, and/or disease processes that have culminated in neuropsychological impairment at clinical illness onset.

Although many studies have examined cognitive impairments in symptomatically stable patients, there is a paucity of research in such patients early in the course of illness. One recent study reported cognitive deficits in a small sample of euthymic patients on a range of functions including intelligence quotient (IQ), memory, executive function, and attention.[6] However, patient and control groups were not matched according to several key variables, including age, sex, and intellectual level, making it difficult to attribute cognitive deficits to the illness itself. In a second study, Gruber et al[7] reported executive dysfunction in a small number of first-episode hospitalized patients relative to controls. However, patients were not clearly clinically stable at testing, the battery was limited to several tests of executive function, and groups were not well matched according to verbal intellectual functioning. Although these preliminary studies suggest that first-episode patients may show cognitive impairment relative to controls, the conclusions are obscured by uneven matching of relevant demographic variables, limited coverage of cognitive domains, questionable symptomatic status, and study of small patient samples.

In order to investigate neuropsychological functioning in first-episode patients, we evaluated a broad range of cognitive domains in a sample of clinically stable patients diagnosed with bipolar disorder following resolution of their first manic episode, and we compared their performance to a closely matched sample of healthy comparison subjects. It was hypothesized that first-episode patients

would show significant impairments in broad domains of attention, memory, and executive function.

METHOD

Participants

Forty-five patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[8] criteria for bipolar I disorder were recruited from the Systematic Treatment Optimization for Early Mania Program at Vancouver Hospital Health Sciences Centre and affiliated sites, as well as by community and hospital referrals from physicians and psychiatrists. Diagnosis of bipolar I disorder and comorbid illnesses was based on a comprehensive clinical interview by an academic research psychiatrist and a Mini-International Neuropsychiatric Interview (MINI).[9] Participants were required to be adults who had experienced their first manic/mixed episode within the 3 months preceding enrollment into the study and to be sufficiently clinically stable to undergo cognitive assessment.

Patient demographic and illness characteristics are presented in Table 1. Nearly all patients presented with a first episode of mania (2 with mixed episode), and psychosis was present in 82% of patients during this initial episode. The mean duration of illness, defined as the time since the first lifetime mood episode of any type, was 3.0 years (SD = 3.6). The initial lifetime mood episode was depressive for 48% of the patients, hypomanic for 14%, and manic for all others. The patients with a depressive first lifetime mood episode had a slightly younger age at onset relative to others (depressive: 17.6 years [SD = 4.5]; other: 20.9 years [SD = 3.7]; $t_{41} = 2.7$, $P = .01$); however, this was likely partly related to the fact that the inclusion criteria limited the possibility of capturing patients with a manic episode illness onset before adulthood. Twenty-four patients had a history of at least 1 depressive episode prior to the first manic episode, and 12 had a history of a hypomanic episode. Nine patients had been previously treated with antidepressants. Prior to the first manic episode, 22 patients had been diagnosed with depression, 6 with anxiety disorder, 2 with brief psychosis (drug induced or not otherwise specified), and 1 with body dysmorphic disorder. Four patients were currently medication naive, 10 were on monotherapy, 26 were taking 2 medications, and 5 were taking 3 medications. The median duration from onset of the first manic episode to eventual treatment with either a mood stabilizer or an antipsychotic was 25 days. Four patients presented with comorbid anxiety disorder. Twenty patients met *DSM-IV* criteria for comorbid substance or alcohol abuse/dependence (excluding nicotine) at time of initial presentation, and 23 met criteria for lifetime abuse/dependence. Because the diagnostic distinction between first-episode bipolar mania and substance-induced mania can be challenging to make in some individuals presenting with substance abuse, patients were also divided into those with and without comorbid substance abuse (see Results section).

Twenty-five healthy comparison subjects matched on age, sex, education, ethnicity, and premorbid IQ were recruited from the community through word of mouth and advertisements posted at the University of British Columbia and affiliated hospitals (Table 1). Controls were also assessed with the MINI, and exclusion criteria included a personal or family history of major Axis I psychiatric disorder in first- or second-degree relatives. Ethics approval was received from the University of British Columbia Clinical Research Ethics Board, and written informed consent detailing the procedures and potential side effects was obtained from all subjects prior to their participation.

