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ORIGINAL ARTICLE

Relationship between cognitive functioning and 6-month clinical and functional outcome in patients with first manic episode bipolar I disorder

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Background. Although cognitive deficits in bipolar disorder have been associated with diminished functional outcome, this relationship has been studied primarily through cross-sectional designs, and has not been studied in patients early in the course of illness. The purpose of this study was to evaluate the impact of cognitive functioning on longitudinal 6-month functional and clinical outcome in recently diagnosed clinically stable patients with bipolar disorder.

Method. A total of 53 recently diagnosed patients with DSM-IV bipolar disorder type I were assessed within 3 months of their first manic episode using a neuropsychological battery measuring verbal/pre-morbid intellectual functioning, learning/memory, spatial/non-verbal reasoning, attention/processing speed and executive function. Functional outcome was assessed at baseline and 6 months using the Multidimensional Scale of Independent Functioning (MSIF) and DSM-IV Global Assessment of Functioning Scale (GAF). Clinical outcome was assessed with symptom ratings and by monitoring onset of new mood episodes.

Results. Memory, particularly verbal learning/memory, was robustly associated with 6-month functional outcome on the MSIF, even after partialling out the influence of mood symptoms and substance abuse co-morbidity. Depression ratings at 6 months, but not cognitive variables, were associated with 6-month GAF scores. Cognitive functioning was not associated with 6-month clinical outcome.

Conclusions. Memory was associated with 6-month longitudinal functional but not clinical outcome in recently diagnosed patients with bipolar disorder. These data further support the distinction between clinical and functional outcome, and emphasize the need for identification of, and development of treatments for, cognitive impairments early in the course of bipolar disorder.

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Key words: Bipolar disorder, functional outcome, memory, neurocognition, neuropsychology.

Introduction

Neuropsychological impairment is a core clinical feature of bipolar disorder that is observed even in euthymic patients (Torres *et al*. 2007; Bora *et al*. 2009). Moreover, cognitive impairments have been associated with diminished functional outcome (Torres *et al*. 2008; Wingo *et al*. 2009), which broadly refers to an individual's functioning (or disability) in various psychosocial contexts including vocational, educational, independent living and social arenas. Diminished functional outcome is commonly observed even in symptomatically recovered patients with bipolar disorder (Zarate *et al*. 2000; MacQueen *et al*. 2001). The most frequent cognitive correlates of functional outcome in bipolar disorder include memory, executive functioning and attention, and these cognitive measures have been linked to both global and specific (e.g. occupational status) measures of functional outcome (Torres *et al*. 2008). Additionally, the relationship between cognition and functional outcome persists even when the influence of current psychiatric symptoms is controlled (Dickerson *et al*. 2004; Martínez-Arán *et al*. 2004).

Observation of a cross-sectional association between cognition and functional outcome is significant

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because it helps predict which patients are likely to struggle in everyday functioning, and it identifies a potential determinant of functional outcome that could be targeted by treatment and rehabilitation. However, a more compelling case for asserting the importance of cognitive deficits could be made by demonstrating that cognitive deficits predict future psychosocial functioning in patients. In one of the few existing longitudinal studies, Jaeger *et al*. (2007) reported that attention and ideational fluency in middle-aged patients with bipolar disorder predicted functional outcome after 1 year, independent of mood symptoms at baseline and follow-up. More recently, two other longitudinal studies have reported symptom-independent associations between baseline cognitive function and 1-year functional outcome involving measures of global cognition and visual/motor processing (Tabares-Seisdedos *et al*. 2008), as well as attention, verbal memory and executive function (Martino *et al*. 2009).

Although these few longitudinal studies extend the cross-sectional findings, they all studied middle-aged patients (aged early- to mid-40s) with established illness. However, because the illness onset typically occurs in the second and early third decades, it is unknown whether cognitive deficits that may be present early in the course of illness also predict future functional status. Evidence of such a relationship would provide strong support for the urgency of identifying cognitive deficits early in the illness, at a point where patients may be more responsive to targeted treatments.

Our group and others have recently demonstrated that clinically stable patients with newly diagnosed bipolar I disorder show cognitive deficits in several domains including verbal memory, executive function and sustained attention (Nehra *et al*. 2006; Gruber *et al*. 2008; Torres *et al*. 2010). The relationship between cognitive impairments and functional outcome, however, has not been studied either concurrently or longitudinally in first-manic-episode patients. Gruber *et al*. (2008) showed that first-episode patients with poorer baseline executive function (i.e. Stroop, trend verbal fluency) showed slower symptomatic recovery at 1 year. However, their outcome measure was clearly clinical/symptomatic rather than functional in nature. The important distinction between symptomatic and functional recovery is relevant, as symptomatic recovery does not guarantee, and often can occur independent of, functional recovery (Coryell *et al*. 1993; Tohen *et al*. 2000; Judd *et al*. 2005; Conus *et al*. 2006).

