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Neurocognitive dysfunction and psychosocial outcome in patients with bipolar I disorder at 15-year follow-up

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Abstract

Objective—Despite increasing interest in cognitive dysfunction in bipolar disorder, little is known about its impact on functional outcome relative to affective symptoms.

Method—A total of 33 bipolar I subjects were evaluated at index hospitalization and prospectively followed up 15 years later. Affective symptoms, cognition, global functioning, work, and social adjustment were assessed at follow-up and analyzed by linear regression.

Results—Global functional impairment was significantly associated with poor performance on a cognitive measure of processing speed (WAIS Digit Symbol). Digit symbol performance also was the sole significant predictor of social functioning. Neither symptom severity nor course of illness features significantly contributed to global and social functioning. In contrast, verbal learning deficits, recent depression, and lifetime hospitalizations all were independently associated with work disability.

Conclusion—Processing speed is robustly associated with social and global functioning in bipolar disorder. Poor work functioning is significantly related to subsyndromal depression, course of illness, and verbal learning deficits. Cognitive and mood symptoms warrant consideration as independent determinants of functioning in patients with bipolar disorder many years after an index manic episode.

Keywords

bipolar disorder; cognition; outcome; executive function; depression

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Declaration of interests

Katherine E. Burdick, Ph.D. – speakers' bureau: Merck, Joseph F. Goldberg, M.D. – speakers' bureau or lecture honoraria: AstraZeneca, Eli Lilly and Co., GlaxoSmithKline, Janssen-Cilag, Merck, Pfizer; consultant or scientific advisory board member: Cephalon, Eli Lilly and Co., Martin Harrow, Ph.D. – None.

Introduction

A growing body of literature has begun to document the nature and extent of cognitive deficits among individuals with bipolar disorder across all phases of illness, including euthymia (1, 2). In contrast to patients with schizophrenia, deficits observed among individuals with bipolar disorder appear to be more circumscribed in nature (3) and coalesce primarily around attentional processing (4), executive function (5), and verbal memory (6). Similar to patients with schizophrenia, persistently impaired work and social functioning have been demonstrated among individuals with bipolar disorder (7–10), although the determinants of functional outcome in bipolar disorder are less well established. Poor outcome in schizophrenia has been associated with core cognitive deficits as well as residual positive and negative symptoms (11). In bipolar disorder, some studies have linked poor global adjustment (12) or work disability (13) with cognitive deficits, while others have identified syndromal (13) or subsyndromal depression (14,15) as proximal contributors to impaired psychosocial functioning. However, the relative contributions of affective symptoms and cognitive deficits to functional outcome in bipolar disorder have received little prior study. This investigation was designed to evaluate relationships between neurocognitive performance and affective symptoms relative to psychosocial functioning in a well-characterized group of patients initially hospitalized for bipolar mania and subsequently followed for a period of 15 years.

Aims of the study

The study aims were i) to identify which cognitive domains bore significant associations with global, social, or work functioning at follow-up and ii) to determine whether the severity of recent depressive symptoms, the presence of recent mania, course of illness markers, or medication status contributed additional predictive power in explaining functional disability. We hypothesized that cognitive impairment would be associated with poor global outcome, problems with social adjustment, and work disability, independent of clinically significant depressive / manic symptoms.

Material and methods

Study group

Subjects for this study were 33 adults derived from the Chicago Follow-up Study, a prospective, longitudinal research program currently based at the University of Illinois College of Medicine and focused on aspects of functional outcome, neurocognition, and clinical psychopathology (e.g., affective symptoms, psychosis, negative symptoms) at a 15-year follow-up in a cohort of individuals initially hospitalized for affective or psychotic disorders during young adulthood (7,8,10,14). Subjects were diagnosed at the time of their index hospitalization according to Research Diagnostic Criteria (16) based on the Schedule for Affective Disorders and Schizophrenia (17) or other semi-structured interviews (18). Diagnostic and clinical interviews were conducted by trained research associates who had achieved adequate inter-rater reliability on clinical assessment and functional outcome measures (intraclass correlation coefficients ≥. 90). Research diagnoses were made at the time of the index hospital assessment by a consensus conference led by one of the authors (M.H.) involving senior research psychologists and clinical research interview staff.