Table 1. Demographic and Illness Characteristics of the Sample

	Patients With Bipolar Disorder[a] (n = 45)		Healthy Controls (n = 25)	
Characteristic[b]	Mean	SD	Mean	SD
Age, y	22.2	3.9	22.5	4.8
Education, y	13.4	2.4	14.3	2.4
North American Adult Reading Test (premorbid intelligence quotient)	107.2	7.1	107.4	7.7
Age at illness onset, y	19.3	4.4		
Age at mania onset, y	22.2	3.7		
Age at depression onset, y	18.2	4.3		
Number of previous depressive episodes	1.2	1.6		
Number of previous hypomanic episodes	0.6	1.8		
Symptom rating scale scores				
Positive and Negative Syndrome Scale positive score	7.8	1.6		
Young Mania Rating Scale	1.8	3.7		
Hamilton Depression Rating Scale	4.3	5.1		
Brief Psychiatric Rating Scale	22.7	5.8		
Global Assessment of Functioning Scale	64.2	12.6		
Lithium dose, mg	956	181		
Divalproex dose, mg	929	361		
	n	%	n	%
Sex, male	23	51	12	48
Ethnicity				
Caucasian	36	80	19	76
Asian	6	13	6	24
Other	3	7	0	0
English first language	40	89	20	80
Premorbid socioeconomic status				
Student	26	58	17	68
Part-time work	2	4	0	0
Full-time work	13	29	7	28
Self-employed	1	2	0	0
Unemployed	2	4	1	4
Medications				
Mood stabilizers	37	82		
Lithium	17	38		
Divalproex	21	47		
Lamotrigine	1	2		
Atypical antipsychotics	30	67		
Antidepressants	3	7		
Anxiolytics	3	7		

[a]Illness characteristics and premorbid socioeconomic status were missing for 1 patient.
[b]No significant group differences based on 2-tailed independent sample *t* tests and χ^2 analyses, $P < .05$.

Cognitive Assessment

Cognitive battery selection was guided by evidence of cognitive impairment in euthymic patients with bipolar disorder[1,2,10] and consisted of standardized clinical measures, including select subtests from the Cambridge

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Neuropsychological Test Automated Battery (CANTAB).[11] Individual test measures were categorized into broader cognitive domains based on prior categorization schemes used in bipolar disorder[1,2] and in the broader field of clinical neuropsychology.[12,13] Recognizing that individual neuropsychological tests frequently measure multiple cognitive domains and that disagreements may arise between different researchers on how to classify tasks, we elected to evaluate differences between groups on individual tasks in addition to broader cognitive domains. The resulting 5 cognitive domains and their inclusive tasks are outlined below, along with further rationale for inclusion of tasks within their respective domains.

Verbal/premorbid IQ. These tasks measured crystallized aspects of intelligence and provided better estimates of premorbid intellectual function than fluid tests.[12] Tests included the North American Adult Reading Test (NAART) full scale IQ[14] and the Kaufman Brief Intelligence Test (K-BIT) vocabulary score.[15]

Visual-spatial/nonverbal reasoning. Tasks in this domain measured fluid, nonverbal/spatial reasoning ability and included the K-BIT matrices score.[15] The Benton Line Orientation total adjusted correct score[16] was included in this domain based on demonstration that it correlates better with nonverbal than verbal intellectual subtests.[17]

Attention/processing speed. This domain consisted of a range of tasks requiring attention and information processing speed, including Trail-Making Test A time to completion,[18] Stroop test word and color naming trials number correct,[19] CANTAB rapid visual information processing discriminability score, and California Verbal Learning Test–Second Edition (CVLT-II) trial 1 words recalled.[20] The latter measure was included in the attention rather than memory domain based on prior factor analysis.[21]

Executive function. These tasks tap into a diverse set of cognitive control/regulation processes that are largely subserved by dorsal prefrontal brain regions.[13] Tasks in this category included measures of verbal and nonverbal working memory, attentional and mental set shifting, verbal fluency, planning, and response inhibition.[12,13] Despite their overlapping features, tests within this broad category also show some differentiation.[22] Thus, group differences in individual tasks were also evaluated. Specific measures included verbal fluency number correct,[12] Stroop color/word trial number correct, Trail-Making Test B time, Wechsler Memory Scale–Third Edition[23] letter/number sequencing, CANTAB intra-/extra-dimensional (IED) set-shifting task number of extra-dimensional shifting errors, CANTAB stockings problems solved in the minimum number of moves, and CANTAB spatial working memory (SWM) between errors.

Learning/memory. The verbal and nonverbal learning and recall/recognition measures included CVLT-II recall trials 1–5, CVLT-II delayed free recall, CANTAB spatial recognition memory percent correct, CANTAB pattern recognition memory percent correct, and CANTAB paired associate learning total errors adjusted score.

