Cognitive Rehabilitation for Bipolar Disorder: An Open Trial for Employed Patients with Residual Depressive Symptoms

Thilo Deckersbach,[1,3] Andrew A. Nierenberg,[1,3] Ronald Kessler,[3] Hannah G. Lund,[1,3] Rebecca M. Ametrano,[1,3] Gary Sachs,[1] Scott L. Rauch[1,2,3] & Darin Dougherty[1,3]

1 Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
2 McLean Hospital, Belmont, MA, USA
3 Harvard Medical School, Boston, MA, USA

Bipolar disorder is characterized by recurrent episodes of depression and/or mania along with interepisodic mood symptoms that interfere with psychosocial functioning. Despite periods of symptomatic recovery, individuals with bipolar disorder often continue to experience impairments in psychosocial functioning, particularly occupational functioning. Two determinants of psychosocial functioning of euthymic (neither fully depressed nor manic) individuals with bipolar disorder are residual depressive symptoms and cognitive impairment (i.e., difficulties with executive functioning, attention, and memory). The present study explored whether a new cognitive remediation (CR) treatment designed to treat residual depressive symptoms and, for the first time to the best of our knowledge, address cognitive impairment would be associated with improvement in psychosocial functioning in individuals with bipolar disorder. Following a neuropsychological and clinical assessment 18 individuals with DSM-IV bipolar disorder were treated with 14 individual sessions of CR. Results indicated that at the end of treatment, as well as at the 3-months follow-up, patients showed lower residual depressive symptoms, and increased occupational, as well as overall psychosocial functioning. Pretreatment neuropsychological impairment predicted treatment response. Improvements in executive functioning were associated with improvements in occupational functioning. These findings suggest that treating residual depressive symptoms and cognitive impairment may be an avenue to improving occupational and overall functioning in individuals with bipolar disorder.

Introduction

Bipolar disorder is characterized by recurrent episodes of depression and/or mania and interepisodic mood symptoms that interfere with psychosocial functioning [1]. Traditionally, the course of bipolar disorder has been viewed as episodic with symptomatic and functional recovery in between mood episodes [2]. This view is increasingly challenged by clinical and epidemiological studies that document a chronic and often disabling course of bipolar disorder [3–6]. For example, rates of unemployment and disability among individuals with bipolar disorder are considerably higher than in the normal population [6]. Two-thirds of patients with bipolar disorder experience a moderate to severe impact of the illness on occupational functioning [7]. Following treatment for a mood episode many patients remain functionally impaired during follow-up periods despite syndromal and/or symptomatic recovery [3,8,9]. In terms of work productivity, individuals with bipolar disorder miss an average equivalent of 1 week of work every month due to missed days at work and impaired work performance [4].

Various determinants of functioning in patients with bipolar disorder have been investigated. These include

(among others) depressive symptoms, early onset, more, and longer recent hospitalizations, comorbidity, lower socioeconomic status, and poorer premorbid functioning (for a recent review, see [10,11]). Based on a review of studies investigating functional outcomes in patients with bipolar disorder, Bauer et al. [12] concluded that depressive symptoms appears to be the determinant most consistently related to lower overall psychosocial functioning [12–16]. Another emerging determinant of functioning is cognitive impairment. Traditionally, cognitive impairments in bipolar disorder have been viewed as being associated with depressed (or manic) mood. Over the past decade, however, neuropsychological studies have demonstrated that patients with bipolar disorder have persistent cognitive impairments even during euthymic phases of the illness (i.e., neither depressed nor manic), including difficulties in executive functioning, attention, and memory (for recent reviews, see [17]). Patients with cognitive impairments have lower psychosocial functioning, including occupational functioning as well as higher rates of disability [18–25] suggesting that cognitive impairment is another factor contributing to lower psychosocial functioning in addition to residual depressive symptoms. Cognitive difficulties reported by individuals with bipolar disorder at work include sluggish thoughts, difficulties focusing, getting started on tasks, organizing complex tasks and managing multiple projects, difficulties remembering, and becoming easily overwhelmed [26,27]. Overall, the estimated cost of lost productivity in individuals with bipolar disorder due to occupational impairment in the United States amounts to $14.1 billion per year [4].

A variety of psychosocial interventions have been developed and/or adapted for bipolar disorder as adjunctive treatments to mood stabilizing medications. These include Interpersonal and Social Rhythm Therapy (IPSRT) [28,29], Family Focused Therapy (FFT) [30] and cognitive-behavioral therapy (CBT) [31–33]. In terms of functional outcomes, IPSRT has been shown to improve occupational functioning more than intensive clinical management during acute mood episodes but not to yield additional gains during an IPSRT maintenance phase [34]. CBT for relapse prevention has been shown to reduce the number and duration of mood episodes but not to improve psychosocial functioning substantially in individuals with bipolar disorder [32,33]. In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), psychosocial treatment (CBT, IPSRT or family therapy) improved relationship functioning and life satisfaction in depressed patients with BP but had no effect on occupational functioning above and beyond a collaborative care control condition [35]. From the perspective of adjunctive psychosocial treatments, these findings suggest a need for the development of additional treatments that address critical determinants of functioning in individuals with bipolar disorder.

