Neurocognitive Impairment and Psychosis in Bipolar I Disorder During Early Remission From an Acute Episode of Mood Disturbance

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Objective: Recent studies have reported greater neurocognitive impairment in euthymic bipolar disorder patients with a history of psychosis relative to patients without such a history. To further explore the relation between psychosis and cognitive dysfunction in bipolar disorder, the current study examined the cognitive functioning of patients during early remission from a discrete episode of mood disturbance. The study aimed to determine whether the presence of psychosis during inpatient hospitalization was associated with greater cognitive impairment at the time of hospital discharge.

Method: Fifty-nine inpatients who met *DSM-IV* criteria for bipolar disorder (24 admitted with psychosis, 35 admitted without psychosis), ages 18–59 years, completed a neuropsychological battery and mood measures 24–48 hours before discharge. The cognitive battery included standardized tests of IQ, attention and working memory, visual memory, verbal memory, and executive functioning.

Results: A multivariate analysis of variance detected group differences on measures of verbal memory ($P < .001$) and executive functioning ($P < .003$), using mood measures and previous number of psychiatric admissions as covariates. Post hoc analysis of between-subjects effects revealed significantly poorer performance on the California Verbal Learning Test-Second Edition, logical memory subtest from Wechsler Memory Scale-Revised, Stroop Word/Color Interference test, and the Wisconsin Card Sorting Test for patients who were admitted to the hospital with psychosis. These results remained significant after matching the groups for past psychosis, with the exception of the logical memory subtest.

Conclusions: The results of this study indicate that patients with bipolar disorder who were admitted to the hospital due to psychosis exhibited significantly more severe cognitive impairment at the time of discharge than patients admitted for an acute mood disturbance without psychosis. These findings may be important for improving discharge planning and the development of more effective outpatient services.

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Patients with bipolar disorder often suffer from debilitating cognitive impairment that persists beyond the remission of mood symptoms.[1] Studies[2,3] show that cognitive deficits are more likely to be present in patients who suffer from a more severe course of illness, as indicated by longer durations of mood disturbance, younger age at onset, and a higher number of inpatient admissions. More recently, researchers have expanded this line of investigation to explore the impact of other clinical variables that are associated with poor illness outcome on the cognitive functioning of patients. In this respect, psychosis has come into focus, as it often constitutes an important clinical marker for a more severe course of illness in bipolar disorder.[4,5]

The few studies that have investigated the impact of psychosis on the cognitive functioning of patients with bipolar disorder have shown mixed results. Several authors found no differences between patients with and without a history of psychotic episodes[6–10]; in contrast, Albus et al[11] reported an overall more compromised performance on cognitive measures in first-break patients who presented with psychotic symptoms. Similarly, Zubieta et al[12] found that patients with a history of psychosis obtained lower scores on measures of attention, verbal memory, and executive functioning than healthy controls. Consistent with these findings, Martinez-Aran et al[2,13,14] observed more severe deficits on related measures in bipolar disorder patients who presented with previous psychotic episodes relative to patients without a history of psychosis. Specific to executive functioning, Bora et al[15] concluded that deficits in cognitive flexibility may be the trait marker of psychotic features among patients with bipolar disorder. In the nonverbal domain of cognitive functioning, Glahn et al[16] reported significantly weaker performance on measures of spatial working memory in patients with a history of psychosis compared with patients without such a history. Although the findings to date appear inconclusive, given the inconsistency across studies, the multiple, independent reports associating psychosis with a more severe course of illness and greater cognitive impairment warrant additional studies in this area.

Further investigation may benefit from expanding the direct implications of studies to patient care. Most of the studies to date have focused primarily on the long-term impact of previous psychotic episodes on the cognitive functioning of euthymic patients. However, in a clinical view, it may be equally important to explore the impact of a discrete psychotic episode on the cognitive functioning of patients during the early phases of recovery from acute disturbance. Understanding how an acute psychotic episode affects the cognitive functioning of patients during early remission may be critical for improving patient care following discharge from inpatient admission. The important clinical question here is whether patients with bipolar disorder who were admitted to the hospital due to psychosis suffer more debilitating cognitive impairment at the time of discharge than patients who required an inpatient admission for an acute mood disturbance without psychosis. The current study examined this question. We hypothesized that patients who were admitted to the hospital with psychosis would perform more poorly upon discharge on neuropsychological tests than would patients who did not experience psychotic symptoms over the course of hospitalization.

