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The impact of neurocognitive impairment on occupational recovery of clinically stable patients with bipolar disorder: a prospective study

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Abstract

Objective—Many patients with bipolar disorder do not regain their premorbid level of occupational functioning even after mood episodes have resolved. The reasons for this are not well understood. We evaluated the relationship between neurocognition and occupational function in bipolar disorder patients, following symptomatic recovery.

Methods—A total of 79 previously employed adults with bipolar I disorder who achieved symptomatic recovery (i.e., at least six weeks clinically euthymic) following a manic episode underwent a neurocognitive evaluation and assessment of occupational functioning. Study participants were evaluated every three months thereafter for up to nine months. Factor analysis was applied to reduce the initial set of neurocognitive variables to five domains: episodic memory, working memory/attention, executive function, visual scanning, and speed of processing. Multiple logistic regression models were used to examine the joint predictive values of these domains for determining occupational recovery.

Results—At the time of symptomatic recovery, four of five neurocognitive factors were significant predictors of concomitant occupational recovery and the fifth, executive function, showed a trend in the same direction. For those not occupationally recovered at baseline, longitudinal analyses revealed that changes between baseline and the three-month follow-up timepoint in most cognitive domains were robust and highly significant predictors of occupational recovery at three months.

Conclusions—These findings indicate that better neurocognitive function in multiple domains and improvement in these domains over time are strongly predictive of subsequent occupational

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recovery. Treatments that target cognitive deficit may therefore have potential for improving long-term vocational functioning in bipolar illness.

Keywords

attention; episodic memory; euthymic; executive function; functional outcome; processing speed; recovery; subsyndromal depression; vocational; working memory

Bipolar disorder is a chronic illness with substantial psychosocial and occupational morbidity. Several studies have shown that, after a manic episode, the majority of patients with bipolar disorder continue to exhibit significant impairment in role functioning, despite symptomatic recovery (1–6). A recent review of outcome studies concluded that 57–65% of patients with bipolar disorder were unemployed (as compared to 6% of the general population), and up to 80% were considered to have at least partial vocational disability following syndromal recovery from a first-lifetime manic or mixed episode (7). It is generally believed that the depressive pole of bipolar disorder is more consistently and strongly associated with functional disability (8, 9) than is the hypomanic/manic pole (10, 11). However, one of the few large-scale outcome studies of first-episode mania found that while the majority of patients (72%) had achieved symptomatic recovery within two years of their initial hospitalization, less than half (43%) had achieved functional recovery, defined as regaining one's premorbid occupational and residential status (6). Despite its prevalence and cost in both personal and societal terms, the reasons for persistent work disability in patients with bipolar disorder remain unclear.

Factors other than mood symptoms may contribute to poor occupational functioning (12, 13). In particular, there is increasing evidence that impairment in specific cognitive domains, i.e., executive function, verbal memory, attention, and processing speed, persists in some patients with bipolar disorder even during periods of euthymia [(14); (see 15, 16 for meta-analyses)]. Impairments in executive functioning, verbal memory, and speed of processing have been consistently associated with poorer functional outcome in schizophrenia (17–19). There is also mounting evidence that cognitive impairment in these domains may contribute to functional disability in bipolar disorder patients (20–24). A recent review of the literature concluded that in the majority of studies (six out of eight) of euthymic patients with bipolar disorder, poorer cognitive function was associated with worse functional outcome, even after controlling for residual mood symptoms, age, and other clinical variables (25). However, most of these studies used very general measures of functional outcome, such as the Global Assessment of Functioning (GAF) (26), which does not separate clinical symptom severity from functional status in the rating of level of overall functioning. Additionally, the relationship between neurocognitive impairment and the ability to resume normal occupational functioning after an acute manic episode resolves has rarely been studied (27). To our knowledge, only one prior study has examined changes in neurocognitive function over time as a predictor of outcome in bipolar disorder patients (28). In this study, positive changes in composite neurocognitive performance over one year emerged as a significant predictor of improved functioning (as assessed by the GAF) over the follow-up period.