We recently developed a cognitive remediation (CR) treatment for bipolar disorder that addresses two main determinants of functioning: (a) residual depressive symptoms and (b) impairments in cognitive functioning (i.e., difficulties with organization, planning, attention, and memory) [26,27]. This treatment blends more traditional CBT elements with those used in CR treatments. It extends above and beyond the well-established CBT targets (e.g., activity management, cognitive restructuring of thought biases, etc.) to cognitive dysfunction and provides tools for addressing impairments in executive function, attention, and memory in order to increase psychosocial functioning. In the current study, we investigated the effects of this treatment on residual depressive symptoms, occupational functioning, and overall psychosocial functioning in an open trial. We hypothesized that this treatment will decrease residual depressive symptoms, reduce occupational difficulties, such as increased absenteeism (i.e., missed days at work) and impaired work performance (when at work) and will improve overall psychosocial functioning.

Method

Participants

Study participants were 18 adults who met DSM-IV criteria for bipolar I disorder (n = 15, 9 females) or bipolar II disorder (n = 3, 2 females) who were recruited through the Bipolar Clinic and Research Program at the Massachusetts General Hospital (MGH). All participants provided written informed consent prior to participation in accordance with approved MGH-IRB approved consenting procedures. Diagnoses of participants with bipolar disorder were determined using the Mini-International Neuropsychiatric Interview (MINI-Plus) [36]. Participants with bipolar disorder were included in the trial if they (a) had low residual depressive symptoms (HAM-D 17 $\leq$ 12) [37], (b) had no or low residual manic symptoms (YMRS $\leq$ 8) [38], (c) did not have an episode of a DSM-IV major depression and/or DSM-IV hypomania or mania in the 8 weeks preceding the screening, (d) were on a stable dose of medication, (e) were at least in a part-time position, and (f) also exhibit low work functioning as defined by a Health Performance Questionnaire (HPQ) work performance ("Presenteeism") score of $\leq$70 (see Assessments) [4,39]. A work performance score of $\leq$70 corresponds to the lowest 15% of employees in the HPQ normative employee cohort [39]. Exclusion criteria were

(a) current DSM-IV major depressive, hypomanic, manic or mixed episode, (b) DSM-IV bipolar disorder subtype rapid cycling, (c) DSM-IV subtype bipolar disorder NOS, (d) DSM-IV schizophrenia or schizoaffective disorder, (e) current or past alcohol or drug dependence, (f) alcohol or drug abuse within the past 12 months, (g) current (past 4 weeks) anxiety disorder, organic mental disorder and/or neurologic conditions as well as any medical conditions affecting cognitive functioning, and (h) a verbal IQ below 80 (see Assessments). Following the initial screening visit, patients completed a pretreatment assessment that included measures of depression, mania, occupational functioning, overall psychosocial functioning, and a neuropsychological assessment (see Assessments). Patients then completed 14-individual sessions of CR (see Treatment) followed by a posttreatment assessment at the end of treatment (after session 14) and a 3-month follow-up assessment using the clinical scales and self-report questionnaires administered at the pretreatment assessment.

Treatment

CR consisted of 14 individual 50 min-treatment sessions conducted over 4 months. For the first 3 months, treatment sessions were held weekly (sessions 1–12) followed by bi-weekly sessions for the next month (sessions 13–14). Treatment consisted of three separate modules each of which comprised four CR sessions. The modules focused on [1] mood monitoring and treatment of residual depressive symptoms, [2] organization, planning and time management, and [3] attention and memory and were delivered in this order. The first module introduced patients to daily mood monitoring, including standard techniques, such as activity management (e.g., increasing pleasurable and mastery based activities, and more structured social rhythms), problem solving, increasing awareness of negative automatic thoughts and cognitive restructuring thereof. In addition, in this module we also implemented emergency control techniques to prevent job loss if a patient was at risk of loosing his/her current job. The techniques used in the second and third module were in part adapted from Safren et al. [40] and Sohlberg and Mateer [41]. Specifically, in the Organization, Planning and Time Management module, patients used schedule and notebooks, kept daily task lists, and were trained in prioritizing activities, breaking down complex tasks into simpler tasks, and making more realistic time estimations for activities/projects. In addition, patients were trained to become more aware of thoughts interfering with functioning at work (i.e., thoughts reflecting difficulties starting tasks, staying on tasks, completing tasks, etc.) and learned to coach themselves more adaptively in the presence of these thoughts. Finally, in the Attention and Memory module, patients learned techniques to structure tasks around their concentration abilities, deal with both neutral as well as affectively valenced distractions, and were trained in the use of external and internal reminder cues as well as the use of encoding strategies to improve memory. Treatment techniques learned in earlier sessions were carried forward and rehearsed in subsequent sessions. The last two sessions focused on the continued use and maintenance of acquired skills and on relapse prevention.

Assessments

HAM-D/YMRS

The severity of depressive symptoms was assessed with the Hamilton Depression Scale (HAM-D, 17 item version) [37]. The severity of residual manic symptoms was assessed with the Young Mania Rating Scale (YMRS) [38].