Follow-up assessments

Comprehensive follow-up interviews including neurocognitive assessments were conducted for the study group approximately 15.7 (mean) ± 3.9 (SD) years after the index hospitalization. The assessment battery included an assessment of past month and past year affective and psychotic symptoms as rated from SADS interviews. Severity of recent depression was assessed using past month ratings on the following items from the SADS: depressed mood,

low self-esteem, suicidal ideation, sleep changes, appetite changes, low energy, poor concentration, anhedonia, agitation, somatic anxiety, and psychic anxiety. Each of these items is rated as absent = 0 or present = 1, with the exception of the anxiety items that range from 0 to 5. The total score across all eleven items represents severity of depression over the past month. For reference, patients who met full criteria for a depressive episode in the prior month (n = 5) had a total mean score of 10.2 ± 1.3 on these items, while those experiencing subsyndromal depression (n = 10) scored 6.9 ± 2.1 and non-depressed individuals (n = 18) had a mean score of 3.2 ± 1.9. Recent mania was assessed using a dichotomous variable of presence / absence of a manic episode in the prior month according to SADS criteria. Medications during the follow-up period were not controlled, but information on naturalistic treatment was obtained at the time of assessment.

The neurocognitive battery (all tests cited in Spreen and Strauss (19)) performed at follow-up included measures of *verbal learning and memory* [California Verbal Learning Test (CVLT) List A 1–5]; *processing speed* (Wechsler Adult Intelligence Scale [WAIS]-Digit Symbol test; trail making test A [Trail A]); *verbal fluency* (FAS); *executive function* [trail making test B (Trail B); and perseverative errors from the Wisconsin Card Sorting Test (WCST)]. In addition, the WAIS Information subtest was administered as a measure of *accessing of general knowledge*.

Global outcome was rated for the year preceding follow-up using an 8-point scale developed by Levenstein and colleagues (20), which has been used successfully in previous studies by our group (7,10,14). This 8-point scale has been used to identify global outcome categories of good overall functioning (scores of 1–2), moderately impaired functioning (scores of 3–6), or very poor global outcome (scores of 7–8). Work disability and social adjustment were separately rated using individual 5-point outcome scales developed by Strauss and Carpenter (21), where higher scores reflect better functional capacity, which also have been previously utilized by our group (7,10,14) and others (21). All subjects provided written, informed consent to participate in the study protocol, which was approved by the Institutional Review Board (IRB) of the University of Illinois College of Medicine.

Statistical analyses

Statistical analyses were performed using SPSS Version 11.5 (SPSS Inc., Chicago, IL, USA). Initial descriptive analyses were carried out to determine the extent of neurocognitive impairment relative to published normative data with all values calculated on a z-score scale for consistency, with a mean of zero and standard deviation of one. Z-scores used in analyses represent standardized scores from normative data controlling for relevant demographic information including age and sex. Normative data for comparison were derived as follows: For WAIS Information and Digit Symbol, the WAIS Manual was utilized (22); CVLT and WCST variables were normed using their respective manuals (23,24); and Trails A and B, and Verbal fluency normative data were derived from Spreen and Strauss (19).

To determine the relationship among symptoms, neurocognitive measures, and functional outcome in patients with bipolar disorder, we conducted a series of stepwise regressions utilizing the backward elimination method. Stepping method criteria were based on F-tests with entry set at P = 0.05 and removal set at P = 0.10 (default setting in SPSS). A total of three regressions were carried out with dependent variables representing the functional outcome measures: global, social, and work functioning. Independent measures included in each of these models included: age, sex, race, recent depression ratings, recent manic episode, total number of medications, number of lifetime hospitalizations, duration of illness, and the seven cognitive measures (information, digit symbol, fluency, Trail A, Trail B, CVLT total list learning, and WCTS perseverative errors).