Procedures

As part of a larger longitudinal study, patients received a comprehensive baseline clinical evaluation including the MINI and other clinical and symptom rating scales (Table 1). Most patients also received routine clinical follow-up visits that included repeat mood ratings. Cognitive testing was conducted when patients were judged to be clinically stable and able to tolerate the 2.5 to 3 hour long neuropsychological battery. The mean mood ratings that were closest in time to the cognitive testing date are presented in Table 1. Overall, 31% of patients were tested on the same day mood ratings were obtained, 49% were tested within 2 days, 67% within 1 week, and 80% within 2 weeks of ratings. The patient's date of remission from his or her first manic episode was estimated based on the discharge date from hospital, chart review, and clinical interview. The mean (SD) duration from remission to cognitive testing was 52.0 (34.6) days. At the time of testing, patients had been on their current medication regimen for a mean (SD) of 59.0 (41.4) days. Data from the current study were collected from July 2004 to August 2007.

Statistical Analysis

For each primary cognitive measure, raw scores were converted into *z* scores ranging from −4 to 4 based on demographics-adjusted normative data derived from the testing manuals of each test. We elected to use these demographics-corrected normative values for patient-control comparisons rather than either raw or control group–corrected scores for several reasons. First, demographics-adjusted scores were deemed to be more accurate than nonadjusted (raw) scores that were not corrected for demographics. Second, the demographics-adjusted scores were based on much larger samples than our own control group (n = 25). Third, the demographics-adjusted *z* scores could easily be combined to calculate cognitive domain scores (see below). Finally, the use of standardized scores minimizes the influence of raw score outliers. According to testing manuals, all tests were adjusted for age. The CANTAB, Benton Line Orientation, Trail-Making Test, and CVLT-II were also adjusted for sex, and the Trail-Making Test, Stroop color and word test, and verbal fluency test were also adjusted for education. The CANTAB tests were further adjusted for NAART score, and the Trail-Making Test was further adjusted for race.

The distribution of resulting *z* scores for each measure was then examined within each group (patients, controls), and values exceeding 3.29 SDs above or below the group mean were flagged as potential outliers. To minimize their influence, extreme scores were adjusted to the value equivalent to 3.29 SDs from the mean of the respective group as previously recommended.[24] The 5 cognitive domain scores were derived by calculating the mean *z* score of all primary measures within each domain.

Patient-control differences in the 5 cognitive domain scores were assessed using multivariate analysis of variance. Group differences in primary measures were further

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evaluated using Bonferroni-corrected univariate *t* tests. All reported effect sizes were Cohen *d* with Hedges' correction. Follow-up analyses evaluating cognitive differences between subsets of patients (eg, presence of substance abuse) were conducted using Bonferroni-corrected univariate *t* tests. The relationship between cognitive functioning and continuous clinical variables was assessed with Pearson *r* for cognitive domain scores, as domain scores were normally distributed. The relationship between clinical variables and primary cognitive variables was assessed with Spearman correlation coefficients, as primary variables were more likely to be nonnormally distributed. Analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois). All statistical tests were 2-tailed and, except where specified, were carried out using a significance level of $\alpha = .05$.

RESULTS

Within patients, there were no data points on any primary cognitive measure that exceeded the criterion of 3.29 SD units above or below the mean. In the control group, 3 of 525 data points (0.6%) exceeded this criterion. Because there was no identifiable reason to exclude these subjects or data points, they were adjusted[24] as follows: one score for IED extra-dimensional shifting errors *z* score was adjusted from −2.61 to −1.78, one score for SWM errors *z* score was adjusted from −4 to −2.92, and one score for line orientation *z* score was adjusted from −0.96 to −0.86.