Health Performance Questionnaire

The primary outcome measure of the study was the World Health Organization (WHO) HPQ as a measure of occupational functioning [4,39]. The HPQ assesses "Absenteeism" (missed days of work) and "Presenteeism" (lost productivity due to low performance while at work) for the 28 days preceding the interview. Absenteeism and Presenteeism are integrated into a summary score of total lost work performance for the 28 days before the interview. Absenteeism is defined both as the absolute number as well as the percentage of workdays the respondent missed in the past 28 days (0–100 scale) due to problems with his/her mental health. Presenteeism is defined on a separate 0–100 scale in which 0 means doing no work at all on days spent at work and 100 means performing at the level of a top worker. This is transformed into lost workday equivalents. For example, if a worker was at work 18 out of 20 workdays in the past 28 days and achieves a 70 on the 0–100 Presenteeism scale, this yields 5.4 lost workday equivalents ($18 \times 0.7 = 12.6$; $18-12.6 = 5.4$). Higher Presenteeism (i.e., more lost workday equivalents) reflects lower performance at work. Absenteeism and Presenteeism are combined into a single measure of total lost work performance using the following formula: percent absenteeism + ([100 − percent absenteeism] × [100 − percent presenteeism])/100 [4]. This combined measure reflects the percent of work days missed due to Absenteeism plus the percent of work "missed" when at work compared to a top worker (Presenteeism). This is transformed into total lost workday equivalents. For

example, if the total lost work performance is 37% in the past 20 workdays, this translates into 7.4 total lost work-day equivalents (20 workdays × 0.37 = 7.4). The dependent variables for the HPQ were: Absenteeism absolute number of workdays missed, Presenteeism lost workday equivalents and Total lost workday equivalents.

Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool

The Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) [42] was used as a broader measure of overall psychosocial functioning. It includes four domains: work (employment, household, and student), relationships, recreation, and global satisfaction. The scores in each domain are summed to a total score ranging between 0 and 20. To assess overall psychosocial functioning independent from occupational functioning, the employment item was excluded from the work domain and overall score (i.e. work domain score reflected household and student activities).

Frontal Systems Behavior Rating Scale

Executive Functioning (i.e., planning and problem-solving) in daily life was assessed using the Frontal Systems Behavior Rating Scale (FrSBe) [43]. The FrSBe is a 46-item behavior rating scale that assesses behavioral changes commonly associated with frontal lobe pathology. It includes three subscales: Apathy, Disinhibition, and Executive Dysfunction. Raw scores are converted to T-scores based on age and gender and education corrected norms [43].

Neuropsychological functioning was assessed using the Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) [44] as well as selected subtests of the Delis–Kaplan Executive Functioning System (D-KEFS) [45] and he Wechsler Test of Adult Reading (WTAR) [46]. The RBANS includes subtests (subscales) for immediate memory, delayed memory, attention, language, and visuospatial functioning, (for a detailed description of subtests and scoring procedures see Randolph et al. [44]). Raw scores are converted to Index Scores (with a mean of 100 and a standard deviation of 16) based on age and gender corrected norms. This yields an RBANS total index score and index scores for each subscale [44]. The D-KEFS subtests, Trail Making and Card Sorting, assess such aspects of executive functioning as cognitive flexibility, concept formation and problem solving [45]. Raw scores of each test are converted into Scale scores based on age corrected norms (for details of administration and scoring see Delis et al. [45]). IQ was estimated using the

WTAR [46]. All assessments were conducted in a blinded fashion.

Statistical Analysis

The impact of CR on residual symptoms (depression, mania), occupational functioning, and general psychosocial functioning as well as behavioral executive functioning, were analyzed using repeated measures analysis of variance (ANOVA) with time (pretreatment, posttreatment and follow-up) as the within subjects factor. A significant effect of time was followed up with simple f-tests. To evaluate the role of bipolar subtype and comorbidity, ANOVAs were repeated using subtype of bipolar disorder (bipolar I disorder = 0, bipolar II disorder = 1) or comorbidity (no = 0; yes = 1) as covariates. We conducted an "Intent-to-Treat" (ITT) analysis of all patients enrolled in the trial with their last visit carried forward as long as they had at least one treatment visit following the pretreatment assessment. We then also performed a "completer" analysis of all patients finishing the trial. Neuropsychological functioning (RBANS and D-KEFS scores) as a predictor of treatment response was analyzed using Pearson correlations.

Results

Study Sample

Seventeen of the 18 enrolled patients met criteria for the ITT analysis (10 females). Fourteen patients completed the study (8 females). One patient dropped out of the study after the screening visit with no further visits. Two patients dropped out of the study after sessions 4 and 6, respectively. One of these patients withdrew from the study after session 6 due to concerns about the time investment associated with the study. The other patient dropped out of the study after session 4 after missing several visits and could not be reached for further appointments. One patient who completed the treatment experienced a manic episode during the follow-up period and could also not be reached for the follow-up. None of the patients who dropped out before the end of the study returned for the follow-up assessment. Two patients received psychological treatment (generic supportive psychotherapy) after the end of study treatment during the follow-up period.

The demographic characteristics of the ITT sample (age, education, IQ) are shown in Table 1. All but three patients were medically healthy by self-report. Two patients reported hypothyrodism that was well-controlled with levothyroxine sodium. One patient suffered from a torn meniscus. All patients were taking mood stabilizing

Table 1 Demographic and neuropsychological characteristics of patients with bipolar disorder (intend-to-treat [ITT] sample)

Demographics	M	SD
Age	36.8	(7.8)
Education	14.5	(2.3)
IQ	105.9	(7.2)
Cognitive measures		
RBANS[a]		
Attention	90.47	(13.71)
Immediate memory	90.12	(14.83)
Delayed memory	91.35	(16.07)
Language	98.23	(14.71)
VisuoConstruction	95.53	(16.03)
RBANS Total	90.65	(14.05)
D-KEFS[b]		
Trail Making		
Visual scanning	9.47	(1.94)
Number sequencing	8.41	(2.32)
Letter sequencing	8.35	(2.34)
Number letter switching	7.12	(3.12)
Motor speed	9.58	(2.46)
Card Sorting		
Card sorting total	8.41	(2.93)
Card sorting recognition	8.94	(2.46)