To summarize, there has been very little research on determining whether cognitive functioning predicts future functional outcome in patients with bipolar disorder, and no such research in first-manic-episode patients. Therefore, the putative cognitive mechanisms underlying either clinical or functional outcome early in the course of illness remain unclear. The primary purpose of the present study was to evaluate the relationship between baseline cognitive functioning and longitudinal functional outcome in stable bipolar patients who recently recovered from their first manic episode. Given the evidence of cognitive impairment early in the course of bipolar illness, the primary hypothesis was that baseline cognitive functioning in memory, attention and executive functioning would be associated with 6-month functional outcome in these patients. A secondary goal was to determine whether the same cognitive predictors would be associated with both functional and clinical/symptomatic outcome at 6 months.

Method

Participants

Subjects consisted of 53 patients enrolled in the Systematic Treatment Optimization Program for Early Mania (STOP-EM), a naturalistic longitudinal study investigating neurobiological, behavioural and psychosocial functioning in patients recently experiencing a first manic episode and diagnosed with bipolar disorder (Yatham *et al*. 2009*a*). Individuals were recruited from University of British Columbia (UBC) and Vancouver General Hospitals and affiliated sites, as well as local physician and psychiatrist referrals. Of 67 consecutive clinic patients who were approached for study participation, 53 patients agreed to participate in the baseline assessment. Patients were diagnosed using DSM-IV criteria based on clinical interview and the Mini International Neuropsychiatric Interview (Sheehan *et al*. 1998). Patients were required to have experienced a first manic or mixed episode with or without psychosis within the past 3 months. Patients enrolled in the program were given open-label maintenance treatment from psychiatrists using updated clinical guidelines for management and treatment of bipolar disorders, and new mood episodes were also treated using best practice guidelines (Yatham *et al*. 2009*b*). Patients were followed as clinically indicated but at least every 6 months in accordance with the research protocol. All participants provided written informed consent prior to participation in the study, and the research protocol was approved by the UBC Clinical Research Ethics Board. The current study reports on data obtained at baseline and the 6-month time-point. Earlier subsets of the neurocognitive (Torres *et al*. 2010) and functional outcome (Kauer-Sant'Anna *et al*. 2009) data were reported previously.

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Patient demographics and clinical characteristics are summarized in Table 1. Of the initial 53 patients, eight were excluded at the 6-month time-point for the following reasons: three voluntarily ceased participation after baseline; three missed the 6-month time-point but resumed participation during later time points; one patient had not yet reached the 6-month time-point; one patient was hospitalized and in a clearly manic and psychotic state. Thus, a total of 45 patients were assessed at 6-month follow-up.

Neuropsychological battery

The cognitive battery was constructed to assess multiple cognitive domains (Torres *et al*. 2010) and included tests that have been implicated in bipolar disorder (Torres *et al*. 2007; Bora *et al*. 2009). Individual measures were categorized into five broad cognitive domains (see below). Due to insufficient sample size, factor analysis could not be employed to guide the categorization of tasks into larger cognitive domains. Thus, categorization was conducted on a rational basis drawing on existing neuropsychological literature (Stuss *et al*. 2002; Lezak *et al*. 2004; Strauss *et al*. 2006) and cognitive research in bipolar disorder (Robinson & Ferrier, 2006; Torres *et al*. 2007, 2010; Stefanopoulou *et al*. 2009).

Verbal/pre-morbid intelligence quotient (IQ)

The North American Adult Reading Test full scale IQ (Blair & Spreen, 1989) and the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990) vocabulary score were employed to measure this domain.

Visual-spatial/non-verbal reasoning

The K-BIT matrices score and the Benton Judgment of Line Orientation (JLO; Benton *et al*. 1994) total adjusted score were used to measure visual-spatial/non-verbal reasoning. The JLO was included in this domain by virtue of the test's preferential correlation with non-verbal/fluid intellectual ability relative to verbal ability (Lee & Cheung, 2005).

Attention/processing speed

The tests employed were Trailmaking test A time (Reitan & Wolfson, 1993), Stroop Test (Golden, 1978) word and color naming trials number correct, Cambridge Neuropsychological Test Automated Battery (CANTAB; Robbins *et al*. 1994) rapid visual information processing discriminability score, and California Verbal Learning Test II (CVLT-II; Delis *et al*. 2000) trial 1 words recalled. Although the latter measure is derived from a memory test, it was included in the attention domain based on prior factor analytic findings (Donders, 2008).