Between-Group Cognitive Differences

Within both groups, all cognitive domain scores were normally distributed based on the Shapiro-Wilk statistic (all $P > .10$). In patients, there was no association between the time elapsed between symptom ratings and cognitive testing and any of the cognitive domain scores (all $P > .30$). Mean cognitive domain scores and associated group difference effect sizes are presented in Table 2. Multivariate analysis of variance results yielded a significant effect of group on domain scores (Wilk $\lambda = 0.78$; $F_{5,64} = 3.6$; $P = .007$). After Bonferroni correction for 5 comparisons ($\alpha = .01$), univariate tests revealed poorer patient performance in spatial reasoning ($F_{1,68} = 8.9$; $P = .004$), memory ($F_{1,68} = 9.8$; $P = .003$), and executive functioning ($F_{1,68} = 12.7$; $P = .001$), but not verbal/premorbid IQ ($F_{1,68} = 0.1$; $P = .76$) or attention ($F_{1,68} = 4.5$; $P = .04$). As previously recommended,[25] the frequency of cognitive impairment in domain scores was estimated by calculating the percentage of individuals who scored at least 1.5 SDs below the mean of the control group. The percentage of patients showing cognitive impairment in verbal/premorbid IQ, spatial reasoning, attention, executive functioning, and memory were 11%, 29%, 18%, 31%, and 31%, respectively. In comparison, controls showed the following frequency of impaired performance, respectively: 8%, 8%, 8%, 12%, and 12%.

Group differences in primary cognitive measures were also evaluated using *t* tests with Bonferroni correction for the number of primary measures within a given cognitive domain (Table 2). Within the spatial reasoning domain ($\alpha = .025$), patients performed worse than healthy comparison subjects on K-BIT matrices ($t_{68} = 2.6$, $P = .01$). In the attention domain ($\alpha = .01$), significant differences were only evident in rapid visual information processing discriminability ($t_{68} = 2.7$, $P = .008$). Across executive tasks ($\alpha = .007$), patients performed poorer on the CANTAB IED ($t_{61.2} = 3.3$, $P = .002$), stockings ($t_{67} = 3.2$, $P = .002$), and SWM measures ($t_{67.8} = 3.8$, $P = .000$). In the memory domain ($\alpha = .01$), healthy comparison subjects outperformed patients on CVLT-II recall trials 1–5 ($t_{65} = 3.0$, $P = .004$).

Cognitive Functioning and Substance Abuse Comorbidity

To evaluate whether group differences in cognition could be attributed to comorbid substance abuse, patients were divided into groups with (n = 20) and without (n = 23) comorbid diagnosis of substance/alcohol abuse. Groups were comparable in age (abuse: 22.5 years [SD = 3.1]; no abuse: 22.4 years [SD = 4.3]; $t_{41} = 0.1$, $P = .93$), age at illness onset (abuse: 19.8 years [SD = 5.2]; no abuse: 18.8 years [SD = 3.7]; $t_{40} = 0.7$, $P = .46$), sex (abuse: 55% male; no abuse: 48% male; $\chi^2 = 0.22$, $P = .64$), education (abuse: 13.1 years [SD = 2.2]; no abuse: 14.0 years [SD = 2.4]; $t_{41} = 1.4$, $P = .18$), and NAART premorbid IQ (abuse: 105.2 [SD = 7.1]; no abuse: 109.3 [SD = 7.0]; $t_{41} = 1.9$, $P = .07$). Table 3 reveals there were no significant differences between these groups on any cognitive domain score. Additionally, a multivariate analysis of variance conducted on domain scores between patients without substance abuse and controls yielded a significant overall group effect (Wilk $\lambda = 0.69$; $F_{5,42} = 3.9$; $P = .006$). After applying Bonferroni correction ($\alpha = .01$), univariate tests revealed poorer patient performance in memory ($F_{1,46} = 7.3$; $P = .01$) and executive functioning ($F_{1,46} = 11.0$; $P = .002$), but not attention ($F_{1,46} = 5.7$; $P = .02$), spatial reasoning ($F_{1,46} = 2.6$; $P = .12$), or verbal/premorbid IQ ($F_{1,46} = 0.22$; $P = .64$).

Cognitive Functioning and Medication Variables

There was no association between the number of psychotropic medications patients were receiving and any of the cognitive domain scores (all *r*'s $P > .20$). To assess the effect of mood stabilizer on cognitive functioning, patients were divided into those treated with lithium (n = 16) or divalproex (n = 20). Groups were comparable on age (lithium: 22.3 years [SD = 3.8]; divalproex: 21.8 years [SD = 3.0]; $t_{34} = 0.44$, $P = .66$), sex (lithium: 63% male; divalproex: 40% male; $\chi^2 = 1.8$, $P = .18$), education (lithium: 13.7 years [SD = 1.7]; divalproex: 12.9 years [SD = 2.4]; $t_{34} = 1.1$, $P = .28$), NAART score (lithium: 107.9 [SD = 5.4]; divalproex: 105.8 [SD = 8.8]; $t_{34} = 0.85$, $P = .40$), and percentage of patients taking atypical antipsychotics (lithium: 70%; divalproex: 81%; $\chi^2 = 0.60$, $P = .44$). Table 4 shows that patients taking lithium outperformed those taking divalproex on spatial reasoning ($t_{34} = 2.8$, $P = .009$) and executive functioning ($t_{34} = 3.3$, $P = .003$). When compared to controls, patients taking lithium showed poorer performance on memory ($t_{39} = 2.9$, $P = .006$), but not other domain scores. However, divalproex-treated patients showed significantly poorer