Age: age in years, education: education in years; IQ: Wechsler Test of Adult Reading (WTAR) IQ estimate; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; D-KEFS: Delis–Kaplan Executive Functioning System; (a) Index Scores (b) scale scores.

medications including lithium (n = 8), valproic acid (n = 4), lamotrigine (n = 9), gabapentin (n = 1), atypical antipsychotics (risperidal, quetiapine, olanzapine, n = 7), and antidepressants (escitalopram, citalopram, sertraline, wellbutrin, n = 8) and remained on a stable dose of mood stabilizing medications throughout the study. Thirteen patients had a history of comorbid DSM-IV disorders in addition to bipolar disorder. These included panic disorder (n = 2), obsessive compulsive disorder (n = 1), posttraumatic stress disorder (n = 2), generalized anxiety disorder (n = 3), alcohol abuse (n = 6), bulimina nervosa (n = 1), and intermittent explosive disorder (n = 1).

At the pretreatment assessment patients exhibited mild to moderate residual depressive symptoms and low residual manic symptoms (see Table 2). Patients were employed as a research biologist, college lecturer, teaching assistant, social workers, journalist, contractors, information technology specialists, legal or office assistants, assistant manager, medical assistants, nurse's aid, retail sales persons, electrician, and research assistant. Seventy-six percent (n = 13) were full-time employed, 24% were part-time employed (n = 4). As shown in Table 2, pretreatment, the HPQ indicated a moderate to severe degree of work impairment as indicated by 9.4 total lost workdays equivalents in the 28 days before the pretreatment assessment. Patients missed on average 2.6 workdays due to mental health reasons (Absenteeism; see Table 2). In terms of impaired work performance when at work (Presenteeism, see Table 2), patients lost the equivalent of 6.8 workdays in the 28 days before the pretreatment

Table 2 Pretreatment, posttreatment and follow-up assessment data of patients with bipolar disorder (intend-to-treat [ITT] sample)

	Pretreatment		Posttreatment		Follow-up		P
	M	SD	M	SD	M	SD	
HAM-D	8.65	3.14	5.41[a]	4.03	6.06[b]	3.77	0.004
YMRS	4.06	2.56	3.47	2.81	3.24	2.39	0.35
HPQ							
-Absenteeism	2.58	3.50	1.94	2.44	2.14	2.85	0.26
-Presenteeism	6.78	2.09	5.10[a]	3.70	5.23[b]	3.32	0.005
-Total lost workday equivalents	9.37	2.79	7.04[a]	4.04	7.38	3.78	0.001
LIFE-RIFT	11.29	3.16	9.76[a]	3.65	9.47[b]	3.22	0.03
FrSBe							
-Executive Dysfunctioning	63.89	10.78	57.06[a]	13.16	57.76[b]	14.46	0.003
-Apathy	58.12	6.49	55.59	9.53	55.18	10.24	0.10
-Disinhibition	53.18	4.20	52.94	4.10	53.35	4.78	0.90

HAM-D: Hamilton Rating Scale for Depression score, 17-item version; YMRS = Young Mania Rating Scale Score; HPQ = Health Performance Questionnaire; Absenteeism = absolute number of work days missed; Presenteeism = Lost workday equivalents (due to low performance at work when at work); Total lost workday equivalents (total number of workdays lost due combined Absenteeism and Presenteeism; for calculations of HPQ scores see Methods; LIFE-RIFT: Range of Impaired Functioning Tool total score; FrSB = Frontal Systems Behavior Rating Scale; Executive Dysfunction = Executive Dysfunction subscale score (T-score); Apathy = Apathy Scale score (T-Score); Disinhibition = Disinhibition Scale score (T = score); P = repeated measures ANOVA P-value; [a]P ≤ 0.05 simple f-test pre- and posttreatment; [b]P ≤ 0.05 simple f-test pre-treatment follow-up; for detailed statistics for the repeated measures ANOVA and follow-up simple f-tests, see text.

assessment in addition to the days missed at work due to mental health reasons.

Pretreatment, the LIFE-RIFT indicated additional mild to moderate impairment in other areas of psychosocial functioning reflecting difficulties in the areas of household activities, relationships, and satisfaction (see Table 2). The FrSBe confirmed difficulties in planning and organizing daily activities as expressed by increased Executive Dysfunction subscale score 1.5 standard deviations above the mean of healthy control subjects [43]. Patients also experienced slightly elevated apathy scores (see Table 2) but no difficulties with disinhibition (see Table 2).

Pretreatment, the neuropsychological assessment indicated cognitive weaknesses in the areas of attention, memory and executive functioning (see Table 1). Specifically, compared to the RBANS norms, pretreatment patients showed below average performance in the areas of attention and memory (both immediate and delayed, see Table 1) but performed close to average in the areas of visuospatial functioning and language. In the D-KEFS Trail Making subtest Number-Letter Sequencing (a measure of cognitive flexibility), patients' performance was one standard deviation below that of the normative comparison sample provided by the D-KEFS whereas they performed average in the Trail Making subtests visual scanning and motor speed. Performance in the D-KEFS Card Sorting Test (i.e., concept formation and problem-solving) was approximately half a standard deviation below that of the normative control sample (see Table 1).

Treatment

Scores of clinician-rated scales and self-rated questionnaires at the end of treatment and follow-up for the ITT sample are shown in Table 2. There were no differences in the scores of pretreatment measures between the 14 completers and patients who dropped out (all $Ps \geq 0.57$).