Executive function

Even though the tasks selected for this domain fall under the broad category of executive functioning and generally involve dorsal prefrontal brain functioning (Stuss *et al*. 2002), it is also likely that individual tasks show some degree of differentiation (Miyake *et al*. 2000). Thus, it was deemed important to conduct analyses of the individual measures below in addition to the main analyses using the executive domain measure (see statistical analysis section). The tasks selected were Controlled Oral Word Association Test (Lezak *et al*. 2004) number correct, Stroop color/word trial number correct, Trailmaking test B time, Wechsler Memory Scale III (Wechsler, 1997) letter/number sequencing, CANTAB intra-extra-dimensional set-shifting task number of extra-dimensional shifting errors, CANTAB Stockings problems solved in minimum number of moves, and CANTAB spatial working memory between errors.

Learning/memory

CVLT-II recall trials 1–5, and delayed free recall, CANTAB spatial recognition memory percent correct, CANTAB pattern recognition memory percent correct, and CANTAB paired associate learning total errors adjusted score were used to measure learning and memory.

Symptom ratings

After enrolment into the study, patients were given a comprehensive baseline assessment that included mood ratings (Table 1). In addition to the scheduled visits (e.g. baseline, 6 months), patients received routine follow-up visits as clinically indicated including repeat symptom ratings. Cognitive testing was conducted when patients were clinically judged to be symptomatically stable. Thus, testing occurred during the baseline assessment session for most patients, but was deferred for some patients if either (1) they were judged to be symptomatic or clinically unstable (through interview and symptom ratings), or (2) there were scheduling conflicts with other appointments such as a magnetic resonance imaging scan. Because many patients had multiple symptom ratings taken during unscheduled follow-up visits, the mean symptom ratings closest to the day of cognitive testing are reported in Table 1. Symptom ratings were conducted by study psychiatrists, and the cognitive battery was administered by trained advanced clinical neuropsychology graduate students. Cognitive testing

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Table 1. *Demographic and clinical variables for baseline and 6-month samples*

	Baseline sample ($n=53$)	6-month sample ($n=45$)	
	At baseline	At baseline	At 6 months
Continuous variables			
Age, years	22.7 (4.1)	23.3 (4)	
Education, years	13.6 (2.3)	13.8 (2.2)	
North American Adult Reading Test (pre-morbid IQ)	107.1 (7.3)	107.3 (7.3)	
Age at illness onset, years	19.4 (4.8)	19.6 (5.1)	
Age at depression onset, years	18.2 (5.2)	18.4 (5.2)	
Number of previous depressive episodes	1.2 (1.5)	1.3 (1.5)	
Number of previous hypomanic episodes	0.5 (1.7)	0.6 (1.8)	
Symptom rating scales			
Positive and Negative Syndrome Scale – Positive Score[a]	7.8 (1.5)	7.7 (1.5)	7.1 (0.3)
Young Mania Rating Scale[b]	1.3 (3.1)	1.1 (3.0)	0.4 (0.9)
Hamilton Depression Rating Scale[c]	4.1 (4.9)	4.0 (4.9)	3.0 (3.8)
Brief Psychiatric Rating Scale	22.9 (5.7)	23.1 (5.9)	20.0 (2.6)
Global Assessment of Functioning Scale	65.3 (12.6)	64.6 (11.5)	75.8 (9.4)
Multidimensional Scale of Independent Functioning	4.2 (2.4)	4.2 (2.4)	2.4 (1.5)
Lithium dose, mg	960 (164)	942 (144)	1000 (328)
Divalproex dose, mg	920 (342)	940 (350)	1054 (373)
Categorical variables			
Male gender	25 (47)	21 (47)	
Ethnicity			
Caucasian	41 (79)	34 (77)	
Asian	6 (12)	5 (11)	
Other	5 (10)	5 (11)	
English first language	48 (91)	40 (89)	
Pre-morbid socio-economic status			
Student	28 (54)	23 (52)	
Part-time work	2 (4)	1 (2)	
Full-time work	17 (33)	16 (36)	
Self-employed	1 (2)	1 (2)	
Unemployed	4 (8)	3 (7)	
Medications			
Mood stabilizers	45 (85)	39 (87)	39 (87)
Lithium	21 (40)	18 (40)	19 (42)
Divalproex	26 (49)	21 (47)	20 (44)
Lamotrigine	1 (2)	1 (2)	0 (0)
Atypical antipsychotics	37 (70)	32 (71)	22 (49)
Antidepressants	4 (8)	4 (9)	7 (16)
Anxiolytics	3 (6)	1 (2)	0 (0)
Initial mixed episode	2 (4)	2 (4)	
Psychosis during initial manic episode	41 (77)	35 (78)	
History of depressive episode	31 (60)	29 (66)	
Co-morbid DSM-IV substance/alcohol abuse or dependence	22 (42)	19 (42)	

IQ, Intelligence quotient.

Continuous variables are given as mean (standard deviation) and categorical variables are given as number (%).

[a] Rated on a scale of 1–7 for seven symptoms, yielding an overall score range from 7 (no symptoms) to a maximum score of 49 (Kay *et al*. 1987).

[b] Young *et al*. (1978).

[c] 21-Item version (Hamilton, 1960).