Table 2. Primary and Global Cognitive Scores Across Groups[a]

	Patients (n = 45)				Controls (n = 25)				
	Raw Score		*z* Score		Raw Score		*z* Score		
Score	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Effect Size
Verbal/premorbid intelligence quotient			0.32	0.57			0.36	0.55	0.06
North American Adult Reading Test	107.2	7.1	0.48	0.48	107.4	7.7	0.49	0.51	0.02
Kaufman Brief Intelligence Test verbal	102.3	11.3	0.16	0.75	103.5	9.6	0.23	0.64	0.09
Spatial reasoning[b,c]			0.49	0.69			0.91	0.48	0.62
Judgment of line orientation[c]	27.4	3.0	0.54	0.85	29.0	2.0	0.93	0.65	0.45
Kaufman Brief Intelligence Test nonverbal[b]	106.6	11.6	0.44	0.78	113.4	7.7	0.89	0.52	0.59
Attention/processing speed			−0.42	0.70			−0.04	0.7	0.50
Trail-Making Test A	26.0	7.8	−0.20	1.18	20.8	6.4	0.52	1.24	0.55
California Verbal Learning Test trial 1	6.5	1.9	−0.47	1.0	7.0	1.6	−0.18	0.89	0.28
Stroop word	100.2	12.9	−0.28	0.94	103.2	13.7	−0.18	1.08	0.09
Stroop color	72.5	11.8	−0.51	1.05	73.7	12.3	−0.43	1.1	0.07
Rapid visual information processing[b]	0.89	0.05	−0.62	1.08	0.92	0.04	0.06	0.84	0.62
Executive[b]			−0.22	0.73			0.39	0.57	0.82
FAS verbal fluency	38.5	9.7	−0.43	0.85	41.4	12.6	−0.19	1.13	0.23
Trail-Making Test B	58.5	23.8	0.09	1.10	46.1	12.6	0.80	1.13	0.58
Stroop interference[c]	47.0	9.3	0.11	0.87	49.7	12.4	0.33	1.22	0.20
Letter/number sequencing	10.8	2.6	−0.06	0.88	12.0	3.1	0.33	1.07	0.37
Intra-/extra-dimensional task[b,c]	7.8	8.9	−0.31	1.30	3.1	5.2	0.42	0.5	0.61
Stockings of Cambridge[b,c]	9.0	2.4	−0.28	1.42	10.4	1.6	0.60	0.88	0.64
Spatial working memory[b,c]	21.0	20.1	−0.64	1.55	9.2	16.7	0.42	0.81	0.72
Memory[b]			−0.07	0.77			0.47	0.52	0.71
California Verbal Learning Test trials 1–5[b,c]	51.6	11.6	−0.09	1.30	58.7	7.7	0.69	0.89	0.61
California Verbal Learning Test delay recall	10.9	3.0	−0.44	1.10	12.7	2.7	0.24	1.05	0.57
Pattern recognition[c]	94.6	7.0	0.92	0.69	97.0	3.3	1.10	0.40	0.27
Spatial recognition	76.8	15.2	−0.42	1.44	83.2	11.8	0.16	1.04	0.40
Paired associates	9.1	6.5	−0.30	1.03	4.9	5.4	0.16	0.74	0.45

[a]Main analysis and effect sizes based on *z* scores, although similar results obtained with raw scores.
[b]Significant group difference after Bonferroni correction.
[c]Used *t* score based on unequal variance between groups.

Table 3. Cognitive Domain Scores by Presence of Substance Abuse[a]

	Substance Abuse (n = 20)		No Substance Abuse (n = 23)		Effect
Score	Mean	SD	Mean	SD	Size
Verbal/premorbid intelligence quotient	0.17	0.54	0.44	0.61	0.43
Spatial reasoning	0.26	0.68	0.69	0.67	0.58
Attention/processing speed	−0.27	0.78	−0.51	0.65	−0.31
Executive	−0.15	0.65	−0.29	0.83	−0.17
Memory	−0.12	0.72	−0.04	0.79	0.10

[a]After Bonferroni correction (α = .01), there were no significant differences between groups on any cognitive domain measure.