Residual Depression and Mania Symptoms (HAM-D and YMRS)

For the ITT analysis, the repeated measures ANOVA indicated a significant drop in residual depressive symptoms (HAM-D; $f(2,32) = 6.77$, $P = 0.004$) but no change in residual manic symptoms over time (YMRS; $(f(3,32) = 1.07$, $P = 0.35)$. Follow-up f-tests showed a decrease in HAM-D scores from pretreatment to posttreatment ($f(1,16) = 18.85$, $P = 0.001$) but no change from posttreatment to follow-up ($f(1,16) = 0.40$, $P = 0.53$).

Occupational Functioning (HPQ)

The repeated measures ANOVA for the HPQ score for total lost work performance (ITT analysis) indicated a main effect for time ($f(2,32) = 8.67$; $P = 0.001$). There was a significant decrease in total lost work performance from pretreatment to posttreatment ($f(1,16) = 11.17$, $P = 0.004$) but no difference between posttreatment and follow-up ($f(1,16) = 0.46$, $P = 0.51$). There was a significant decrease in presenteeism from pre- to posttreatment ($f(1,16) = 7.39$, $P = 0.015$) but not for the HPQ absenteeism ($f(1,16) = 1.92$, $P = 0.19$). Changes from posttreatment to follow-up were insignificant for both absenteeism ($f(1,16) = 0.85$, $P = 0.37$; see Table 2) and presenteeism ($f(1,16) = 0.08$, $P = 0.78$; see Table 2).

General Psychosocial Functioning (LIFE-RIFT)

The repeated measures ANOVA indicated a main effect for time ($f(2,32) = 3.78$, $P = 0.03$; ITT analysis). Psychosocial functioning increased from pretreatment to posttreatment ($f(1,16) = 5.38$, $P = 0.03$) and did not significantly change from posttreatment to the 3-month follow-up ($f(1,16) = 0.18$, $P = 0.68$, see Table 2).

Executive Functioning (FrSBe)

For Executive Dysfunction (difficulties with organization and planning; ITT analysis) there was a main effect for time ($f(2,32) = 7.24$, $P = 0.003$). Executive Dysfunction decreased from pretreatment to posttreatment $f(1,16) = 14.89$, $P = 0.001$) but there was no change between posttreatment and follow-up ($f(1,16) = 0.17$, $P = 0.67$). There was no significant change over time for FrSBe Apathy scores ($f(2,32) = 2.43$, $P = 0.10$) and FrSBE disinhibition scores ($f(2,32) = 0.11$, $P = 0.90$).

The aforementioned analyses were repeated excluding the patients who dropped out at session 5 and 6 and the patient who was lost to follow-up (completer analysis, n = 14). All observed significant changes remained significant (all $Ps < 0.05$). For the FrSBe Apathy scale there was a significant decrease over time (main effect time: $f(2,26) = 5.42$, $P = 0.01$). FrSBe Apathy scores dropped from pre- to posttreatment ($f(1,13) = 5.33$, $P = 0.04$) but there was no change between posttreatment and follow-up ($f(1,13) = 0.67$, $P = 0.43$).

Moderators and Mediators of Treatment Response

The above ITT and completer analyses were repeated including the type of bipolar disorder (I or II), lifetime comorbid anxiety disorder ("yes" = 1, "no" = 0), past alcohol abuse ("yes" = 1, "no" = 0) and supportive

psychotherapy during follow-up ("yes" = 1, "no" = 0) separately as covariates. While this did not change the pattern of results (all significant changes remained significant at the $P < 0.05$ level), the increase in presenteeism from pre- to posttreatment was somewhat smaller when a history of comorbid anxiety disorders was included as a covariate ($f(1,15) = 5.43$, $P = 0.03$; ITT analysis). Changes in presenteeism, LIFE-RIFT, and FrSBe Executive Dysfunction and Apathy also remained significant ($P < 0.05$) when baseline HAM-D scores were included as a covariate both in the ITT and completer analysis. There were no significant correlations between any of the neuropsychological measures and the pre-treatment HPQ total lost work performance, presenteeism or absenteeism (range of rs: r = -0.41 to r = 0.32). However there was a trend toward more decrease in presenteeism for patients with higher RBANS total score (r = 0.47, $P = 0.06$). Finally, we investigated whether changes in presenteeism from pre- to posttreatment remained when changes in depressive symptoms (HAM-D) or changes in FrSBe Executive Dysfunction were included as a covariate. Changes in presenteeism from pre- to posttreatment in the ITT analysis remained significant when adjusted for baseline HAM-D ($f(1,15) = 7.93$, $P = 0.01$) or changes in HAM-D scores from pre- to posttreatment ($f(1,15) = 6.74$, $P = 0.02$), but dropped to nonsignificance when changes in FrSBE Executive Dysfunction from pre- to posttreatment were partialled out ($f(1,15) = 2.79$, $P = 0.12$).