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was conducted on the same day as mood ratings for 32% of the patients, within 1 day for 45%, within 1 week for 66%, and within 2 weeks for 83%. The cognitive battery took approximately 2.5 h to administer and patients were given periodic 5–10 min breaks to maintain effort and prevent fatigue.

Functional outcome measures

The primary instrument for assessment of functional outcome was the Multidimensional Scale of Independent Functioning (MSIF), which has been developed for use in psychiatric patients and validated in patients with bipolar disorder (Jaeger *et al*. 2003; Berns *et al*. 2007). The MSIF is a structured interview scale measuring the individual's functional status during the previous month in three major environments: work, educational, and residential. The MSIF requires the rater to take into account contextual factors such as the patient's role expectations, level of support, and performance in order to derive a global rating for each of the three environments. We employed the Overall Global rating which represents a summary rating across the three major functional environments. The anchors for the Overall Global ratings are: 1 = essentially normal functioning, 2 = very mild disability, 3 = somewhat disabled, 4 = moderately disabled, 5 = significantly disabled, 6 = extremely disabled, 7 = totally disabled. To conform with prior studies, we also used the Global Assessment of Functioning Scale (GAF), a clinician-rated scale of psychological, social, and occupational functioning which is rated from 0 (lowest) to 100 (highest) based on anchors describing varying levels of functioning (Endicott *et al*. 1976). Both measures were collected at baseline and 6 months.

Statistical analysis

For each specific cognitive measure, raw scores were converted to *Z* scores ranging from −4 to 4 based on demographics-corrected normative data contained within the test manual for each test. Scores were adjusted so that higher *Z* scores reflected better performance. *Z* scores were used to facilitate computation of domain scores and because they tended to handle outliers better than raw scores. Within each major cognitive domain, *Z* scores for inclusive measures were averaged to derive a mean cognitive domain score. Although the primary dependent variables were the domain scores, secondary analyses were also conducted on the individual measures because (1) for some complex and multifaceted domains such as executive functioning, use of a summary 'executive' score could potentially obscure effects that might be driven by a specific executive ability, and (2) other researchers might categorize cognitive tasks in a slightly different manner. In sum, the analytical approach focusing on both cognitive domain and individual measures was employed to strike a balance between (1) using a rationally based approach to data reduction that involved classification of like tasks into broad cognitive domains and that benefited from the psychometric advantages of averaging performance on multiple tasks, and (2) presenting data on individual primary cognitive measures in order to retain the ability to generate hypotheses about the potential impact of individual cognitive functions (e.g. subcomponents of executive function) on outcome variables.

Distributions of cognitive domain scores, mood ratings, and functional outcome measures were screened as described by Tabachnick & Fidell (2007), and data were transformed when appropriate (see Results section). To test the main hypothesis, hierarchical multiple regression was utilized employing functional outcome (MSIF or GAF) as the dependent measure, and cognitive and mood symptom variables as predictors. To control for mood, mood ratings were entered first into the regression equation, followed by simultaneous entry of the five cognitive domain scores. Pearson correlations were used to explore the association between individual cognitive test scores and functional and clinical outcomes (e.g. depression ratings). Changes in functional outcomes and mood ratings between baseline and 6 months were evaluated using paired two-tailed *t* tests or the non-parametric Wilcoxon test. Multivariate analysis of variance was used to evaluate differences in cognitive domain scores between patients with and without new onset of depressive symptoms between baseline and 6 months.

Results

Baseline clinical variables, cognitive functioning and functional status

Demographic, clinical and functional variables for the baseline sample are summarized in Table 1. Mean mood ratings reveal that patients were clinically stable. Cognitive data for individual tests and domain scores are included in Table 2. Cognitive domain scores and baseline GAF were normally distributed (Shapiro–Wilk, $p > 0.05$); however, a logarithmic transformation was applied to baseline MSIF ratings (lnMSIF), a square root transformation to Hamilton Depression Rating Scale (sqrHAMD) scores, and an inverse transformation to Young Mania Rating Scale (invYMRS) ratings. The resulting distributions for these variables yielded improved skew and kurtosis statistics (all between −1 and +1). The correlation between GAF and MSIF was $r = -0.30$ ($p < 0.05$), and between GAF and lnMSIF was $r = -0.35$ ($p < 0.05$).

