Cognitive Impairment in Euthymic Bipolar Patients With and Without Prior Alcohol Dependence

A Preliminary Study

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Background: Few studies of the neurocognitive performance of patients with bipolar disorder have been performed while patients are in the euthymic state.

Methods: Twenty-five euthymic bipolar patients (12 with and 13 without a history of alcohol dependence) were compared with 22 normal control subjects on a neuropsychological test battery assessing a range of cognitive domains. The relationship between subjects' neurocognitive performance and the course-of-illness variables (lifetime episodes and duration of mania, depression, or both), as well as current lithium level, was determined.

Results: The results indicated differences across the groups, with the bipolar patients with and without alcohol dependence performing more poorly than controls on tests of verbal memory. Furthermore, bipolar subjects with a history of alcohol dependence had additional decrements in executive (ie, frontal lobe) functions when compared with controls. For subjects in the bipolar group, lifetime months of mania and depression were negatively correlated with performance in verbal memory and several executive function measures.

Conclusions: Our findings support the presence of persistent neurocognitive difficulties in patients with long-standing bipolar disorder who are not in the psychiatrically acute state or who are suffering the effects of alcohol abuse and suggest that there may be an aggregate negative effect of lifetime duration of bipolar illness on memory and frontal or executive systems.

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The nature and extent of neurocognitive dysfunction in persons with bipolar disorder remain unclear. Although several studies have assessed neurocognitive functions in persons with bipolar disorder, most have studied patients in either the acutely manic or acutely depressed state. The interpretation of such studies is difficult as clinically significant levels of depression or psychosis can account for most if not all of the cognitive deficits observed.

To date, to our knowledge, only 4 studies have examined the neurocognitive performance of patients with bipolar disorder when examined in the euthymic state. Coffman and colleagues documented clinically significant levels of diffuse cognitive impairment in a group of 30 ambulatory outpatients meeting the criteria for bipolar affective disorder with psychotic features relative to a group of normal control subjects. Savard and colleagues found that patients with bipolar disorder were impaired on the Category Test relative to the other subjects. Waddington and colleagues compared 2 subgroups of 40 bipolar patients—15 of whom had evidence of involuntary movements associated with tardive dyskinesia—on a neuropsychological test of psychomotor speed (Trail Making Test). Although the investigators found that the subjects with tardive dyskinesia performed worse on the Trail Making Test, the study contained no normal control group. In a fourth study, Sapin and colleagues administered several neuropsychological measures of visuospatial function to 20 euthymic, drug-free patients with bipolar disorder and 20 normal controls. Although no statistical differences between the 2 groups were found on any neuropsychological measures of visuospatial function and attention, no measures of memory or other frontal lobe functions were included in the study.

These studies suggest that some individuals with bipolar disorder may have persistent cognitive deficits that are present in the nonacute phase of their illness. However, most investigators did not adminis-
SUBJECTS AND METHODS

SUBJECTS

This study was reviewed and approved by the Institutional Review Board of the Veterans Affairs Medical Center, West Los Angeles, Calif; informed consent was obtained from all subjects before enrollment in the study. Consecutive patients admitted to an outpatient Bipolar Clinic (Veterans Affairs Medical Center) were recruited as subjects while normal controls were recruited from flyer advertisements and by word of mouth among Veterans Affairs Medical Center personnel. Any subject with a history of head injury with loss of consciousness exceeding 1 hour, history of seizure disorder, learning disability, migraine headache, liver function abnormalities, alcoholic dementia, abuse of alcohol within the past 6 months, prior history of cocaine abuse or dependence, diabetes, hypertension, or other neurologic illness was excluded from the study, as was any subject who had electroconvulsive therapy administered within 2 years of the neuropsychological testing.

Subjects were administered the Structured Clinical Interview for Diagnostic Symptoms. Subjects who did not meet criteria for any Axis I psychiatric disorder as assessed by the Structured Clinical Interview for Diagnostic Symptoms were included as the normal controls. Bipolar subjects who met the Structured Clinical Interview for Diagnostic Symptoms criteria were excluded from this study if they met the criteria for any other current or past DSM-IV Axis I disorder, including substance abuse disorders, except those with a history of alcohol dependence. Approximately 50% of bipolar subjects met the criteria for a history of alcohol dependence. These subjects were not excluded from the study if sobriety had been maintained for 6 months or longer. The lifetime frequency and duration of alcohol use was further assessed with a detailed questionnaire. Urine specimens for toxicologic screens were obtained from all subjects before neuropsychological testing to confirm an illicit drug-free state. No subject was included in the control or bipolar group if the results of urine toxicologic screens were positive for drugs.