Results

Demographic information at the time of follow-up is summarized in Table 1. *Medication*: Most subjects took more than one medication in the month prior to assessment; 15 (45%) had been taking lithium (mean (SD) dose = 1158.8 (554.3) mg / day), 4 (12%) were taking carbamazepine (mean (SD) dose = 550.0 (191.5) mg / day), 5 (15%) were taking an antidepressant, 11 (33%) were taking an antipsychotic (nine of whom were also taking an anticholinergic), and 5 (15%) were taking a benzodiazepine. Because of the limited sample size, we were unable to stratify by medication class, but we did evaluate the effects of medication on neurocognitive functioning. Pearson's correlations indicated that the greater the total number of medications a patient was taking, the lower their performance on WAIS Information ($r = -0.43$; $P = 0.01$), Digit Symbol ($r = -0.40$; $P = 0.02$), and Trail A ($r = -0.44$; $P = 0.01$). No other correlations were significant. Given the potential for medication load to influence cognition and its implication with regard to illness severity, we incorporated total number of medications into the regression models to allow for an independent assessment of associations among other variables after controlling for medication effects.

Neurocognitive performance in patients with bipolar disorder

Based on published normative data, the bipolar disorder subjects demonstrated intact or above-average performance on the following measures: WAIS Information, WAIS Digit Symbol, and verbal fluency. Mild deficits were noted on the WCST at a level that is typically described as clinically non-significant (less than one-half a standard deviation below normal). Our sample of patients with bipolar disorder demonstrated clinically significant deficits (i.e. > 1 SD below average) on verbal learning and memory as measured by the CVLT, and attention / processing speed (Trail A & Trail B) (Fig. 1). As this was a comparison with published normative data rather than a healthy control group, we could not directly test for between-group differences statistically and data are provided for descriptive purposes only.

Symptom severity at the time of assessment

Patients were evaluated for recent depressive symptomatology (items rated over the past month) using 11 items derived from the SADS interview. The patient group had a total mean (±SD) score of 5.4 ± 3.2 on the depression items, with five patients (15 %) meeting full criteria for a depressive episode in the past month. Seven patients (21%) met full criteria for a manic episode in the month prior to assessment. These variables were included in the linear regressions to determine the effects of recent symptoms on psychosocial outcome.

Associations between cognition, symptom severity, and functional outcomes

A series of stepwise linear regressions were conducted to determine the relationship between cognition, symptoms, and functional outcome. Stepwise regression using the backward elimination method was chosen owing to its ability to assess the covariance among measures and to provide statistically independent effects among several variables.

Global functional outcome

Global ratings of psychosocial functioning indicated moderate overall impairment in the bipolar sample rated for the full 12-month period prior to assessment (mean = 3.7 ± 2.0 on a scale ranging from 1 to 8 where 1 is no impairment and 8 is total disability). Stepwise regression (full model $F = 8.26$; df = 2; $P = 0.001$) revealed that significant predictors of global function were WAIS Digit Symbol performance (Beta = −0.51; $t = -3.4$; $P = 0.002$) and recent depressive symptoms (Beta = 0.33; $t = 2.2$; $P = 0.033$). No other variable contributed significantly to the model (all P-values > 0.13).

Social functioning

The mean Strauss–Carpenter social function score was 2.9 ± 1.4, indicating a mild–moderate degree of impaired social adjustment. When stepwise regression was applied to the social functioning measure, the only significant predictor remaining in the model (full model F = 5.16; df = 1; P = 0.30) was WAIS Digit Symbol (Beta = 0.38; t = 2.3; P = 0.030), with faster processing speed associated with better social functioning.

Work functioning

The mean Strauss–Carpenter work function rating for the full sample was 2.4 ± 1.8 (on a scale of 0–4, with four representing excellent functional status and 0 reflecting total disability). When modeling the effects of our variables of interest on work functioning using a backward elimination method, three variables remained in the model as significant predictors of work function (full model F = 10.06; df = 3; P < 0.001): CVLT total learning performance (Beta = 0.34; t = 2.6; P = 0.02); recent depression (Beta = −0.38; t = 2.9; P = 0.008); and number of lifetime hospitalizations (Beta = −0.44; t = 3.3; P = 0.003). As expected, greater verbal learning impairment, more severe recent subsyndromal depression, and an increased number of lifetime hospitalizations each contribute independently to poorer occupational outcome. Because all subjects had a similar duration of illness, we were interested in following up the number of hospitalizations finding and we conducted a post hoc analysis of ‘good’ work outcome (with a rating of 3 or 4) subjects (n = 18) vs. subjects with ‘poor’ occupational status (ratings less than 3; n = 15) using independent t-tests. We found a significant difference in number of hospitalizations such that there was nearly a threefold increase in hospitalizations in the poor work outcome group (mean = 11.4 ± 12.2) when compared with the good outcome group (mean = 3.9 ± 2.5) (t = 2.33; df = 31; P = 0.034).