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Table 2. *Baseline cognitive functioning*

	Raw score	Z score[a]
Verbal/pre-morbid IQ	–	0.30 (0.58)
North American Adult Reading Test	107.1 (7.3)	0.47 (0.48)
Kaufman Brief Intelligence Test verbal	101.8 (11.1)	0.12 (0.74)
Spatial reasoning	–	0.48 (0.66)
Judgment of Line Orientation	26.2 (3.1)	0.52 (0.82)
Kaufman Brief Intelligence Test non-verbal	106.6 (11.1)	0.44 (0.74)
Attention/processing speed	–	−0.46 (0.68)
Trailmaking test A	27.5 (8.9)	−0.40 (1.22)
California Verbal Learning Test trial 1	6.5 (1.9)	−0.45 (1.00)
Stroop word	100.6 (14.2)	−0.28 (1.02)
Stroop color	71.8 (12.4)	−0.63 (1.02)
Rapid visual information processing	0.89 (0.05)	−0.56 (1.09)
Executive	–	−0.24 (0.71)
COWAT verbal fluency	37.8 (10.2)	−0.49 (0.91)
Trailmaking test B	58.9 (23.3)	0.02 (1.10)
Stroop interference	46.4 (9.6)	0.09 (0.94)
Number letter sequencing	10.7 (2.5)	−0.08 (0.86)
Intra-extra-dimensional task	7.5 (8.6)	−0.26 (1.23)
Stockings of Cambridge	8.9 (2.2)	−0.31 (1.34)
Spatial working memory	21.1 (19.2)	−0.65 (1.45)
Memory	–	−0.12 (0.72)
California Verbal Learning Test trials 1–5	51.7 (11.6)	−0.08 (1.30)
California Verbal Learning Test delayed recall	11.0 (3.0)	−0.43 (1.12)
Pattern recognition	94.4 (6.8)	0.87 (0.66)
Spatial recognition	75.0 (15.9)	−0.60 (1.45)
Paired associates	8.6 (6.5)	−0.32 (0.89)

IQ, Intelligence quotient; COWAT, Controlled Oral Word Association Test.

Values are given as mean (standard deviation).

[a] Based on demographics-corrected normative data supplied with test manual for each test.

Mood and cognitive predictors of baseline functional outcome

In the first step of the regression model using lnMSIF as the dependent measure, baseline mood symptom ratings were unrelated to lnMSIF scores [$R^2 = 0.05$, $F(2, 50) = 1.3$, $p = 0.27$; both β's $p > 0.25$]. Addition of the cognitive domain variables failed to add significantly to the model [$\Delta R^2 = 0.02$, $\Delta F(5, 45) = 0.18$, $p = 0.97$, all five β's $p > 0.45$]. For the GAF, mood symptoms [$R^2 = 0.14$, $F(2, 50) = 4.1$, $p = 0.02$] and, in particular, HAMD scores ($\beta = -0.38$, $t = -2.7$, $p = 0.01$), were significant predictors of GAF scores; however, addition of the cognitive variables did not contribute to predicting GAF scores [$\Delta R^2 = 0.04$, $\Delta F(5, 45) = 0.39$, $p = 0.85$].

Clinical and functional outcome at 6 months

Demographic and clinical variables for both the baseline sample and the subset of patients seen at 6 months are presented in Table 1. The mean duration between baseline cognitive assessment and 6-month functional outcome assessment was 172 (S.D. = 55) days. The eight patients excluded from data analysis at 6 months were slightly younger [excluded: 19.6 (S.D. = 2.9) years; included: 23.3 (S.D. = 4.0) years; $t = 2.5$, degrees of freedom (df) = 51, $p = 0.02$] and had fewer years of education [excluded: 12.0 (S.D. = 1.7) years; included: 13.8 (S.D. = 2.2) years; $t = 2.2$, df = 51, $p = 0.03$] than the 45 patients with 6-month data. However, groups showed comparable age of illness onset, gender composition, pre-morbid IQ and baseline GAF scores (all N.S., $p > 0.25$).

A square root transformation was applied to 6-month HAMD ratings (sqr6HAMD) and 6-month MSIF scores (sqr6MSIF). As during baseline, patients at 6 months were well-treated and showed minimal clinical symptoms (Table 1). For example, on the 6-month YMRS, 82% of patients obtained a rating of 0, 2% a rating of 1, 13% a rating of 2, and 2% a rating of 4. Accordingly, all but one patient met mania remission criteria for the YMRS (Berk *et al*. 2008). HAMD ratings were also low although more variable than mania ratings at 6 months (Table 1). Based on a

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Table 3. *Hierarchical regression analyses of the relationship between cognitive functioning and 6-month functional outcome*

Dependent measure	Model	Predictor variable[a]	Adjusted R^2 of model	β	t	p
sqr MSIF	1	inv baseline YMRS	0.067	−0.198	−1.257	0.216
		sqr baseline HAMD		0.027	0.167	0.868
		sqr 6-month HAMD		0.248	1.597	0.118
	2	inv baseline YMRS	0.328	−0.244	−1.718	0.094
		sqr baseline HAMD		−0.028	−0.190	0.851
		sqr 6-month HAMD		0.123	0.907	0.371
		Verbal/pre-morbid IQ		−0.225	−1.395	0.172
		Spatial reasoning		0.244	1.026	0.312
		Attention/processing speed		−0.121	−0.668	0.508
		Executive		0.322	1.451	0.155
		Memory		−0.648	−3.207	0.003
GAF	1	inv baseline YMRS	0.315	0.048	0.353	0.726
		sqr baseline HAMD		0.081	0.579	0.566
		sqr 6-month HAMD		−0.613	−4.608	0.000
	2	inv baseline YMRS	0.358	0.039	0.281	0.780
		sqr baseline HAMD		0.037	0.254	0.801
		sqr 6-month HAMD		−0.548	−4.147	0.000
		Verbal/pre-morbid IQ		0.204	1.293	0.204
		Spatial Reasoning		−0.050	−0.217	0.830
		Attention/processing speed		0.093	0.526	0.602
		Executive		−0.036	−0.168	0.867
		Memory		0.189	0.954	0.346