METHOD

Subjects

Fifty-nine inpatients at McLean Hospital who met *DSM-IV* diagnostic criteria for bipolar I disorder completed the neuropsychological battery. In this sample, 41 patients were admitted with manic symptoms, 8 were admitted for depression, and 10 patients were hospitalized with a mixed mood presentation.

The sample consisted of 33 men and 26 women, of whom 10 identified an affiliation with an ethnic minority group. The age range was 18–59 years. Participants were classified into 2 groups based on the presence (n = 24) or absence (n = 35) of psychotic symptoms during the current admission. In the former group, 7 participants experienced their first psychotic episode in the context of the current admission, and in the latter group, 11 patients reported previous psychotic episodes.

Consistent with previous studies,[14] psychosis was defined here by the presence of either delusions or hallucinations. Patients did not present psychotic symptoms at the time of testing. The presence of psychosis was determined through cross-validating clinical information among 3 sources: diagnostic interviews, medical record notes, and direct communications with the treatment team. Agreement in reporting psychotic symptoms (delusions or hallucinations) prior to or during admission determined the presence of a psychotic condition. There were 6 cases in which patients denied psychotic symptoms that were clearly documented in the medical chart. After receiving a detailed description of the observed symptoms from the relevant admitting or treating physician, the research team assigned all 6 patients to the group with psychosis. There were no cases in which patients reported psychotic symptoms that were overlooked by the treatment team or during admission. There were 2 cases in which the research team suspected the presence of psychosis during the diagnostic interview. Both patients were not included in the sample, and the treatment team was notified of these clinical observations. The absence of psychosis at the time of discharge was determined by failure to detect psychotic symptoms by the research clinician who interviewed the patients and the treatment team.

Inclusion/Exclusion Criteria

All of the participants in this study were adult (age ≥ 18 years) inpatients who met *DSM-IV* diagnostic criteria for bipolar I disorder. To reduce the impact of severe mood symptoms on participants' test performance, inclusion criteria also required a Beck Depression Inventory-Second Edition (BDI-II)[17] score < 15, a Beck Hopelessness Scale (BHS)[18] score < 10, and a Young Mania Rating Scale (YMRS)[19] score < 15 at the time of testing. Exclusion criteria included electroconvulsive therapy during the 12 months prior to admission, a history of neurologic illness or injury, and lifetime diagnoses of substance abuse or dependence. This information was obtained through structured diagnostic interviews and a review of medical records.

Diagnosis and Procedure

After the treatment team on the unit determined that a potential participant had reached sufficient stability for discharge, the patient was approached by a trained clinician to sign an informed consent form for the study. The clinician administered the Structured Clinical Interview for Axis I DSM-IV Disorders-Part I[20] to confirm a bipolar I diagnosis. The diagnostic procedure also integrated information from family members and outpatient treatment providers that was available in the medical record or through verbal communications with the treatment team. After the diagnostic procedure was completed, a trained examiner administered the neuropsychological battery and mood measures. This procedure occurred 24–48 hours prior to discharge.

The Neuropsychological Battery

In this study, we employed a neuropsychological test battery with well-documented norms and satisfactory estimates of reliability and validity. The battery was designed to assess IQ, attention and working memory, visual memory, verbal memory, and executive functioning. IQ estimates were obtained with the Wechsler Abbreviated Scale of Intelligence (WASI).[21] Measures of attention included the Digit Span subtest from the Wechsler Adult Intelligence Scale-Third Edition,[22] Trail Making Test, Parts A and B,[23] and the letter and symbol cancellation task.[24] We assessed verbal memory with the logical memory subtest from the Wechsler Memory Scale-Revised[25] and the

Table 1. Demographic Characteristics and Mood Measures of Patients Admitted With Bipolar I Disorder With and Without Psychosis (N = 59)