The purpose of this study was to assess the cross-sectional and prospective longitudinal association between neurocognition and occupational function in subjects with bipolar disorder who had recently achieved symptomatic recovery following a manic episode. Using the Life Functioning Questionnaire (LFQ) (29), a gender-neutral measure of occupational function that assesses both quality and quantity of work impairment, we sought to answer the following questions: (i) Does neurocognitive function at the time of symptomatic recovery from a manic episode differentiate patients who achieve occupational recovery

from those who do not? (ii) In those who do not achieve occupational recovery concurrently with symptomatic recovery, does neurocognitive function at the time of symptomatic recovery predict short-term occupational recovery? (iii) Is change in cognitive function, either globally or in specific domains, associated with short-term occupational recovery? Given prior findings, in both patients with schizophrenia and bipolar disorder, which indicate deficits in executive functions, verbal memory, and speed of processing are associated with poor functional outcome, we hypothesized that better baseline neurocognitive function in these domains would be associated with concurrent occupational recovery, and that cognitive *improvement* in these domains over time would be associated with occupational recovery over the follow-up period.

Methods

Participants and measures

Subjects were recruited through outpatient facilities at the University of California, Los Angeles (UCLA), the West Los Angeles Veteran Affairs Medical Center (VA), and through media advertisements. The study included the assessment of subsyndromal depressive symptoms, neurocognitive function, and stressful life events, and was approved by the VA Greater Los Angeles and UCLA Institutional Review Boards. All patients signed informed consent documents after the study procedures were fully explained. Inclusion criteria for study participants were: an age of 18–65 years, a diagnosis of bipolar I disorder by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders (SCID) (30), having had a manic episode within the past six months, and a history of having worked in the year prior to their recent manic episode. Clinicians were trained to high standards of reliability (i.e., Kappa scores of > 0.90 with a ‘gold standard’ set of ratings on three separate SCID interviews). Patients were excluded from the study if they had a significant alcohol or substance use disorder (abuse/dependence) within the past three months, rapid cycling within the year prior to the manic episode, or an organic mood disorder (e.g., head trauma or cerebrovascular accident preceding their first manic episode).

A total of 207 patients with bipolar I disorder were enrolled in the study during or shortly after a manic episode. Following the manic episode, patients were followed monthly for up to six months during Phase I of the study. The SCID, Young Mania Rating Scale (YMRS) (31) and the 28-item version of the Hamilton Depression Rating Scale (HAMD-28) (32) were administered at each monthly visit to determine whether patients experienced symptomatic recovery (euthymia), defined as not meeting criteria for a SCID diagnosis of mania, hypomania, or a major depressive episode, and additionally having a YMRS score ≤ 7 for at least six weeks. Participants who did not attain symptomatic recovery after six months of longitudinal follow-up were excluded from further follow-up. Participants were also excluded if they met criteria for a depressive episode, defined by the SCID mood disorders module, or if they developed a substance use disorder at any point during the follow-up. Patients who achieved symptomatic recovery were eligible for Phase II of the study, in which mood symptoms continued to be assessed monthly using the YMRS, HAMD-28, and SCID mood modules. Additionally, role function and neurocognitive function were assessed at each timepoint, as described below and in Figure 1.

Of the 207 participants who enrolled, 67 participated in Phase I for one month or less (40 did not meet inclusion criteria, 18 dropped out soon after consenting to participate, 7 were noncompliant with the study protocol or with medication within the first month, 1 relapsed into depression, and 1 relapsed into alcohol use disorder). Of the 140 remaining subjects, only 79 (56%) achieved symptomatic recovery within the first six months (Phase I) following the acute manic episode and completed a baseline neuropsychological assessment.

These 79 individuals participated in Phase II of the study, and are included in the current analyses.

Phase II of the study involved a baseline evaluation and, for some subjects, a longitudinal follow-up evaluation. The Phase II baseline visit involved neurocognitive testing and assessment of both symptomatic status and current occupational function, as defined below. As occupational recovery was the primary target of interest, once patients attained this criterion they were no longer followed. However, if patients were not occupationally recovered at the baseline visit, they had monthly visits until they met occupational recovery criteria for two consecutive months or for a maximum of nine months if they did not achieve occupational recovery. Neurocognitive assessments were performed every three months.