Table 4. Cognitive Domain Scores in Lithium- and Divalproex-Treated Groups

	Divalproex (n = 20)		Lithium (n = 16)		Effect
Score	Mean	SD	Mean	SD	Size
Verbal/premorbid intelligence quotient	0.15	0.72	0.42	0.41	0.41
Spatial reasoning[a]	0.15	0.63	0.77	0.73	0.84
Attention/processing speed	−0.54	0.64	−0.46	0.67	0.11
Executive[a]	−0.64	0.68	0.11	0.70	0.99
Memory	−0.28	0.73	−0.10	0.75	0.22

[a]Significant group differences after Bonferroni correction (α = .01).

spatial reasoning ($t_{43} = 5.0$, $P < .000$), executive function ($t_{43} = 5.5$, $P < .000$), and memory ($t_{43} = 4.0$, $P < .000$) relative to controls. No significant correlations were observed between dose of either lithium or divalproex and any of the cognitive domain scores (all *r*'s $P > .15$). Patients were also divided into those who were treated with (n = 30) and without (n = 15) an atypical antipsychotic. While these groups were comparable with regard to frequency of treatment with either lithium ($\chi^2 = 1.18$, $P = .28$) or valproate ($\chi^2 = 0$, $P = 1.0$), no significant differences on any cognitive domain scores were observed between these groups (all *t* tests $P > .05$).

Cognitive Functioning and Symptom Variables

Table 5 reveals that after Bonferroni correction for the number of comparisons, there were no significant correlations between cognitive measures and mood or psychotic symptom ratings.

Cognitive Functioning and Other Clinical Variables

Cognitive domain scores were not significantly associated with age of illness onset (all *r*'s $P > .05$), duration of illness (all *r*'s $P > .35$), age at onset of manic episode (all *r*'s $P > .10$), duration of untreated illness at first manic episode (all *r*'s $P > .30$), duration of first manic episode (all *r*'s $P > .10$), or time between end of first manic episode and cognitive testing (all *r*'s $P > .05$). There was no significant difference between patients with (n = 29) and without (n = 15) a history of any prior mood episode on any cognitive domain score (all $P > .30$). Similarly, there was no significant difference between patients with (n = 24) and without (n = 18) a history of prior depressive episode on any cognitive domain score (all $P > .10$). Additionally, no differences in domain scores were

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Table 5. Correlation Between Cognitive Measures and Symptom Ratings[a]

Measure	Symptom Rating Scale		
	Positive and Negative Syndrome Scale[b]	Young Mania Rating Scale	Hamilton Depression Rating Scale
Verbal/premorbid intelligence quotient			
North American Adult Reading Test	−0.24	−0.12	0.19
Kaufmann Brief Intelligence Test verbal	−0.29	−0.10	0.22
Spatial reasoning			
Judgment of line orientation	−0.29	−0.08	0.10
Kaufmann Brief Intelligence Test nonverbal	−0.31	−0.45	−0.01
Attention/processing speed			
Trail-Making Test A	−0.29	−0.12	−0.03
California Verbal Learning Test trial 1	−0.25	−0.11	−0.07
Stroop word	−0.07	0.11	0.12
Stroop color	−0.32	−0.10	0.20
Rapid visual information processing	−0.19	−0.33	0.05
Executive			
FAS verbal fluency	−0.13	0.08	0.13
Trail-Making Test B	−0.13	−0.04	0.20
Stroop interference	−0.18	−0.03	0.08
Letter/number sequencing	−0.20	−0.23	0.19
Intra-/extra-dimensional task	−0.07	−0.12	0.17
Stockings of Cambridge	−0.32	−0.21	0.04
Spatial working memory	−0.20	−0.06	0.19
Memory			
California Verbal Learning Test trials 1–5	−0.26	−0.20	0.06
California Verbal Learning Test delayed recall	−0.12	−0.17	−0.01
Pattern recognition	−0.45	0.05	−0.03
Spatial recognition	−0.10	−0.16	−0.12
Paired associates	−0.20	0.02	0.13

[a]Spearman correlation coefficients with α adjusted for number of comparisons ($P = .0008$).
[b]Positive symptom score.

observed between those with (n = 12) and without (n = 32) history of prior hypomanic episode (all $P > .15$).