Subjects with bipolar disorder were observed in the outpatient setting for at least 3 months to ensure euthymia before the experimental procedures were administered. Euthymia was defined as having a Hamilton Depression Scale score below 7 and a Young Mania Rating Scale score below 6 for 3 consecutive monthly assessments, just before neuropsychological testing. Urinary free cortisol levels were determined by first performing a dichloromethane extraction of the cortisol from an aliquot of the 24-hour urine sample in antibody-coated tubes (Coat-A-Count tubes, Diagnostic Products, Inglewood, Calif). Once the dichloromethane was evaporated, diluent was added and standard radioimmunoassay procedures were performed.

MATERIALS

Subjects were administered a battery of neuropsychological tests covering 5 cognitive domains. The instruments administered for each domain were as follows: (1) verbal memory, California Verbal Learning Test; (2) nonverbal memory, Rey-Osterrieth Complex Figure and 3-minute delayed recall; (3) executive, controlled oral word list generation (Controlled Oral Word Association Test, aka, FAS); (4) Stroop Color and Word Test; and (5) psychomotor, Trail Making Test, parts A and B.

In addition, estimates of premorbid intellectual functioning were obtained from each subject’s performance on the Wechsler Adult Intelligence Scale–Revised and the vocabulary subtest from the Wechsler Adult Intelligence Scale–Revised. All tests were administered by trained psychology graduate research assistants (including D.C.T.) in a quiet testing room; the test administrators were blind to subject status. Tests were administered according to standard administration instructions.

STATISTICAL PROCEDURES

The distributions of scores for each variable were examined to ensure that they approximated a normal distribution. Variables containing a skewed distribution were normalized using appropriate transformations.

Analysis of variance (ANOVA) was performed on key demographic variables to determine if there were any significant differences across groups.

Analysis of variance was then performed on the neurocognitive variables by group to determine whether a significant main effect for group by test was present. Pairwise comparisons were then performed on the neurocognitive variables to determine which groups significantly differed from each other. All results at P≤.05 were judged to be significant. To decrease the risk of a type I error, emphasis in the interpretation of significant findings was placed on a pattern of significant results occurring in clusters of tests within the cognitive domains previously listed as opposed to inconsistent or isolated findings across domains. The overall error rate was also controlled for by making pairwise comparisons using the Tukey test of honestly significant differences. Bivariate correlations were calculated between psychiatric (eg, number of months depressed) and neurocognitive (eg, verbal memory recall) variables.
group of bipolar patients with a history of alcohol dependence differs cognitively from patients with bipola
disorder and no such history and (2) whether there is
a relationship between cognitive impairment and course
of illness in this population (ie, duration and number of
episodes of mania or depression). This study was con-
ducted to further investigate these issues.

RESULTS

DEMOGRAPHIC DATA

As Table 1 indicates, ANOVA revealed no significant dif-
f erences in subject demographic variables for age, educa-
tional level, and estimated premorbid intelligence. As noted
in the table, subjects in the bipolar group with alcohol de-
pendence had a reasonably young age of onset of alcohol-
ism, a mean duration of alcoholism of longer than 10 years,
and a mean duration of sobriety of longer than 8 years.

NEUROPSYCHOLOGICAL TESTS

Table 2 reveals the results of the ANOVA for the 3 sub-
ject groups, given by each cognitive domain assessed. No
significant differences in visuospatial, nonverbal memory,
or psychomotor speed abilities were found. However, con-
sistent differences across groups were evident in 2 cog-
nitive domains: measures of verbal memory and execute-
tive systems function.