Outcome measures

The primary functional outcome measure used was the LFQ (29), a five-minute gender-neutral self-report measure of role function in four domains: workplace, duties at home, leisure time with family, and leisure time with friends. In prior studies, the LFQ has demonstrated both excellent test-retest reliability and high internal consistency, and has been validated against the Social Adjustment Scale-Self Report (33), a lengthier measure of community adjustment commonly used in depression treatment. Using a 4-point scale, a patient can indicate whether they feel they have no problems (a score of 1), mild problems (a score of 2), moderate problems (a score of 3), or severe problems (a score of 4) in a certain domain. Four items were rated in each of four domains listed above. As the present analysis focused on occupational recovery, we used the four LFQ workplace questions to assess both quantity and quality of job functioning. These four items assess occupational functioning including amount of time worked (quantity worked), job performance (quality of work), conflict with coworkers, and enjoyment (interest and satisfaction at work). For participants who were not working at the time of symptomatic recovery, a rating of four was assigned to each of the work questions. If participants were working again but not at their premorbid level (e.g., part time instead of full time) this was captured in the *amount of time worked* item. Participants with a mean rating of ≤ 1.5 on the above questions were considered occupationally recovered.

Data preprocessing: derivation of neurocognitive domains and handling of missing data

The neurocognitive battery, intended to assess a range of cognitive domains, included the following tests: California Verbal Learning Test (CVLT) (34), Weschler Memory Subscales (Logical Memory and Visual Reproduction) (35), Wisconsin Card Sorting Test (WCST) (36), Letter-Number Sequencing (LNS) (37), Trail Making Test (Trails A and B) (38); and two computerized measures, the Degraded Stimulus Continuous Performance Test (DSCPT) (39) and Span of Apprehension (39). The following key summary variables from each measure were selected for our analyses: total recall, trials 1–5 and recognition hits (CVLT); total score for immediate and delayed memory (Logical Memory) and total score for immediate and delayed memory (Visual Reproduction); category completion and perseverative errors (WCST); LNS forward and reorder; Trails A score in seconds and Trails B residual score (Trails B adjusted for Trails A time); sensitivity = d' (DSCPT); and number correct for small (3-letter) and large (12-letter) arrays (Span of Apprehension).

Due to the modest sample sizes, particularly at the end of the three-month follow-up period, we used multiple imputation (36) to fill in missing values rather than dropping individual subjects or variables. Next, we used dimension reduction techniques, specifically principal factor analysis, to identify a more parsimonious set of composite scores, which captures most of the predictive information contained in the original battery. Variables were assigned to the factor on which they loaded most strongly, and domain scores were calculated by

standardizing (mean-centering and scaling) and then averaging the individual component measures. Our factor analysis identified five neurocognitive domains which explained over 70% of the observed variability in neurocognitive performance: episodic memory (CVLT total recall, CVLT recognition hits, Logical Memory, and Visual Reproduction); working memory/attention (LNS forward, LNS reorder, and DSCPT vigilance); executive function (WCST category completion and perseverative errors); visual scanning (easy span and hard span); and speed of processing (Trails A score). Table 1 shows the percentage of variability explained by each of these domains. The Trails B residual score did not associate with any of the factors and was eliminated from further analyses.