	Bipolar I Patients With Psychosis (n = 24)		Bipolar I Patients Without Psychosis (n = 35)			
Variable	Mean	SD	Mean	SD	*t*	*P* Value
Education, y	14.2	1.78	14.3	2.44	−0.05	.96
Age, y	37.2	12.5	37.5	13.4	−0.08	.93
Age of first psychiatric admission for mood disturbance, y	24.9	9.6	28.7	11.8	1.20	.20
Previous number of psychiatric admissions	5.50	5.31	5.82	5.92	−0.19	.85
Young Mania Rating Scale score	7.25	4.60	6.63	3.60	0.57	.57
Beck Depression Inventory-II score	8.33	3.29	7.91	3.58	0.45	.65
Beck Hopelessness Scale score	3.88	4.06	4.50	2.99	0.67	.50

California Verbal Learning Test-Second Edition (CVLT-II)–Short Form.[26] To assess perceptual organization and visual memory, we administered the Rey Complex Figure Test.[27] The battery also consisted of several measures of executive functioning, including the Stroop Word/Color Interference test,[28] the Controlled Oral Word Association Test (COWAT) FAS letters format and animal naming task,[29] and the Wisconsin Card Sorting Test-64 Card Version.[30] Administration of the battery required approximately 2 hours.

Statistical Analysis

Preliminary analyses of demographic and clinical data applied the Pearson χ^2 and *t* tests. Because the neuropsychological test battery included multiple measures in several cognitive domains, group differences in test scores were determined by a multivariate analysis of variance (MANOVA). To control for residual mood symptoms and illness severity, analyses used the mood measures administered at the time of testing (ie, BDI-II and YMRS scores) and previous number of psychiatric hospitalizations as covariates. The same procedure was repeated for each cognitive domain separately: attention and working memory, visual memory, verbal memory, executive functioning, and IQ. Analysis of variance (ANOVA) of post hoc between-subjects effects in test performance on individual measures applied the same covariates.

To avoid redundancy in reporting insignificant results, we explored only between-group effects for individual measures within cognitive domains that reached statistical significance during the MANOVA procedure. To control for group differences in past psychotic episodes, subsequent analysis repeated previously significant comparisons after excluding patients without a history of psychosis from the group that presented to the current admission without psychosis. This analysis compared patients who were admitted to the hospital with (n = 24) and without (n = 11) psychosis, in which the latter group consisted only of patients who reported a history of psychosis. Analyses applied standardized scaled scores for the cognitive measures (mean = 50, SD = 10; CVLT-II immediate and delayed recall and recognition scores: mean = 0, SD = 1), with lower values representing poorer performance.

RESULTS

Clinical and Demographic Variables

Table 1 presents means, standard deviations, and test statistics of the clinical and demographic variables. As Table 1 indicates, no group differences emerged in clinical variables with respect to residual mood symptoms, previous number of psychiatric admissions, or age at first hospitalization. Further analysis also failed to detect differences in the number of medications patients were prescribed on the day of testing or diagnostic subtype upon admission. Group comparisons of demographic variables also did not reveal significant differences in age, gender, years of formal education, marital status, or ethnic minority status.

Cognitive Measures

Attention, working memory, and IQ. The MANOVA procedure revealed no group differences on measures of attention and working memory (Wilks λ, $F_{7,48} = 0.28$, $P < .95$). Consistent with this result, none of the analysis of covariance (ANCOVA) tests for differences on the individual measures approached significance. The MANOVA and ANCOVA procedures also did not detect significant group differences on the WASI IQ measures (Wilks λ, $F_{7,48} = 0.71$, $P < .65$), which included full-scale IQ, verbal IQ, performance IQ, block design, matrix reasoning, vocabulary, and similarities.

Memory. Analysis detected highly significant group differences in measures of verbal memory (Wilks λ, $F_{7,48} = 9.11$, $P < .001$). As Table 2 reveals, the ANCOVA procedure indicates that the bipolar disorder group without psychosis performed significantly better than the group with psychosis on immediate and delayed recall of passages (logical memory) and on the acquisition and immediate and delayed recall of a word list (CVLT-II). When patients without a history of psychosis were excluded from analysis, results remained significant only on immediate and delayed recall of the word list (see Table 3). No group differences emerged in visual memory (Wilks λ, $F_{7,48} = 0.31$, $P < .87$), as measured by the Rey Complex Figure Test.