In the verbal memory domain, significant differ-
ences were found across the groups in the total number of
words acquired across the 5 learning trials of the Califor-
nia Verbal Learning Test, with the bipolar groups with
and without alcohol dependence performing worse than
the controls. Free recall of the words performed immedi-
ately after an interference task (“short-delay free recall”)
was significantly lower (P = .003) in the bipolar group with
alcohol dependence compared with the controls. Free re-
call of the list after a 20-minute delay (“long-delay free re-
call”) was again significantly poorer (“long-delay cued re-
call”) and following a 20-minute span (“long-delay cued
recall”), the bipolar groups with and without alcohol de-
pendence performed more poorly than the controls.

The mean number of words learned for each of the
5 California Verbal Learning Test learning trials for the
patient groups was examined. The controls consistently
learned and recalled more words than did the subjects
in the 2 clinical groups. A post hoc review of the perfor-
mance of individual subjects in the bipolar groups with
and without alcohol dependence on the California Ver-
bal Learning Test revealed that those who demon-
strated greatest variability across the learning trials were
those who had been psychiatrically hospitalized for manic
or depressive episodes within the preceding 5 years.

In the executive or attention domain, ANOVA re-
vealed significant differences across the 3 groups for the
Wisconsin Card Sorting Test total number of categories
achieved and the number of perseverative errors. Bipola-
lar subjects with alcohol dependence achieved signifi-
cantly fewer categories (P = .02) than subjects in the con-
trol group.

Table 1. Demographic Variables for the Bipolar Groups With and Without Alcohol Dependence and the Control Group*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without Alcohol Dependence (n=13)</th>
<th>With Alcohol Dependence (n=12)</th>
<th>Control Group (n=22)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.84 (13.36)</td>
<td>52.87 (8.55)</td>
<td>51.73 (12.60)</td>
<td>.77</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.85 (2.67)</td>
<td>15.17 (2.33)</td>
<td>14.98 (1.88)</td>
<td>.54</td>
</tr>
<tr>
<td>Age at onset of illness</td>
<td>27.15 (11.77)</td>
<td>25.33 (6.98)</td>
<td>. . .</td>
<td>.65</td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>22.31 (10.13)</td>
<td>29.17 (10.99)</td>
<td>. . .</td>
<td>.12</td>
</tr>
<tr>
<td>No. of depressive episodes</td>
<td>7.75 (8.62)</td>
<td>6.27 (6.51)</td>
<td>. . .</td>
<td>.65</td>
</tr>
<tr>
<td>No. of months depressed</td>
<td>33.67 (38.47)</td>
<td>42.75 (43.40)</td>
<td>. . .</td>
<td>.63</td>
</tr>
<tr>
<td>No. of manic episodes</td>
<td>4.83 (4.75)</td>
<td>10.22 (10.71)</td>
<td>. . .</td>
<td>.14</td>
</tr>
<tr>
<td>No. of months manic</td>
<td>15.02 (27.93)</td>
<td>31.53 (30.39)</td>
<td>. . .</td>
<td>.23</td>
</tr>
<tr>
<td>Age at onset of alcoholism, y</td>
<td>. . .</td>
<td>29.53 (7.80)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Duration of alcohol use, y</td>
<td>. . .</td>
<td>15.15 (11.58)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Duration of abstinence, y</td>
<td>. . .</td>
<td>8.27 (7.66)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Estimated verbal intelligence quotient (American version of the National Adult Reading Test) score</td>
<td>119.38 (7.48)</td>
<td>113.33 (11.57)</td>
<td>114.37 (10.77)</td>
<td>.27</td>
</tr>
<tr>
<td>Vocabulary scaled score</td>
<td>12.92 (2.90)</td>
<td>12.42 (1.67)</td>
<td>11.55 (2.26)</td>
<td>.23</td>
</tr>
<tr>
<td>Lithium level, mmol/L</td>
<td>0.72 (0.30)</td>
<td>0.66 (0.19)</td>
<td>. . .</td>
<td>.55</td>
</tr>
<tr>
<td>Free 24-h urinary cortisol level, nmol/d</td>
<td>156.27 (85.30)</td>
<td>129.26 (63.51)</td>
<td>157.87 (82.02)</td>
<td>.57</td>
</tr>
<tr>
<td>Total 24-h urinary cortisol level, nmol/L</td>
<td>3618.18 (1381.98)</td>
<td>3634.43 (1586.42)</td>
<td>4041.94 (1829.22)</td>
<td>.78</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale score</td>
<td>31.91 (3.93)</td>
<td>32.50 (4.70)</td>
<td>. . .</td>
<td>.75</td>
</tr>
<tr>
<td>Total No. of hospitalizations</td>
<td>3.50 (3.37)</td>
<td>5.73 (4.82)</td>
<td>. . .</td>
<td>.21</td>
</tr>
</tbody>
</table>