Statistical analysis

The primary goal of this study was to assess the relationship between neurocognition and occupational recovery, both cross-sectionally and longitudinally. In order to identify potential confounders, we first examined the associations between baseline recovery and individual demographic and course of illness measures using two-sample *t*-tests or χ^2 tests. The primary analyses used multiple logistic regression to determine the joint contributions of the neurocognitive domain scores to the prediction of functional recovery, adjusting for key demographic and clinical covariates as identified in the preliminary analyses. Because age and subsyndromal symptoms of depression have been shown in numerous previous studies (9, 13, 24, 40) to affect both cognition and occupational function, they were included in all of the logistic models regardless of whether they showed baseline group differences in our sample. In accordance with our three primary research questions, Model 1 evaluated the relationship between neurocognitive performance and occupational recovery at baseline; Model 2 analyzed baseline neurocognitive scores as predictors of occupational recovery at three months; and Model 3 used change scores in neurocognitive domains from Time 1 to Time 2 as predictor variables to assess whether improvement in neurocognitive function between baseline and three months was associated with three-month occupational recovery. In addition to the significance of the individual variables, overall performance of the models was examined using the area under the receiver operating characteristic curve (AUC) which is a plot of the false positive rate versus the false negative rate for a binary predictive model. The AUC summarizes the ability of a logistic model to discriminate between the outcome groups. Values above 0.8 are generally considered good and values over 0.9 are considered outstanding. All analyses were two-tailed with alpha set at $p < 0.05$.

Results

Descriptive statistics and summary of functional recovery status

Of the 79 symptomatically recovered bipolar disorder patients who participated in the Phase II baseline assessment, 45 (57%) met criteria for occupational recovery at that timepoint based on the LFQ (see Table 2). There were no significant differences in age, gender, education, or prior course of illness variables between patients who were recovered at baseline ($n = 45$) versus those who were not. However, there was a trend toward higher depression severity ($p = 0.06$) in the unrecovered group, and thus subsequent analyses adjusted for depression severity, as assessed by the HAMD-28. The groups did not differ in terms of current medication status ($n = 34$; $p > 0.15$ for all comparisons).

Joint models of occupational recovery

Next we used logistic regression to determine whether the five neurocognitive domains were collectively associated with functional recovery, and if so, whether each one contributed unique explanatory power to the joint model. Table 3 shows the *p*-values and odds ratios for each of the neurocognitive domains and covariates for the three multiple logistic regression models. In Model 1, after adjusting for age and baseline depression severity, baseline

episodic memory, visual scanning, working memory/attention, and speed of processing were all significant predictors of baseline functional recovery and executive function was trending. Age and depression were also highly significant predictors in this model, which did moderately well at predicting recovery with an AUC of 0.815. The most robust cognitive predictors of baseline functional recovery were working memory/attention and speed of processing; after adjusting for other neurocognitive domains and covariates, a one unit increase in these respective domains was associated with 2.49 times and 2.62 times greater odds of achieving functional recovery than nonrecovery ($p < 0.0001$ and $p = 0.0002$, respectively). These results indicate that working memory/attention and speed of processing make unique individual contributions to a patient's chances of occupational recovery, after accounting for the remaining cognitive domains.

Model 2 explored the relationship between baseline neurocognitive, demographic and clinical measures, and three-month occupational recovery in the group that was not functionally recovered at baseline. Of the 34 patients who had not achieved occupational recovery at the time of symptomatic recovery, 9 (26%) were lost to follow-up after their baseline assessment, and 25 (74%) participated in a three-month visit. Of these 25, 8 (32%) were occupationally recovered at this follow-up visit. There was no evidence of a significant difference between the unrecovered patients who were lost to follow-up and those who continued in the study in terms of age, depression severity, and baseline neurocognitive scores (all p -values > 0.25).

After adjusting for age and depression severity, none of the neurocognitive domains were significant predictors of three-month outcome, although episodic memory showed a trend ($p = 0.08$). Baseline age was a significant predictor ($p = 0.01$) of occupational function at three months, but baseline depression severity was not. This model overall had relatively poor AUC of 0.718.

Model 3 assessed the relationship of three-month functional recovery with changes in neurocognitive function and depression over three months. Cognitive changes in all domains except speed of processing were highly significant predictors of occupational recovery, and speed of processing showed a trend, $p = 0.06$. Age at baseline was also significant in the model ($p = 0.03$), but change in depression severity over the follow-up period was not. The gains associated with episodic memory, attention/working memory, and executive function were all particularly striking (see Table 3). This model also had the best fit, with a robust AUC of 0.938. Notably, for all neurocognitive domains, the occupationally recovered patients improved and the unrecovered did not. Although within-group changes did not reach significance due to the small sample sizes, the within-group effect sizes for the three most significant domains from the joint model (episodic memory, attention/working memory, and executive function) were in the medium range. Moreover, the individual effect sizes for differences in change score between recovered versus unrecovered patients were medium to large for these same three domains: 1.05 for attention/working memory, 0.80 for episodic memory, and 0.49 for executive function (see Table 4).