Executive functioning. The MANOVA procedure yielded highly significant group differences in measures of

Table 2. Group Comparison of Scaled Scores of Verbal Memory and Executive Functioning Measures (N = 59)

	Bipolar I Patients With Psychosis (n = 24)		Bipolar I Patients Without Psychosis (n = 35)		Tests of Between-Subjects Effects			
Measure	Mean	SD	Mean	SD	MD	MS	F^a	*P* Value
Verbal memory								
Logical memory, immediate recall	40.5	10.1	48.0	10.3	7.5	249.5	2.46*	.05
Logical memory, delayed recall	38.9	6.8	47.1	11.3	8.2	154.5	3.49*	.05
CVLT-II, acquisition	34.1	12.5	45.7	8.70	11.6	506.0	4.51**	.003
CVLT-II, short delay recall	−2.27	0.67	−0.5	1.05	1.77	11.4	13.1***	.0001
CVLT-II, long delay recall	−2.12	0.85	−0.97	1.13	1.15	4.97	4.48**	.003
CVLT-II, recognition	−1.77	1.42	−0.082	1.41	0.95	4.22	2.05	.10
Executive functioning								
FAS	50.8	15.3	55.8	9.11	5.05	195.1	1.34	.26
Animal naming test	41.8	8.93	45.6	8.93	3.80	61.4	0.73	.57
Stroop Word/Color Interference test	41.0	8.09	50.9	9.21	9.90	396.6	5.12***	.001
WCST, number of categories completed	0.95	0.85	2.40	1.51	1.45	8.67	5.19***	.001
WCST, nonperseverative errors	30.0	8.7	39.2	11.5	9.20	352.3	3.12*	.02
WCST, perseverative errors	37.5	10.2	40.5	8.35	3.00	147.1	7.82	.13

[a] $df = 4$.
*$P < .05$, **$P < .01$, ***$P < .001$.
Abbreviations: CVLT-II = California Verbal Learning Test-Second Edition, FAS = controlled oral association test, MD = mean difference, MS = mean square, WCST = Wisconsin Card Sorting Test.

Table 3. Group Comparison of Scaled Scores of Verbal Memory and Executive Functioning Measures, Excluding Patients Without a History of Psychosis (n = 35)

	Bipolar I Patients Admitted With Psychosis (n = 24)		Bipolar I Patients Admitted Without Psychosis (n = 11)		Tests of Between-Subjects Effects			
Measure	Mean	SD	Mean	SD	MD	MS	F^a	*P* Value
Verbal memory								
Logical memory, immediate recall	40.5	10.1	48.4	12.4	7.91	202.2	1.68	.18
Logical memory, delayed recall	38.9	6.80	47.0	13.6	8.10	161.3	1.73	.16
CVLT-II, acquisition	34.1	12.5	44.6	6.46	10.5	268.3	2.13	.10
CVLT-II, short delay recall	−2.27	0.67	−0.31	0.92	1.96	7.50	12.5***	.0001
CVLT-II, long delay recall	−2.12	0.85	−0.72	0.95	1.40	4.20	5.43**	.002
CVLT-II, recognition	−1.77	1.42	−0.90	1.51	0.87	3.46	1.68	.17
Executive functioning								
FAS	50.8	15.3	56.3	8.01	5.50	144.1	0.75	.56
Animal naming test	41.8	8.93	45.5	9.96	3.68	44.5	0.48	.74
Stroop Word/Color Interference test	41.0	8.09	47.8	6.66	6.79	160.4	2.91*	.03
WCST, number of categories completed	0.95	0.85	1.90	0.36	0.95	3.65	3.20**	.01
WCST, nonperseverative errors	30.0	8.7	39.7	9.54	9.72	242.5	3.02*	.03
WCST, perseverative errors	37.5	10.2	39.9	7.43	2.72	134.7	1.61	.13

[a] $df = 4$.
*$P < .05$, **$P < .01$, ***$P < .001$.
Abbreviations: CVLT-II = California Verbal Learning Test-Second Edition, FAS = controlled oral association test, MD = mean difference, MS = mean square, WCST = Wisconsin Card Sorting Test.

executive functioning (Wilks λ, $F_{7,48} = 3.67$, $P < .003$). The ANCOVA procedure revealed poorer performance for the bipolar disorder group with psychosis on the Stroop Word/Color and the Wisconsin Card Sorting tests (see Table 2). These results remained significant after the exclusion of patients without a history of psychosis (see Table 3).