sqr, Square root transformation; MSIF, Multidimensional Scale of Independent Functioning; inv, inverse transformation; YMRS, Young Mania Rating Scale; HAMD; Hamilton Depression Rating Scale; IQ, intelligence quotient; GAF, Global Assessment of Functioning Scale.

[a] Note: 6-month mania ratings excluded as predictor due to low variability.

remission cut-off score of 7 or lower on the HAMD (McIntyre *et al*. 2006), 18% of the sample did not meet remission criteria for depression. Only two patients reported an onset of mania and two an onset of hypomania between baseline and 6 months, whereas 32% reported onset of a depressive episode during that period. Regardless, there was no significant difference between baseline and 6-month HAMD scores (Wilcoxon $Z=-0.94$, $p=0.35$).

Regarding changes in functional outcome, Table 1 shows that patients at 6 months showed significantly improved MSIF (Wilcoxon $Z=-4.1$, $p<0.001$) and GAF ($t=6.5$, df = 44, $p<0.001$) scores relative to baseline. The percentage of patients falling under each of the 6-month MSIF rating categories was as follows: 1 = 33%, 2 = 29%, 3 = 13%, 4 = 13%, 5 = 7%, 6 = 4%, 7 = 0%. The correlation between either 6-month MSIF or sqr6MSIF and 6-month GAF ratings was $r=-0.57$ ($p<0.001$). Several potential clinical predictors of 6-month functional outcome were evaluated including baseline treatment with valproate ($n=21$) *v*. lithium ($n=17$), baseline treatment with ($n=32$) *v*. without ($n=13$) antipsychotics, 6-month treatment with valproate ($n=20$) *v*. lithium ($n=19$), 6-month treatment with ($n=22$) *v*. without ($n=23$) antipsychotics, history of ($n=35$) *v*. absence ($n=10$) of psychosis, and co-morbid ($n=19$) *v*. absence ($n=26$) of substance abuse. Of these, only co-morbid substance abuse was associated with worse functional outcome on sqrMSIF ($t=2.2$, df = 43, $p=0.04$).

Mood and cognitive predictors of 6-month functional outcome

Table 3 summarizes the two main regression analyses predicting 6-month functional outcome. In the first model, baseline and 6-month mood ratings did not predict 6-month MSIF scores after the first step [$R^2=0.13$, $F(3,41)=2.1$, $p=0.12$]. However, addition of the cognitive variables contributed significantly [$\Delta R^2=0.32$, $\Delta F(5,36)=4.2$, $p=0.004$], and memory was the only domain score contributing unique variance ($\beta=-0.65$, $t=-3.2$, $p=0.003$). When the same analysis was conducted including substance abuse in the model, results continued to reveal that only memory predicted 6-month MSIF ($\beta=-0.66$, $t=-3.3$, $p=0.002$). In the model predicting 6-month GAF, addition of the mood variables contributed significantly to

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Table 4. *Association between baseline cognitive functioning and 6-month functional and clinical outcome*

	Functional outcome		Clinical outcome
Cognitive measure	sqr MSIF	GAF	sqr 6-month HAMD
Verbal/pre-morbid IQ	−0.30	0.31	−0.03
North American Adult Reading Test	−0.32	0.32	−0.02
Kaufman Brief Intelligence Test verbal	−0.25	0.28	−0.04
Spatial reasoning	−0.24	0.25	−0.06
Judgment of Line Orientation	−0.23	0.20	0.06
Kaufman Brief Intelligence Test non-verbal	−0.17	0.23	−0.17
Attention/processing speed	−0.29	0.31	−0.11
Trailmaking test A	0.11	0.07	0.00
California Verbal Learning Test trial 1	−0.38	0.32	−0.03
Stroop word	−0.18	0.15	−0.07
Stroop color	−0.15	0.16	−0.16
Rapid visual information processing	−0.43	0.34	−0.12
Executive	−0.10	0.22	−0.02
COWAT verbal fluency	−0.15	0.33	−0.07
Trailmaking test B	−0.12	0.22	0.07
Stroop interference	−0.07	0.14	−0.07
Number letter sequencing	−0.17	0.23	−0.10
Intra-extra-dimensional task[a]	0.03	−0.02	−0.03
Stockings of Cambridge	−0.05	0.13	0.06
Spatial working memory[a]	0.02	0.04	−0.01
Memory	−0.53*	0.40	−0.21
California Verbal Learning Test trials 1–5	−0.50*	0.34	−0.14
California Verbal Learning Test delayed recall	−0.30	0.15	−0.09
Pattern recognition	−0.28	0.16	−0.13
Spatial recognition	−0.30	0.24	−0.03
Paired associates[a]	−0.33	0.39	−0.39