Discussion

The present findings indicate that 15 years after an index hospitalized manic episode, patients with bipolar disorder demonstrated above-average performance on a measure of accessing of general knowledge but relative deficits on measures of attention / processing speed, and verbal learning, when compared with normative data. These results are consistent with several studies indicating domain-specific cognitive impairment in patients with bipolar disorder that seems to persist over time and is present even during periods of remission (1,2).

At the time of follow-up assessment, approximately half of the bipolar sample was characterized as depressed or recently depressed, with the remainder relatively free from depressive symptoms in the past month. Approximately 21% of the sample had experienced a manic episode within the past month. We found a significant deleterious effect of recent depression on outcome measures related to occupational and global status but no significant independent impact on social capacity. In contrast, recent mania did not significantly influence functional outcome in any of the domains assessed (work, social, and global). These data are consistent with results from a previous study in large cohort of patients with bipolar disorder (n = 441), in which even modest changes in depressive symptomatology resulted in significant changes in functional disability, while changes in manic symptoms were not consistently associated with psychosocial function (25). A number of studies now converge to suggest that depression, even at subsyndromal levels, contributes significantly to various aspects of psychosocial function (26–30).

We also identified a relationship between an increased number of hospitalizations and poorer occupational status in the current sample of patients with bipolar disorder. Because of the prospective nature of this study, index cases were followed up as a cohort such that duration of illness was comparable for all subjects. Therefore, the number of hospitalizations in this

cohort was not simply reflective of a longer time spent ill but is rather a marker of a worse clinical course characterized by more frequent and severe episodes. Indeed, patients characterized by poor occupational functioning had nearly three times as many episodes over the same time frame as those patients with good work outcome. Thus, it is not surprising that patients who spent more time in episodes, and more specifically in the hospital, were less likely to maintain gainful employment. These data are consistent with prior studies indicating that the number of past episodes is significantly associated with functional outcome in bipolar patients (30).

When examining the relationship between neurocognition and functional outcome after controlling for recent affective symptoms, medication status, course of illness factors, and relevant demographic variables, a single measure of processing speed (WAIS Digit Symbol) was significantly and positively correlated with social adjustment and with global long-term outcome over a 12-month period. Performance on a measure of verbal learning and memory (CVLT) was significant predictive of occupational outcome, as has also been shown in schizophrenia (30). These results are consistent with several prior studies that report a significant influence of neurocognitive performance on functional outcome, even after controlling or covarying for current affective symptoms. Indeed, both processing speed and verbal learning /memory have been consistently associated with functional outcome in patients with euthymia (31–33).

Although we were not able to assess the independent contributions of specific drug classes because of a limited sample size, we did evaluate the effects of total medication load (total number of medications) on functional outcome in our regression models. Once accounting for all of the other clinical and cognitive factors, number of medications was not significantly related to outcome in any of the three domains. Only a handful of studies have previously examined the effects of medication on functional measures in patients with bipolar disorder; one reported no effect of lithium or benzodiazepines but did not assess the effects of antipsychotics or anticholinergics (34). Two studies indicated that adherence with some psychotropic regimens leads to a greater potential for employment (35,36). In contrast to our findings, one study found a significant negative effect of increasing numbers of medications prescribed on psychosocial outcome; however, the authors used dichotomous groups of low and high functioning bipolars and did not covary for important clinical factors such as chronicity or recent depressive severity (37). In addition, prior investigations have identified a weak but significant influence of some psychotropic agents (e.g. lithium) on neurocognitive functioning in patients with bipolar disorder (38). A higher medication load likely reflects greater illness severity, and after controlling for variables such as number of hospitalizations and subthreshold affective symptoms, medications per se do not contribute directly to impaired everyday function.