Discussion

Despite symptomatic improvements or recovery following mood episodes many individuals with bipolar disorder experience difficulties in daily functioning. The present study explored whether an adjunctive cognitive-behavioral treatment, initiated in the euthymic phase of the disorder can lower residual depressive symptoms and improve occupational functioning through targeting depressive symptoms and cognitive impairments in executive functioning, attention and memory. Patients included in this study missed the equivalent of 9 days of work in the month before starting cognitive remediation treatment, indicating substantial occupational difficulties. The degree of impairment observed for our study participants was similar to that reported for individuals with bipolar disorder in the National Comorbidity Replication Survey (NCS-R) [4], who had one or more depressive episodes in the past 12 month before the NCS-R survey. This suggests that our cohort of patients with bipolar disorder with occupational difficulties is representative for the bipolar disorder population. Consistent with our hy-

pothesis we found decreased residual depressive symptoms, and conversely, increased occupational and overall psychosocial functioning following treatment and at follow-up. Overall, study participants were characterized by cognitive weaknesses in the areas of attention, memory and self-reported executive functioning. Improvements in occupational functioning remained significant when decreases in residual depressive symptoms were partialled out, but were reduced to nonsignificance when changes in self-reported executive functioning (FrSBe) were factored in. This suggests that changes in executive functioning, in part, account for the improvements in occupational functioning observed in the present study. Study participants with more pronounced objective cognitive weaknesses also tended to benefit less from CR, which may suggest that a more severe underlying neurobiological impairment may limit the expected maximum benefit from a cognitive rehabilitation intervention. Changes in functioning are unlikely to reflect the effects of medication because patients were on a stable dose of mood stabilizing medications and assessments were conducted in a blinded fashion.

While bipolar disorder subtype, concomitant supportive psychotherapy, or past alcohol abuse did not affect the pattern of results, treatment effects were somewhat reduced when past anxiety disorders were factored in. This is consistent with the observation in this treatment that patients with bipolar disorder with a history of anxiety disorders at various points during the treatment tended to have more anxious reactions to work situations (e.g., catastrophic thoughts, worries) that at times caused additional interference with functioning. These patients may benefit from including additional CBT components that help patients cope with anxiety symptoms. Following treatment, patients exhibited comparatively more improvements in presenteeism compared to absenteeism. Our treatment was strongly geared toward improving functioning when at work, but in retrospect fell short in sufficiently addressing risk factors for missing work days (e.g., lack of motivation). Our revised treatment, which is currently being tested in a randomized controlled trial (comparing CR with psychoeducative supportive psychotherapy), includes a functional analysis component that assesses and addresses risk factors for missing workdays.

Our treatment falls along the lines of manualized compensatory cognitive training programs as opposed to recovery-oriented approaches, which aim at the restoration of ones compromised neural processes [47]. Compensatory and restorative approaches to cognitive remediation have successfully been implemented for individuals with schizophrenia (for a recent review, see Medalia and Choi [48]). There is converging evidence

that patients with bipolar disorder and schizophrenia have impairments largely in the same cognitive domains (attention, memory executive functioning) although impairments observed in patients with schizophrenia are more severe [49]. Recent advances in the field of cognitive remediation in schizophrenia include techniques to boost intrinsic motivation by the modification of instructional techniques and contextualizing cognitive training exercises [48]. Our CR treatment blends established CBT techniques for depressive symptoms with compensatory cognitive remediation strategies in the second phase of the treatment. Combining CBT with CR techniques has also been shown to be successful in a recent study by Mohlman et al. [50] who combined these two approaches in elderly patients with GAD.

Overall, caution is advised when interpreting results of open trials. In the absence of a randomized control group, it remains uncertain to what extent treatment yielded effects above and beyond those that could have been observed with either no treatment, generic supportive psychotherapy or existing manualized adjunctive psychosocial protocols that have already been tested for bipolar disorder (e.g., IPSRT, family therapy, cognitive behavior therapy for medication adherence, depression or relapse prevention). It is encouraging, though, that the cognitive remediation treatment tested here compares favorably in terms of effects on functioning to already existing CBT treatments for relapse prevention [32,33] as well as to the effects of IPSRT on occupational functioning in the maintenance phase [34].

Acknowledgments

Conflict of Interest

Dr. T. Deckersbach's research has been funded by NIMH, NARSAD, TSA, and OCF. He has received honoraria and/or consultation fees from Medacorp, MGH Psychiatry Academy, and Boston University. He has also participated in research funded Janssen Pharmaceuticals, The Forest Research Institute, Shire Development Inc., Medtronic, Cyberonics, and Northstar.

In the past 3 years, Dr. A. Nierenberg consulted to or served on advisory boards of Abbott Laboratories, Appliance Computing Inc, Brain Cells Inc, Bristol Myers Squibb, EpiQ, Pam Labs, PGx Health, Forest Pharmaceuticals, Eli Lilly & Co, GlaxoSmithKline, Janssen, Pharmaceutica, Jazz Pharmaceuticals, Merck, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, Schering-Plough, Sepracor, Shire, Somerset, Takeda, and Targacept. He has received research support from Cyberonics, Cederroth, Forest Pharmaceuticals, Medtronics, NIMH, NARSAD, the Stanley Foundation through the Broad Institute, Ortho-McNeil-Janssen, Pfizer, Pam Labs, and Shire. Past research support includes Bristol Myers Squibb, Cederroth, Forest Pharmaceuticals, Eli Lilly and Company, Glaxo Smith Kline, Janssen, Lictwer Pharma, Pfizer pharmaceuticals, and Wyeth Ayerst. He received honoraria from the MGH Psychiatry Academy (MGHPA activities are supported through Independent Medical Education (IME) grants from the following pharmaceutical companies in 2008: Astra Zeneca, Eli Lilly, and Janssen Pharmaceuticals). He earns fees for editorial functions for CNS Spectrums through MBL Publishing and Psychiatric Annals through Slack Inc. He receives honoraria as a CME Executive Director for the Journal of Clinical Psychiatry through Physicians Postgraduate Press. No other speaker bureaus for the past 3 years. Past speaker bureaus include Bristol Myers Squibb, Cyberonics, Forest Pharmaceuticals, Eli Lilly and Company, Glaxo SmithKline, and Wyeth Ayerst. Royalties have been received from Cambridge University Press and Belvoir Publishing. Dr. Nierenberg owns stock options in Appliance Computing, Inc. He owns copyrights to the Clinical Positive Affect Scale and the MGH Structured Clinical Interview for the Montgomery Asberg Depression Scale exclusively licensed to the MGH Clinical Trials Network and Institute (CTNI).