Assessment of model stability

We performed two additional analyses to confirm our results. First, because of the small sample size at three-month follow-up and the moderate number of predictors, we assessed the stability of the third logistic regression model using a bootstrap re-sampling procedure (41). This technique is used to empirically estimate the uncertainty in a parameter of interest when standard distributional assumptions do not apply or calculation of the theoretical distribution is intractable. Here we obtained bootstrap distributions for the p -values of the neurocognitive domain change-scores to determine how confident we were of these variables' significance in the joint model. Our results proved to be highly stable, with

episodic memory, working memory/attention, and visual scanning all significant in over 98% of the bootstrap models. Executive function remained significant in 81% of the models. However, speed of processing and age were significant in only 55–60% of models, suggesting a lower degree of certainty about these variables.

The second set of confirmatory analyses concerned the imputation for missing data. While most variables had only a few missing values, due to a technological failure, the WCST measures that comprise the executive functioning domain were lost for a moderate number (35%) of subjects. Since the reason for the missing values was completely unrelated to the study targets, and there were strong relationships among the study measures, multiple imputation procedure should be both unbiased and accurate in its estimates of the missing values. In confirmation of this, we note that (i) subjects who were and were not missing the WCST did not differ beyond what would be expected by chance; (ii) running the factor analysis without the WCST produced the same neurocognitive domains and the same domains were significant when the logistic models were refit without the executive functioning score; and (iii) fitting the models without subjects who were missing the WCST produced the same patterns of estimates as in the original results although overall significance was reduced with the smaller sample size. Collectively these analyses make it clear that the findings for neurocognitive domains other than executive functioning were unaffected by the imputation and results for the WCST were stable and unlikely to be biased.

Discussion

Our results demonstrate that cognitive measures at the time of symptomatic recovery, particularly in the domains of working memory/attention and speed of processing, are strongly associated with concurrent occupational recovery, even after accounting for the effects of age and depression severity. There was also a trend toward better episodic memory at baseline predicting three-month functional recovery. Most notably, cognitive *improvements* across multiple domains over this same time period were also highly predictive of functional recovery three months later.

Few studies have been performed to date examining either cross-sectional or longitudinal neuropsychological predictors of occupational outcome in bipolar disorder. In the current study, even after controlling for subsyndromal symptoms, neurocognitive impairments in the domains of episodic memory, visual scanning, working memory/attention, and speed of processing were independently associated with concurrent occupational impairment. Similarly, in a cross-sectional study Wingo et al. (13) found that among euthymic or mildly depressed bipolar disorder patients, fewer years of education, not being married, and greater duration of illness were independently associated with poorer functional recovery (defined as regaining individual premorbid residential and vocational status), even after controlling for residual depressive symptoms, diagnostic subtype, and psychiatric comorbidity. Additionally, Wingo and colleagues observed a trend for functionally unrecovered bipolar disorder patients to have poorer verbal fluency performance than recovered patients. Other cross-sectional studies have also observed a relationship between verbal memory deficits and poor psychosocial functioning in euthymic bipolar disorder patients (20, 42).

While we found that baseline cognitive impairment across multiple domains was significantly associated with concurrent functional (occupational) impairment, we did not find evidence of a significant relationship between baseline cognitive performance and subsequent functional recovery. In contrast, Jaeger et al. (27) found that baseline neurocognitive functioning in the attentional and speed of processing domains (specifically, Trail Making A and Stroop word reading and color naming tests) predicted functional

outcome, as assessed by the Multidimensional Scale of Independent Functioning (43), over a longer (12-month) follow-up period. Similarly, Martino et al. (12) in a study of 35 subjects found that both baseline cognitive impairment (in the domains of attention, executive function, and verbal memory) and length of time spent with subsyndromal depressive symptomatology were independently associated with poorer long-term functional outcome over a 12-month period. There were some key methodological differences that could account for these discrepant findings: (i) our follow-up analysis included *only* those study participants who had not occupationally recovered at baseline; (ii) unlike our study, the prior investigations did not specifically enroll patients who had previously been employed.