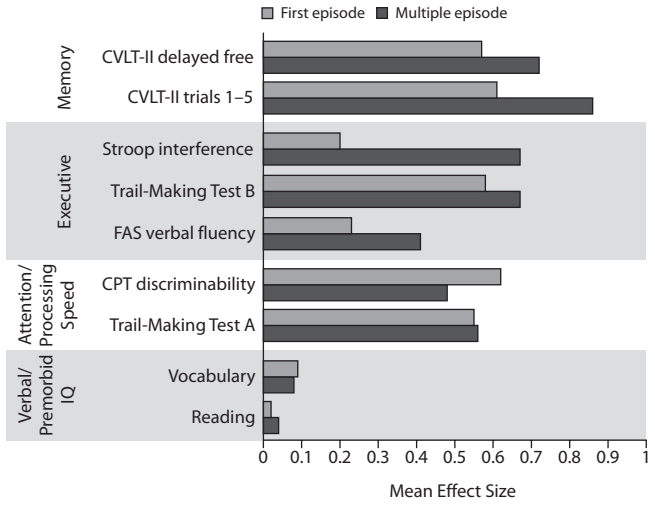
DISCUSSION

The main finding of this study is that neuropsychological deficits are present in clinically stable patients with bipolar disorder very early in the course of illness following resolution of the initial manic episode. Moderate effect size differences between patients and healthy comparison subjects were evident on tasks assessing multiple cognitive domains, including sustained attention, learning and memory, several aspects of executive function, and nonverbal/spatial reasoning. Because patients and controls were comparable in age, sex, education, and premorbid intellectual function, these factors were most likely not responsible for the differences between groups. Moreover, other potential confounds, including comorbid substance abuse and medication variables, do not appear to fully account for the extent of cognitive impairment observed in patients. Given that there was no significant correlation between cognitive variables and mood symptom ratings, it is also unlikely that cognitive deficits resulted from resolving residual manic symptoms from the first manic episode or subsyndromal depressive symptoms of an emerging depressive episode. Despite this, we cannot entirely rule out the possibility that cognitive deficits will not show any improvement with time. Because we are following this sample longitudinally, we will be able to determine the stability of cognitive impairment presented herein.

Although smaller in magnitude, the cognitive deficits in our first-episode sample resemble those observed in other clinically stable patients with bipolar disorder and include deficits in verbal memory, sustained attention, working memory, and attentional/mental set-shifting ability.[1,2,4,10,26–28] These results, alongside neuroimaging findings in first-episode patients,[29–31] suggest that the proposed dysfunction within a distributed brain network involving prefrontal-subcortical and limbic brain regions[32,33] may be present as early as illness onset. The present findings, however, cannot address whether the cognitive deficits at first episode reflect preexisting impairments or develop exclusively at illness onset. Nevertheless, evidence of cognitive impairment in unaffected first-degree relatives of patients with bipolar disorder[34,35] suggests that cognitive deficits at first episode at least partly reflect preexisting genetic vulnerability.

The current findings indicate that cognitive impairments in clinically stable patients with bipolar disorder are most likely not attributed solely to disease progression, prolonged treatment effects, or increased illness burden. These data, however, do not rule out the possibility that some aspects of cognitive impairment may be progressive.[35,36] Indeed, current conceptualizations posit that bipolar disorder is most likely characterized by both early and progressive dysfunction.[33,37] A gross comparison of our first-episode cognitive data to previously published non–first-episode euthymic samples (extracted from meta-analytic data[1,2]) provides a preliminary framework for determination of the longitudinal course of cognitive impairment in the illness. Figure 1 reveals that the magnitude of cognitive impairment in our first-episode

Figure 1. Magnitude of Cognitive Impairment in First-Episode (our sample) and Multiple-Episode (previously published) Patients Relative to Healthy Comparison Subjects[a]



[a]Values for multi-episode patients were taken from 2 existing meta-analyses[1,2] comparing euthymic patients to controls, as none of the samples included in these meta-analyses were first-episode. Effect sizes reflect comparisons between patient groups and healthy comparison subjects. Note that multi-episode data were collected at different places and times relative to first-episode data.
Abbreviations: CPT = Continuous Performance Test, CVLT-II = California Verbal Learning Test–Second Edition, IQ = intelligence quotient.