Dr. R. Kessler has been a consultant for GlaxoSmithKline Inc., Kaiser Permanente, Pfizer Inc., Sanofi-Aventis, Shire Pharmaceuticals, and Wyeth-Ayerst; has served on advisory boards for Eli Lilly & Company and Wyeth-Ayerst; and has had research support for his epidemiological studies from Bristol-Myers Squibb, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Ortho-McNeil Pharmaceuticals Inc., Pfizer Inc., and Sanofi-Aventis.

Dr. Gary S. Sachs serves on the speakers bureaus of Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Memory Pharmaceuticals, Novartis, Pfizer, Sanofi-Aventis, and Wyeth; he serves as an advisory board member or consultant for Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, CNS Response, Concordant Rater Systems, Elan Pharmaceuticals, Eli Lilly, GlaxoSmithKline, Janssen, Memory Pharmaceuticals, Merck, Novartis, Organon, Otsuka, Pfizer, Repligen, Sanofi-Aventis, Schering Plough, Sepracor, Shire,

Sigma-Tau, Solvay Pharmaceuticals, and Wyeth; and his spouse holds shares in Concordant Rater Systems.

Dr. S. Rauch has received honoraria and/or consultation fees from Neurogen, Sepracor, Novartis and Medtronic. He has also participated in research funded by Medtronic, Cyberonics, Cephalon and Northstar.

Dr. D. Dougherty has received honoraria and/or consultation fees from Medtronic, Eli Lily, Jazz Pharmaceuticals, Northstar, Wyeth, Bristol Myers Squibb, Brand Ideas, McNeil, Reed Elsevier, Trancept Pharmaceuticals, Cyberonics, JK Associates, Inc., American Psychiatric Publishing, Inc., Advocate Health and Hosp. Corp., DHHS/NIH, Leerink Swann LLC, Oxford University Press, Professional Practice Group/Psychiatry Syracuse, Y&R Inc., and DBA Sudler & Henessy. He has also participated in research funded by Medtronic, Eli Lily, Northstar, McNeil, Cyberonics, Forest, and Cephalon.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed., DSM-IV. American Psychiatric Association, 1994.

2. Trede K, Salvatore P, Baethge C, Gerhard A, Maggini C, Baldessarini RJ. Manic-depressive illness: Evolution in Kraepelin's Textbook, 1883–1926. *Harv Rev Psychiatry* 2005;**13**:155–178.

3. Tohen M, Zarate CA Jr., Hennen J, et al. The McLean-Harvard First-Episode Mania Study: Prediction of recovery and first recurrence. *Am J Psychiatry* 2003;**160**:2099–2107.

4. Kessler RC, Akiskal HS, Ames M, et al. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. *Am J Psychiatry* 2006;**163**:1561–1568.

5. Morris CD, Miklowitz DJ, Wisniewski SR, Giese AA, Thomas MR, Allen MH. Care satisfaction, hope, and life functioning among adults with bipolar disorder: Data from the first 1000 participants in the Systematic Treatment Enhancement Program. *Compr Psychiatry* 2005;**46**:98–104.

6. Kogan JN, Otto MW, Bauer MS, et al. Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Bipolar Disord* 2004;**6**:460–469.

7. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord* 2001;**67**:45–59.

8. Keck PE Jr, McElroy SL, Strakowski SM, et al. Twelve-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *Am J Psychiatry* 1998;**155**:646–652.

9. Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E. Functional impairment in the remission phase of bipolar disorder. *Bipolar Disord* 2005;**7**:281–285.

10. Huxley N, Baldessarini RJ. Disability and its treatment in bipolar disorder patients. *Bipolar Disord* 2007;**9**:183–196.

11. Merikangas KR, Ames M, Cui L, et al. The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. *Arch Gen Psychiatry* 2007;**64**:1180–1188.

12. Bauer MS, Kirk GF, Gavin C, Williford WO. Determinants of functional outcome and healthcare costs in bipolar disorder: A high-intensity follow-up study. *J Affect Disord* 2001;**65**:231–241.

13. Judd LL, Schettler PJ, Solomon DA, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. *J Affect Disord* 2008;**108**:49–58.

14. Leon AC, Solomon DA, Mueller TI, et al. A brief assessment of psychosocial functioning of subjects with bipolar I disorder: The LIFE-RIFT. Longitudinal Interval Follow-up Evaluation-Range Impaired Functioning Tool. *J Nerv Ment Dis* 2000;**188**:805–812.

15. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: Primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2006;**163**:217–224.

16. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Arch Gen Psychiatry* 2008;**65**:386–394.

17. Goldberg JF, Burdick KE, editors. Cognitive dysfunction in bipolar disorder. Washington DC: American Psychiatric Publishing, 2008.

18. Atre-Vaidya N, Taylor MA, Seidenberg M, Reed R, Perrine A, Glick-Oberwise F. Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. *Neuropsychiatry Neuropsychol Behav Neurol* 1998;**11**:120–126.

19. Martinez-Aran A, Vieta E, Colom F, et al. Cognitive impairment in euthymic bipolar patients: Implications for clinical and functional outcome. *Bipolar Disord* 2004;**6**:224–232.