We could only identify one other study in the literature that conducted repeated cognitive assessments in bipolar disorder patients, in order to examine change in cognitive functioning over time in relationship to functional outcome (28). In this study, global neurocognitive function at baseline—or improvement in this score over one year—predicted changes in functioning as assessed by the GAF. While we did not find a significant relationship between baseline cognitive performance and subsequent functional recovery, our finding of robust associations between cognitive improvement over time and functional recovery is consistent with these findings.

A strength of our study is that we employed data reduction methods (factor analysis) in order to allow greater specification of the cognitive domains most associated with occupational recovery. We did not find that a single cognitive domain was clearly superior to the others in its predictive power; rather, multiple domains, i.e., episodic memory, visual scanning, attention/working memory, executive function, and speed of processing, all uniquely contributed to cross-sectional and longitudinal prediction of functional recovery. Improvements over time, particularly in the domains of episodic memory, attention/working memory, and executive function, were extremely robust predictors of occupational recovery over this time period. Although it is possible that our analyses were underpowered to detect baseline predictors of subsequent recovery, the highly significant relationships detected between neurocognitive improvement and occupational recovery suggest that even if baseline scores were predictive, the relationship is much weaker than the relationship between neurocognitive change over time and recovery.

These findings have potentially important clinical implications. Despite achieving symptomatic recovery from mania, a substantial proportion of patients nevertheless continue to experience functional impairment. Given that cognitive deficits across multiple domains emerged as independent predictors of occupational outcome, cognitive rehabilitation is a rational treatment target in bipolar disorder. Cognitive remediation has been associated with significant, though modest, improvements in cognitive performance and psychosocial functioning in schizophrenia patients (44). However, surprisingly few studies on the prevention or remediation of cognitive impairments in bipolar disorder have been conducted to date (45). The development of treatments that target cognitive impairment may have an impact on the ultimate functional status of patients with bipolar disorder. Recently, two small studies have reported that rehabilitative interventions, such as cognitive remediation and supported employment, may improve vocational outcomes for bipolar disorder patients (46, 47). This will require replication in larger investigations, but is an important area of future investigation in bipolar disorder.

Several studies have found that subsyndromal depressive symptoms are associated with both cognitive impairment and functional disability (40, 48). For this reason, we controlled for depressive symptoms in our analyses and still found multiple domains of neurocognitive function uniquely contributing to occupational impairment. This suggests that neurocognitive impairment impacts one's ability to return to work, independent of the

effects of residual depressive symptoms. These results are consistent with the findings of at least two other studies, which assessed clinical (subsyndromal depressive) symptoms and neurocognitive symptoms and their impact on functional outcome (12, 49).

Slightly over half (57%) of the bipolar disorder patients in our sample were functionally recovered at the time of symptomatic recovery, but a substantial minority of patients (43%) were not. These findings comport with prior literature indicating that for a large percentage of bipolar disorder patients, functionally recovery lags behind symptomatic recovery. However, by the six-month follow-up timepoint after symptomatic recovery was obtained, a high rate of subjects in our sample had achieved occupational recovery (71%). This rate is higher than others reported in the literature, which have found that less than half of bipolar disorder patients are employed by six months following hospitalization (5, 50). These findings could be due to careful physician follow-up to ensure medication adherence and, again, the fact that the patients followed all had a history of employment prior to the manic episode. Thus, it may be that the poor *outcome* reported as percentages of employed persons for many bipolar disorder patients in the literature is a reflection of over-enrollment in the beginning of the study of persons who were not working to begin with. We also excluded patients with alcohol or substance use abuse/dependence within the past three months; given that comorbid substance use clearly contributes to occupational disability, as well as neurocognitive impairment in patients with bipolar disorder (e.g., 51, 52), the exclusion of patients with this acute co-morbidity may also contribute to the relatively high rates of occupational recovery we observed. Similarly, recurrent depressive episodes, including subsyndromal depression, are associated with occupational impairment (12, 40, 53), and we maintained strict criteria for euthymia over the follow-up period. Most follow-up studies do not include this information, but results previously reported on unemployment rates in subjects with bipolar disorder after recovery from a manic episode or hospitalization may be a misrepresentation of the percentage of persons in the bipolar disorder community who have a poor outcome following a manic episode by not accounting for such factors.