Several limitations warrant acknowledgement in the current study. The relatively small sample size makes the present findings preliminary in nature and in need of replication with larger subject groups. The findings are limited by the absence of a healthy control group or a comparison group of strictly euthymic patients with bipolar disorder. Indeed, some prior studies have suggested that observed deficits in attention, memory, and executive functioning appear to be related to functional impairment among patients with bipolar disorder who are affectively symptomatic but not among patients with euthymia (29), while others clearly indicate an association between cognition and functional capacity even in remitted bipolar patients (31, 37). These conflicting reports underscore the need for future serial studies to track the longitudinal relationship between cognitive function and psychosocial outcome across illness phases in the same patient cohort. The present cross-sectional nature of the assessment of cognitive performance, depressive symptoms, and psychosocial functioning does not allow for causal inferences among these variables, and the possibility cannot be excluded that cognitive

deficits or depressive symptoms may have arisen after, rather than before or concurrent with, functional impairment. Finally, the use of psychotropic medications was not controlled for via randomization; however, we were able to calculate medication load and include this factor in our analyses. Future work conducted in the course of longer term clinical trials may better assess the direct impact of medications on psychosocial functioning in bipolar disorder.

In summary, recent depressive symptoms, a greater number of hospitalizations, and processing speed deficits appear to be related to impaired functional outcome in patients with bipolar disorder 15 years after an index manic episode. Processing speed deficits contribute to poor global functioning and social adaptation, while verbal learning /memory impairment influence occupational status even after controlling for recent affective symptoms, course of illness features, other cognitive measures, and medication load. The present findings highlight the fundamental nature of cognitive impairment as a separable dimension from residual or persistent depressive features in a substantial number of individuals with bipolar disorder at follow-up and point to the need for assessing cognitive status as well as affective symptoms in future studies of functional outcome.

Significant outcomes

- At long-term follow-up (15 years after an index manic episode), patients with bipolar disorder show persistent deficits in attentional processing and verbal memory and are cross-sectionally characterized by moderate levels of affective symptomatology. Functional impairment is common.
- Neurocognitive capacity is associated with social, work, and global functioning in patients with bipolar disorder at long-term follow-up.
- Subthreshold symptoms of depression are more closely related to work and global dysfunction and do not appear to play an independent role in predicting social activity level in patients with bipolar disorder at long-term follow-up.
- A more severe course of illness as defined by an increased number of hospitalizations is a significant, independent predictor of occupational impairment in bipolar disorder.

Limitations

- Medication use did not occur by randomized assignment, precluding causal inferences about their influence on cognitive function or outcome.
- A matched comparison sample of healthy volunteers was not obtained, and subjects' performance on cognitive function was evaluated relative to published norms.
- Neuropsychological testing was conducted at follow-up in bipolar subjects who completed a 15-year assessment, but not previously at the time of their index hospitalization, limiting the potential to identify possible longitudinal declines in cognitive functioning from a baseline state.

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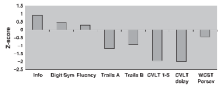

Fig. 1.

Bipolar patients neurocognitive performance vs. normative data: The data depicted represent neurocognitive performance of our patient sample in comparison with published normative data. The X-axis labels the neurocognitive measures administered, and the *Y*-axis is a Z-score scale, with a mean of zero and standard deviation of one. Abbreviations include Info (Wechsler Adult Intelligence Scale-R WAIS-R Information); Digit Sym (WAIS-R Digit Symbol); Fluency (Controlled Oral Word Test COWAT letter fluency FAS); Trail A (trail making test Part A); Trail B (trail making test Part B); CVLT 1–5 (California Verbal Learning Test Total Trials 1–5); WCST Persev (Wisconsin Card Sorting Test Perseverative Errors).

Table 1

Demographics

	Mean (SD)
Age in years	40.2 (6.2)
Sex% female	46%
Race % Caucasian	67%
Education in years	15.3 (3.6)