20. Martinez-Aran A, Vieta E, Torrent C, et al. Functional outcome in bipolar disorder: The role of clinical and cognitive factors. *Bipolar Disord* 2007;**9**:103–113.

21. Dittmann S, Seemuller F, Schwarz MJ, et al. Association of cognitive deficits with elevated homocysteine levels in euthymic bipolar patients and its impact on psychosocial functioning: Preliminary results. *Bipolar Disord* 2007;**9**:63–70.

22. Gildengers AG, Butters MA, Chisholm D, et al. Cognitive functioning and instrumental activities of daily living in

late-life bipolar disorder. *Am J Geriatr Psychiatry* 2007;**15**:174–179.

23. Altshuler LL, Bearden CE, Green MF, van Gorp W, Mintz J. A relationship between neurocognitive impairment and functional impairment in bipolar disorder: A pilot study. *Psychiatry Res* 2008;**157**:289–293.

24. Dickerson FB, Boronow JJ, Stallings CR, Origoni AE, Cole S, Yolken RH. Association between cognitive functioning and employment status of persons with bipolar disorder. *Psychiatr Serv* 2004;**55**:54–58.

25. Brissos S, Dias VV, Carita AI, Martinez-Aran A. Quality of life in bipolar type I disorder and schizophrenia in remission: Clinical and neurocognitive correlates. *Psychiatry Res* 2008;**160**:55–62.

26. Deckersbach T, Armistead M, Otto MW. Cognitive rehabilitation for bipolar disorder. Annual Meeting of the Association for the Advancement of Behavior and Cognitive Therapies, Philadelphia, PA, 2007.

27. Deckersbach T, Lund H, Ametrano R, Thompson-Hollands J, Nierenberg A. Cognitive-behavioral approaches for improving inter-episode functioning in bipolar disorder. Annual Meeting of the Association for the Advancement of Behavior and Cognitive Therapies, Orlando, FL, 2008.

28. Frank E. Interpersonal and social rhythm therapy: A means of improving depression and preventing relapse in bipolar disorder. *J Clin Psychol* 2007;**63**:463–473.

29. Frank E, Swartz HA, Boland E. Interpersonal and social rhythm therapy: An intervention addressing rhythm dysregulation in bipolar disorder. *Dialogues Clin Neurosci* 2007;**9**:325–332.

30. Miklowitz DJ, Goldstein MJ. Bipolar disorder: A family focused treatment approach. New York: Guilford Press, 1997.

31. Cochran SD. Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders. *J Consult Clin Psychol* 1984;**52**:873–878.

32. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: Outcome of the first year. Arch Gen Psychiatry 2003;**60**:145–152.

33. Lam DH, Hayward P, Watkins ER, Wright K, Sham P. Relapse prevention in patients with bipolar disorder: Cognitive therapy outcome after 2 years. *Am J Psychiatry* 2005;**162**:324–329.

34. Frank E, Soreca I, Swartz HA, et al. The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. *Am J Psychiatry* 2008;**165**:1559–1565.

35. Miklowitz DJ, Otto MW, Frank E, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: Results from a 9-month randomized controlled trial. *Am J Psychiatry* 2007;**164**:1340–1347.

36. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;**59**(Suppl 20):22–33;quiz 4–57.

37. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;**23**:56–62.

38. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. *Br J Psychiatry* 1978;**133**:429–435.

39. Kessler RC, Barber C, Beck A, et al. The World Health Organization Health and Work Performance Questionnaire (HPQ). *J Occup Environ Med* 2003;**45**:156–174.

40. Safren SA, Perlman CA, Sprich S, Otto MW. Mastering your adult ADHD. A cognitive-behavioral treatment program. New York: Oxford University Press, 2005.

41. Sohlberg MM, Mateer CA. Cognitive rehabilitation. An integrative neuropsychological approach. New York: The Guilford Press, 2001.

42. Leon AC, Solomon DA, Mueller TI, Turvey CL, Endicott J, Keller MB. The Range of Impaired Functioning Tool (LIFE-RIFT): A brief measure of functional impairment. *Psychol Med* 1999;**29**:869–878.

43. Grace J, Malloy PF. Frontal Systems Behavior Rating Scale (FrSBe) Professional Manual. Lutz, FL: Psychological Assessment Resources, 2001.

44. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *J Clin Exp Neuropsychol* 1998;**20**:310–319.

45. Delis DC, Kaplan E, Kramer JH. Delis–Kaplan Executive Function System (D-KEFS) Examiner's Manual. San Antonio, TX: The Psychological Corporation, 2001.

46. The Psychological Corporation. The Wechsler Adult Reading Test (WTAR). San Antonio, TX: The Psychological Corporation, 2001.

47. Maples NJ, Velligan, DI. Cognitive adaptation: Establishing environmental supports to bypass cognitive deficits and improve functional outcomes. *Am J Psychiatr Rehabil* 2008;**11**:164–180.

48. Medalia A, Choi J. Cognitive remediation in Schizophrenia. *Neuropsychol Rev* 2009;**19**:353–364.

49. Reichenberg A, Harvey PD, Bowie CR, et al. Neuropsychological function and dysfunction in Schizophrenia and psychotic affective disorders. *Schizophr Bull* 2009;**35**:1022–1029.

50. Mohlman J. More power to the executive? CBT plus executive training for late life generalized anxiety disorder. *Cogn Behav Pract* 2008;**15**:306–316.