Several limitations of this study should be noted. In particular, 26% of our sample was lost to follow-up following the initial assessment. Retaining patients with bipolar disorder in longitudinal protocols is challenging; nevertheless, we were able to follow 75% of the subjects who had attained symptomatic but not occupational recovery. In addition, our high rate of occupational recovery over the follow-up period led to an unexpectedly small number of subjects remaining in the protocol after the three-month visit. However, despite the relatively small ratio of subjects to variables, we were able to demonstrate, using a bootstrap resampling technique, that the results of our longitudinal analyses were very stable, particularly for the three strongest predictor variables (i.e., working memory/attention, episodic memory, and executive function). Another limitation is that our measure of occupational function, although completed at multiple timepoints, did not specifically assess for occupational stability (i.e., how long one remained in the same job). Although not assessed systematically, none of the patients in our sample changed jobs frequently throughout the study. Most subjects, when returning to employment, returned to work with their previous employers and maintained that job throughout the follow-up. Nevertheless, occupational stability is an important aspect of functioning that has not yet been well-addressed in the literature and warrants further investigation. In addition, other aspects of illness history, in particular, a history of psychotic symptoms, were not investigated here. The presence of psychotic symptoms during mood episodes may be associated with poorer neurocognitive function (54) and possibly worse occupational outcome. This issue requires further study in longitudinal investigations. Finally, most patients in our study were taking psychotropic medications; given that medication status did not differ between patients who were occupationally recovered and unrecovered at baseline, we do not believe that medication presents a significant confound.

Conclusions

Collectively, these findings suggest that neurocognitive performance at the time of symptomatic recovery from a manic episode and neurocognitive improvement over time may be important predictors of occupational recovery in patients with bipolar illness. Persistent neurocognitive dysfunction may play a significant role in the substantial societal and financial costs associated with this chronic mental illness (27). While caution is warranted in interpreting these findings to indicate that cognitive improvement may be *causally* related to occupational outcome (e.g., whether neurocognitive performance drives occupational function or vice versa cannot be clearly delineated in our analytic model), it is tempting to speculate that treatments which target improvement in these cognitive domains may facilitate long-term work functioning in bipolar illness. Psychosocial treatments such as interpersonal, cognitive-behavioral, and psychoeducational therapies all show promise for improving symptomatic and functional outcomes in bipolar disorder patients (7). Neurocognitive remediation might also improve vocational functioning in bipolar disorder. Further research in this area is critical to pinpoint the causes of long-term functional disability in patients with bipolar disorder and better target treatments capable of enhancing functional outcome.

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Fig. 1.
Flow chart of Phase I and Phase II study procedures.

Table 1

Composition of the neurocognitive factors and the percentage of variability in overall neurocognitive performance explained by each factor

Factor	Component variables	Percent variability explained
Episodic memory	CVLT total recall CVLT recognition hits Logical Memory Visual Reproduction	33.2
Visual scanning	Easy span Hard span	13.8
Working memory/attention	DSCPT vigilance LNS forward LNS reorder	9.8
Executive function	WCST category completion WCST perseverative errors	8.0
Speed of processing	Trail Making Test A	7.8

Cognitive domain scores created using principal factor analysis (with varimax rotation and Heywood adjustments using SAS PROC Factor, SAS Institute Inc., Cary, NC, USA). CVLT = California Verbal Learning Test; DSCPT = Degraded Stimulus Continuous Performance Test; LNS = Letter-Number Sequencing; WCST = Wisconsin Card Sorting Test.