* All data given as the mean (SD). The race of members of each group is as follows: bipolar group without alcohol dependence, 1 African American and 12 whites; bipolar group with alcohol dependence, 1 African American, 1 Hispanic, and 10 whites; and control group, 5 African Americans, 1 Asian American, 1 Hispanic, and 15 whites. Ellipses indicate data not applicable.
† No significant differences were found among the groups for any of these variables, even after transformation of time variables (duration of bipolar illness [logarithm]), number of manic episodes (square root), and number of months manic (logarithm).
The relationship between course-of-illness variables from the life chart indicated in Table 3 and performance on the neuropsychological measures was examined. Correlations between these variables and the cognitive measures were obtained separately from the bipolar groups with and without alcohol dependence to control for any effect or contribution of prior alcohol dependence.

We also examined the number of subjects in each of the 2 clinical groups who were prescribed various psychiatric medications and found that both groups were proportional in the types of medications taken by their respective subjects.

The results of the correlations between the neuropsychological and course-of-illness variables are given only for the bipolar group without alcohol dependence in Table 3. Significant negative correlations were present between the lifetime number of months depressed and months manic and performance on the California Verbal Learning Test. Further significant correlations were found between the duration and number of episodes of lifetime mania and subjects’ performance on 2 executive function measures of the Wisconsin Card Sorting Test. Performance on the Trail Making Test part B (a test of psychomotor speed and set shifting associated with frontal lobe function) was significantly associated with duration of lifetime depression, with poorer performance associated with longer duration of depression. For the bipolar group with alcohol dependence, significant ($P = .05$) correlations were found only for age of onset of an alcohol use disorder and several neurocognitive variables.

**COMMENT**

This study indicates that selective neurocognitive dysfunction is present in patients with bipolar disorder in the euthymic state. Specifically, impairment exists in verbal memory and frontal executive functioning; no differences between bipolar patients and controls were found in measures of visuospatial function or psychomotor speed. These deficits cannot be explained by state factors, such as the presence of an acute manic or depressive episode, because all subjects had been euthymic for at least 3 months before the neuropsychological testing. Further, our results revealed that the number of months of mania or depression that persons with bipolar illness have experienced during.
numbers, and cell death. Because hypercortisolemia can result in elevated cortisol levels, producing damage to the hippocampus and effecting lasting dysfunction—even after the acute episode has resolved. Hippocampal dysfunction, if present, could partially explain the impaired performance found on neuropsychological measures of learning and memory.25

Alternatively, it is possible that the bipolar subjects who abused alcohol may have had a more malignant form of bipolar disorder. Indeed, the mean number of episodes and months of lifetime mania in the bipolar group with alcohol dependence was almost double that of the bipolar group without alcohol dependence (although the differences did not reach statistical significance because of the large SD of this variable in our limited sample). While comorbid alcoholism might lead to medication non-compliance and, thus, to more frequent relapses into affective episodes, bipolar subjects with more refractory illness may be more likely to self-medicate with alcohol. In either case, more months of illness in this comorbid group could ostensibly result in greater neurocognitive impairment.

While the bipolar group without alcohol dependence did not differ significantly from controls on frontal measures, significant correlations between poor performance on the Wisconsin Card Sorting Test (in categories achieved and number of perseverative errors) and number of lifetime episodes and months of mania in this “pure” bipolar group were present. This may reflect progressive frontal lobe damage or disruption of frontal or subcortical circuits or fronto-mesolimbic circuits. Associated with this type of impairment would be changes in cognitive functions that are mediated by that circuit.

Most of the patients in both bipolar groups were taking lithium, another factor that could account for our findings. However, there is considerable controversy in the field about this issue, with some studies finding deleterious effects and others finding no effects of lithium on cognition. In the only carefully documented longitudinal follow-up study of a cohort of patients treated with lithium who were observed for 6 years, Engelsmann and colleagues found remarkably stable neurocognitive performance in their sample during this interval, with only 1 of 10 memory subtests showing a statistically—although not clinically—significant decline.