DISCUSSION

The results of the current study indicated more severe cognitive deficits in patients with bipolar disorder who were admitted to the hospital with psychotic symptoms than in patients who were hospitalized for an acute mood disturbance without psychosis. Analyses revealed that the presence of psychosis at the time of admission was associated with greater impairment in verbal memory at the time of discharge, as indicated by more compromised performance on a passage memory test and a list-learning task. Patients who presented to the hospital with psychosis also exhibited more severe impairment in executive functioning, especially on tasks that measure cognitive flexibility (ie, ability to adjust a course of action in response to corrective feedback) and the ability to inhibit dominant or automatic reactions in favor of responses relevant to task demands. Group differences in executive functioning and verbal memory remained significant after matching for past psychosis. However, in

the domain of verbal memory, this was the case only on measures of the list-learning task, which tends to be more sensitive to executive dysfunction.

The results of this study are consistent with several previous reports[2,12–15] that have emphasized greater impairment in verbal memory and executive functioning among euthymic patients with a history of psychosis. In fact, it is possible that previous psychotic episodes contributed to the group differences in cognitive functioning observed in the current sample. At the same time, it is notable that the differences remained highly significant after controlling for certain variables that would be related to the overall severity of illness (ie, previous number of inpatient admissions and the presence of residual mood symptoms). This result may advance speculation about the degree to which the observed group differences relate more directly to the nature of the current episode. It is thus possible that early remission from psychosis may be accompanied by greater cognitive impairment relative to early remission from an acute mood disturbance without psychosis.

Understanding the potential impact of a discrete psychotic episode on cognitive functioning in the early stage of remission may be important for clinical care. In the hospital, the presence and effects of cognitive impairment may remain largely inconspicuous due to the minimal functional demands that this environment poses on the brain. Upon discharge, however, patients may face the challenge of functioning in an unsupervised environment at a time when their cognitive abilities are most compromised. Previous reports[2,31–33] highlight the relationship between cognitive impairment and psychosocial disability in bipolar disorder. In particular, executive and consequent memory impairments can compromise patients' ability to negotiate the demands of everyday life in unprotected settings. After discharge, cognitively impaired patients may encounter major difficulties in keeping appointments, managing medication, sustaining proper nutritional and fluid intake, and maintaining hygiene. These difficulties may increase stress, trigger affective instability, and ultimately result in rapid decompensation and readmission. Longitudinal evidence suggests that about 60% of bipolar disorder patients experience poor posthospital adjustment.[6] This may be partly due to the untoward effects of cognitive impairment, exacerbated by a recent psychotic episode. The results of the current study warrant careful discharge planning with regard to the assessment of cognitive functioning for bipolar patients who were admitted for psychosis.

Several limitations of the current study deserve mention. The study reports a correlation between psychosis and cognitive functioning, which may limit conclusions about the degree to which acute psychosis contributes to poor cognitive outcome upon discharge. A follow-up assessment several months after discharge would allow for the examination of the relationship between psychosis, cognitive recovery, and functional outcome. In the context of the naturalistic environment of the hospital setting, the current study also did not control for the cognitive effects of medication, although the groups did not differ in terms of number of prescribed medications on the day of testing. The exclusion criterion of lifetime diagnoses of substance abuse or dependence was quite strict and limited the generalizability of findings. In terms of cognitive measurement, the current study may have failed to detect group differences in visual memory, as the Rey Complex Figure Test is particularly sensitive to the adverse effects of executive dysfunction, which were present in both groups. Finally, the current sample did not allow for the analysis of ethnicity, which again may limit the generalization of results.

Despite these limitations, the current study indicates a potential link between the presence of psychosis and cognitive impairment during the early phase of remission from acute disturbance. These results may inform clinical care and may highlight the need to increase the accommodations and support that bipolar disorder patients receive after discharge from the hospital.

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