Table 2

Demographics

Variable	Recovered (n = 45)	Unrecovered (n = 34)	p-value (<i>t</i> -test or χ^2 test)
Age, mean (SD)	35.02 (11.53)	38.18 (11.83)	0.24
Education, mean (SD)	15.46 (2.48)	15.10 (1.75)	0.47
Age of onset, mean (SD)	29.00 (12.30)	31.06 (12.18)	0.46
No. of prior manic episodes, mean (SD) ^a	6.39 (16.62)	11.96 (26.35)	0.25
No. of prior depressive episodes, mean (SD)	4.74 (6.97)	7.57 (11.21)	0.17
YMRS score, mean (SD)	4.88 (5.53)	3.66 (4.22)	0.29
HAMD-28 score, mean (SD)	8.76 (5.78)	11.71 (7.95)	0.06
Ethnicity (%)			0.54
Caucasian	49	56	
African American	13	6	
Asian	9	18	
Latino	11	6	
Other	18	15	
Gender, female (%)	47	47	0.97
Marital status (%)			0.86
Single	56	49	
Married	20	21	
Widowed/divorced	24	30	
In therapy: yes (%)	64	67	0.77
Medication usage:			
Valproic acid	59	60	1.00
Lithium	27	17	0.40
Olanzapine	15	13	1.00
Risperidone	5	17	0.13
Lorazepam	0	7	0.18
Carbamazepine	0	3	0.42
Other	32	17	0.18

YMRS = Young Mania Rating Scale; HAMD-28 = 28 item Hamilton Depression Rating Scale.

^aTwo patients had > 100 manic episodes or too many to count and were thus not included.

Table 3

Multiple logistic regression models

Domain	Baseline predictors of baseline functional recovery (n = 79)		Baseline predictors of three-month functional recovery (n = 25)		Change predicting three-month functional recovery (n = 25)	
	OR	p-value	OR	p-value	OR	p-value
	AUC = 0.816		AUC = 0.718		AUC = 0.938	
Episodic memory	1.55	0.0184 ^b	1.89	0.0811	> 10.00	< 0.0001 ^c
Visual scanning	2.21	0.0061 ^c	1.14	0.6616	5.25	0.0003 ^c
Working memory/attention	2.49	< 0.0001 ^c	1.62	0.1965	> 10.00	< 0.0001 ^c
Executive function	1.59	0.0864	1.82	0.1671	> 10.00	0.0063 ^c
Speed of processing	2.62	0.0002 ^c	1.50	0.1071	3.78	0.0615
HAMD-28	0.95	< 0.0001 ^c	0.98	0.5549	0.93	0.9612
Age ^a	0.33	< 0.0001 ^c	0.61	0.0134	0.99	0.0256 ^b

AUC = area under the receiver operating characteristic curve; HAMD-28 = 28-item Hamilton Depression Rating Scale.

^aNote that age is baseline value rather than a change score, as change in age would be constant over this period for all subjects.

^bp < 0.05.

^cp < 0.01.

Changes in neurocognitive factors from baseline to three-month visit, categorized by three-month recovery status (n = 25)

Table 4

Variable	Recovered (n = 8) Mean (SD)	Unrecovered (n = 17) Mean (SD)	Effect size for group difference in change score (Cohen's <i>d</i>)
Episodic memory	0.24 (0.59), <i>d</i> = 0.41	-0.11 (0.35), <i>d</i> = 0.31	0.80 ^a
Visual scanning	0.03 (0.95), <i>d</i> = 0.03	-0.02 (0.93), <i>d</i> = 0.02	0.05
Attention/working memory	0.39 (0.61), <i>d</i> = 0.64	-0.17 (0.50), <i>d</i> = 0.34	1.05 ^b
Executive function	0.18 (0.60), <i>d</i> = 0.30	-0.09 (0.53), <i>d</i> = 0.17	0.49
Speed of processing	0.14 (0.69), <i>d</i> = 0.20	-0.06 (1.15), <i>d</i> = 0.05	0.19

d represents effect size for change in neurocognitive performance over time (within-group).

^a *p* < 0.10.
^b *p* < 0.05.