**Table 3. Correlations of Psychiatric Variables With Neuropsychological Measures (Bipolar Group Without Alcohol Dependence Only)**

<table>
<thead>
<tr>
<th>Neuropsychological Measure According to Cognitive Domain*</th>
<th>Lithium Level</th>
<th>Manic Episodes</th>
<th>Total No. of Months Manic</th>
<th>Depressive Episodes</th>
<th>Total No. of Months Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total words learned (CVLT)</td>
<td>-0.01</td>
<td>-0.51</td>
<td>-0.51</td>
<td>-0.33</td>
<td>-0.68†</td>
</tr>
<tr>
<td>Short-delay free recall</td>
<td>-0.01</td>
<td>-0.46</td>
<td>-0.62†</td>
<td>-0.36</td>
<td>-0.71†</td>
</tr>
<tr>
<td>Short-delay cued recall</td>
<td>-0.20</td>
<td>-0.31</td>
<td>-0.62†</td>
<td>-0.36</td>
<td>-0.59†</td>
</tr>
<tr>
<td>Long-delay free recall</td>
<td>-0.08</td>
<td>-0.60†</td>
<td>-0.67†</td>
<td>-0.43</td>
<td>-0.68†</td>
</tr>
<tr>
<td>Long-delay cued recall</td>
<td>-0.21</td>
<td>-0.53</td>
<td>-0.55</td>
<td>-0.39</td>
<td>-0.67†</td>
</tr>
<tr>
<td>Frontal-executive functions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS total words</td>
<td>0.04</td>
<td>-0.13</td>
<td>-0.46</td>
<td>-0.17</td>
<td>-0.33</td>
</tr>
<tr>
<td>WCST Categories</td>
<td>0.09</td>
<td>-0.73†</td>
<td>-0.30</td>
<td>0.14</td>
<td>-0.20</td>
</tr>
<tr>
<td>Perseverative errors</td>
<td>-0.05</td>
<td>0.80†</td>
<td>0.58†</td>
<td>0.06</td>
<td>0.43</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color naming</td>
<td>-0.50</td>
<td>0.11</td>
<td>0.19</td>
<td>-0.24</td>
<td>-0.04</td>
</tr>
<tr>
<td>Word reading</td>
<td>-0.44</td>
<td>0.31</td>
<td>0.70†</td>
<td>0.03</td>
<td>0.40</td>
</tr>
<tr>
<td>Interference</td>
<td>-0.36</td>
<td>0.41</td>
<td>0.30</td>
<td>-0.06</td>
<td>0.23</td>
</tr>
<tr>
<td>Executive or set shifting</td>
<td>-0.13</td>
<td>0.01</td>
<td>0.42</td>
<td>0.13</td>
<td>0.69†</td>
</tr>
</tbody>
</table>

* CVLT indicates California Verbal Learning Test; FAS, Controlled Oral Word Association Test; and WCST, Wisconsin Card Sorting Test.
†P<.05.
‡P<.01.
In our study, because all subjects had been treated with lithium, we cannot conclusively disentangle the effects of lithium vs episodes of mania, depression, or both on cognitive test performance. Nevertheless, we do not believe our results are due solely to chronic lithium exposure for several reasons. First, we did not find significant correlations between current lithium level and cognitive test performance. Second, the studies previously reviewed suggest that cognitive deficits associated with lithium are typically slight at most, while the deficits we found in this study were more severe. Third, the significant relationships between cumulative months of mania or depression and neurocognitive performance on selective cognitive measures implicate some contribution of these factors to test performance. Therefore, while we cannot exclude the contribution of long-term lithium (or other medication) exposure to our findings, it is likely that medication effects alone do not account for the present results.

Our findings in this small sample support the presence of persistent neurocognitive difficulties in patients with long-standing bipolar disorder who are not in the psychiatrically acute state or who are suffering the effects of acute alcohol use. The relationship of this impairment to lifetime months of the illness raises the possibility that early diagnosis and active treatment could potentially reduce the neurocognitive morbidity associated with bipolar disorder.

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