sample is minimal and comparable to that of previously published multi-episode patients on tasks of premorbid/verbal intellectual ability and the included measures of attention/processing speed. For the remainder of tasks, which include measures of executive function and verbal memory, consistently smaller cognitive deficits are present in first-episode relative to multi-episode patients. This finding suggests that cognitive impairment in these domains may progress somewhat with advancing illness course. The discrepancy in performance between first- and multi-episode patients is particularly prominent for the Stroop interference task. This finding raises the possibility that the anterior cingulate prefrontal system, which has been shown to be one of the major neural substrates supporting Stroop task performance,[13] may be particularly susceptible to progressive dysfunction as the illness advances. Clearly, our preceding analysis provides only a cursory and preliminary glance into the potential course of cognitive impairment in bipolar disorder. More extensive longitudinal study of the same patients will be necessary to directly test whether specific cognitive deficits and their respective brain systems show preferential dysfunction across the course of bipolar illness.

Our finding that alcohol/substance abuse was unlikely to account for the memory and executive deficits seen in first-episode patients is at odds with a prior report that identified substance abuse to be associated with poorer cognitive outcome in patients with bipolar disorder.[38] One possible explanation for these discrepant findings is that first-episode patients, who are younger and earlier in their course of illness, inevitably have had less opportunity to develop lengthy substance abuse histories. Therefore, the recognized deleterious effects of lengthy substance abuse may not have had a chance to impact negatively upon cognitive functioning in a measurable manner. With increasing substance use, more chronic or cumulative cognitive deficits are likely to emerge in patients who are older and further along in the course of illness. These data suggest that early identification and treatment of substance abuse in patients may improve cognitive outcomes.

The present study was conducted within the context of a naturalistic treatment setting and, thus, was not designed to directly and prospectively evaluate the influence of different medications upon cognition. Thus, all findings from analyses that examined the relationship between medication status and cognitive functioning should be considered exploratory and require further study. Nevertheless, post hoc analyses in this sample revealed that lithium-treated patients showed better cognitive functioning in multiple domains than those treated with divalproex. One exception to this was noted in memory functioning, which was impaired in both drug groups, and which may, thus, represent a particularly robust illness-related deficit. The few existing clinical studies comparing these 2 drugs have found little to no cognitive difference between them[39,40]; however, these samples were not first-episode. If replicated, our finding of better cognitive functioning in lithium-treated first-episode patients could identify an early advantage conferred by lithium treatment that may diminish across either prolonged treatment or disease progression.[41] At this stage, however, it is too early to tell whether this lithium advantage is indeed robust and, if so, whether in first-episode patients it may reflect reported neuroprotective mechanisms of lithium.[42] Alternatively, rather than reflecting relative improvement on lithium, it may be that divalproex-treated first-episode patients experience adverse cognitive side effects. Again, the preliminary and post hoc drug findings in this report require replication and further study. Even though we did not identify any major demographic or clinical variables that could account for cognitive differences between lithium- and divalproex-treated groups, it is important to note that patients were not randomly assigned to treatment groups. Thus, other variables associated with selection of patients to receive either medication may have contributed to observed cognitive differences between groups. For example, it is possible that patients with preexisting cognitive deficits may have received divalproex more frequently than lithium. In addition to using randomized designs, future first-episode studies should employ larger samples as well as a drug-naive first-episode comparison group to help determine the extent to which cognitive difficulties are medication independent.

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Several limitations of this study warrant consideration. First, even though patients and controls were well matched according to relevant demographic variables, both groups had average to high average premorbid/current intellectual functioning, which is most likely not representative of the range of patients with bipolar disorder. The overrepresentation of "high-functioning" participants explains why, in several instances, patients performed significantly worse than their appropriately matched (also high-functioning) healthy controls (see effect sizes in Table 2), yet showed better performance relative to age-corrected normative values (see *z* scores for patients in Table 2). The relevant comparison in this study was between patients and matched control participants (regardless of whether raw or norm referenced values were used), which ultimately supports the validity of the finding of poorer cognitive functioning in our patient sample. Nevertheless, future studies should employ samples with lower intellectual functioning in order to replicate and extend the generalizability of these findings. Another limitation is that even though mean mood ratings were low and consistent with euthymic levels, ratings were not obtained on the day of testing for all patients. However, because ratings were obtained within a few days of testing for most patients, it is unlikely that patients experienced dramatic shifts in mood between testing and mood ratings. Additionally, there was no correlation between cognitive performance and time elapsed between ratings and cognitive testing. In light of these limitations, the present study may provide insights into the nature and etiology of a critical phenotypic feature of bipolar illness and points to the need to identify cognitive deficits early in the course of bipolar disorder.

Drug names: divalproex (Depakote and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others).

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