sqr, Square root transformation; MSIF, Multidimensional Scale of Independent Functioning; GAF, Global Assessment of Functioning Scale; HAMD, Hamilton Depression Rating Scale; IQ, intelligence quotient; COWAT, Controlled Oral Word Association Test.

[a] Due to skewed distributions, Spearman correlations were also calculated. In all instances results were unchanged.

* Significant ($p = 0.002$, Bonferroni corrected).

the model [$R^2 = 0.36$, $F(3, 41) = 7.7$, $p < 0.001$]. However, addition of the cognitive variables in the second step did not contribute to the model [$\Delta R^2 = 0.11$, $\Delta F(5, 36) = 1.6$, $p = 0.20$]. In the full model, only 6-month depression ratings were associated with 6-month GAF ($\beta = -0.55$, $t = -4.1$, $p < 0.001$).

To further explore the relationship between individual cognitive measures and 6-month functional outcomes, Pearson correlations between all cognitive variables and both functional outcomes are presented in Table 4. These data reveal that the strong relationship between memory and 6-month MSIF was largely driven by verbal learning.

Association between baseline cognition and 6-month clinical outcome

Due to the low scores and lack of variability in both Positive and Negative Syndrome Scale (PANSS) and YMRS scores at 6 months (Table 1) it was not possible to calculate correlations between baseline cognitive variables and 6-month mania or psychosis ratings. Regarding depression outcome, none of the cognitive domain or individual cognitive scores was significantly associated with 6-month HAMD ratings (right column, Table 4). Patients were also divided into groups that either experienced ($n = 14$) or did not experience ($n = 30$) a new depressive episode between baseline and 6 months. A multivariate analysis of variance on the five cognitive domain scores revealed no difference between groups [Wilk's $\lambda = 0.94$, $F(5, 38) = 0.49$, $p = 0.78$]. Regarding individual cognitive measures, the group experiencing depression showed worse performance only on the K-BIT non-verbal matrices ($t = 2.3$, df = 42, $p = 0.03$) and CANTAB spatial recognition memory ($t = 2.4$, df = 42, $p = 0.02$); however, the significance of these findings is questionable given the large number of comparisons ($n = 21$).

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Discussion

The main finding of this study is that cognitive functioning in stable, post-first-manic-episode patients with bipolar disorder was preferentially associated with 6-month functional but not clinical/symptomatic outcome.

Regarding clinical outcome, at 6 months, patients had achieved a high level of symptomatic recovery, especially in manic and psychotic symptoms. Mean depressive symptoms were also relatively low at 6 months despite the fact that 18% of patients evidenced at least mild depressive symptoms defined as a score of $\geqslant 8$ on the HAMD (McIntyre *et al*. 2006). Functional outcomes at 6 months were less favourable. Although patients showed a clear improvement in psychosocial functioning from baseline to 6 months, 37% continued to show at least mild disability and approximately one quarter showed at least moderate disability at 6 months. These data are consistent with prior studies that have tracked symptomatic and functional recovery in patients with psychotic affective disorder (Tohen *et al*. 2000), psychotic mania (Conus *et al*. 2006) and mania (Kauer-Sant'Anna *et al*. 2009; Yatham *et al*. 2009*a*) early in the course of illness.

Evaluation of the potential cognitive correlates of symptom status at 6 months was only possible for the 6-month depressive ratings, as there was a floor effect in 6-month manic and psychotic symptom ratings. Regardless, results failed to reveal an association between cognitive variables and 6-month depression ratings. Cognitive variables also failed to predict onset of a new depressive episode between baseline and 6 months, another indicator of clinical outcome. These findings are at odds with Gruber *et al*. (2008) who reported an association between the Stroop interference test and verbal fluency (trend) and longitudinal clinical outcome in first-episode patients. The discrepant findings, however, might be related to several methodological differences between the two studies including the follow-up period (1 year *v*. 6 months) and the type of measure used to quantify clinical outcome (self-report of time to recovery *v*. objective mood measures). Regardless of these discrepancies, our data suggest that using objective indicators of clinical outcome, cognitive variables do not reliably predict 6-month clinical outcome in remitted first-manic-episode patients.

In contrast to clinical outcome, there was a robust association between cognitive variables and 6-month functional outcome. However, this relationship was dependent on the functional outcome measure employed. When the functional measure was an objective and comprehensive structured questionnaire (MSIF), there was a strong and unique association between verbal learning/memory and subsequent functioning that could not be attributed to other variables with demonstrated association with functional outcome such as baseline or 6-month mood symptoms and substance abuse co-morbidity. A differential pattern of association was observed on the brief clinician-rated GAF, as the strongest predictor of 6-month functioning was 6-month depressive ratings, whereas cognitive variables were not associated with the 6-month GAF. One possible explanation for this is that raters may be preferentially attending to concurrent depressive symptoms when they are making ratings on the GAF. Thus, the briefly rated GAF may be providing a less pure and objective measure of functional status.

By demonstrating that cognition in stable first-manic-episode patients predicts 6-month functional but not clinical outcome, these data provide further support for the distinction between clinical/symptomatic outcome and functional outcome (Tohen *et al*. 2000; Judd *et al*. 2005). Moreover, the cognitive correlates of functional outcome (e.g. verbal learning/memory) observed in the present study overlap with the persistent cognitive deficits reported in bipolar disorder (Torres *et al*. 2007; Bora *et al*. 2009), as well as the deficits reported in recently diagnosed patients (Nehra *et al*. 2006; Torres *et al*. 2010). This suggests that the verbal learning/memory deficits underlying psychosocial functioning early in the disorder are likely to reflect persistent disease-related impairments.

Contrary to what has been reported in non-first-mania-episode samples (Torres *et al*. 2008; Wingo *et al*. 2009), we failed to observe an association between measures of executive functioning and 6-month functional outcome. One possible explanation for this is that tests of executive function tend to show poorer reliability relative to other cognitive measures (e.g. IQ, memory, attention) (Strauss *et al*. 2006). Thus, differential psychometric properties may have limited the ability to detect executive–functional outcome correlations (Chapman & Chapman, 1973). Another possibility is that the deleterious impact of executive deficits may not be as prominent early in the illness. It may be that as the illness progresses executive impairments also worsen (Robinson & Ferrier, 2006), and eventually these deficits begin to exert a more significant impact upon psychosocial functioning. Regardless, the current data point to memory, and particularly verbal memory, as a cognitive ability that may be identified as a potential target for treatment and remediation early in the course of illness. Although further research is needed, a further implication is that amelioration of verbal memory difficulties might have a positive

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impact upon patients' future psychosocial functioning.

Several limitations of the present study need to be considered. First, there was a surprising lack of association between baseline cognition and concurrent baseline psychosocial functioning. This may have been due to the fact that even though patients were symptomatically recovered at the time that baseline functional measures were obtained, most had not yet attempted to return to their previous roles and functional level. As a result, baseline ratings may have overestimated disability, thus compromising the validity of baseline functional measures and the power to detect the expected association between baseline cognition and functioning. Another limitation is that due to patients' high levels of symptomatic recovery at 6 months it was not possible to assess the degree to which baseline cognition might predict future manic or psychotic symptoms. Such an analysis may be possible by extending the follow-up period well beyond 6 months, as patients will be more likely to experience relapse in these symptoms (Yatham *et al*. 2009*a*). As it stands, the implication of a differential effect of cognition upon clinical and functional outcome should be limited to the first 6 months following initial diagnosis.

The present longitudinal dataset was subject to a modest level of attrition. In this case, the eight patients excluded from the 6-month analysis were slightly younger and had lower education, but were otherwise comparable clinically to the included sample. It is possible that the excluded individuals would have had more symptoms or less recovery at 6 months than those who continued. If so, it is not clear what the effect of including these individuals would have had on the observed association between memory and 6-month functional status. It is possible that inclusion of these individuals would have actually increased the size of the memory–outcome correlation by virtue of potentially introducing a wider range of both cognition and functional outcome. Despite any possible truncation in either cognition or outcome that may have occurred through attrition, we were still able to detect robust associations between baseline memory functioning and subsequent functional outcome. Another caveat that should be acknowledged is that the present findings apply to first-mania-episode patients who had recently been diagnosed with bipolar disorder, and not first-mood-episode patients, as the majority of patients had previously experienced at least one depressive episode. Nevertheless, patients were still very early in the course of illness. Finally, although patients were judged to be clinically stable at the time of cognitive testing, a final limitation is that (1) not all patients received symptom ratings on the exact day of cognitive testing, and (2) there was not a predefined period of time that patients were required to be asymptomatic. Thus, even though symptom ratings describe a clinically stable sample, we cannot entirely rule out that subclinical symptoms had no impact on cognitive performance.

In light of these limitations, the present study revealed a significant and robust association between baseline memory functioning and future psychosocial functioning in newly diagnosed patients with bipolar disorder. The next steps should include replication of these findings, extension of the follow-up period, and determination of how either progression or alleviation of cognitive deficits early in the course of illness continue to relate to both clinical and functional outcome.

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