Neuropsychologic Impairments in Bipolar and Unipolar Mood Disorders on the CANTAB Neurocognitive Battery

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**Background:** Cognitive deficits associated with mood disorders, especially bipolar disorder, have been the focus of limited systematic investigation.

**Methods:** We tested 35 bipolar (21 in depressed state and 14 in mixed or manic state) and 58 nonbipolar depressed consecutively admitted young adult inpatients and 51 matched healthy individuals on the Cambridge Neuropsychological Test Automated Battery, a computerized neurocognitive battery.

**Results:** The mixed/manic bipolar patients demonstrated robust deficits in episodic and working memory, spatial attention, and problem solving. In contrast, depressed bipolar and nonbipolar patients demonstrated impairments only in episodic memory.

**Conclusions:** Neuropsychologic findings with the Cambridge Neuropsychological Test Automated Battery indicate widely distributed deficits in cognitive domains subserved by temporal, parietal, and frontostriatal systems in bipolar patients during mixed/manic states of illness. Significant deficits in bipolar and nonbipolar depressed patients were restricted to episodic memory, suggesting a more selective dysfunction in mesial temporal lobe function during episodes of depression. These findings highlight the different cognitive profiles of mania and depression, demonstrate similar patterns of neuropsychologic deficits in bipolar and nonbipolar depression, and point to a need for further research investigating the characteristics, causes, course, and treatment of severe cognitive deficits associated with mixed/manic phases of bipolar disorder. Biol Psychiatry 2000;48:674–685 © 2000 Society of Biological Psychiatry

**Key Words:** Working memory, problem solving, cognition, depression, bipolar disorder, neuropsychology

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**Introduction**

In contrast to the extensive investigation of neuropsychologic deficits in schizophrenia, relatively few investigators have characterized changes in neurocognitive status associated with mood disorders. Although there has been some growing interest in cognitive effects of depression in recent years (Murphy et al 1998; Sweeney et al 1998), surprisingly few studies have examined the neuropsychologic status of patients with bipolar disorder.

In unipolar depression, neuropsychologic deficits have been reported in the domains of psychomotor speed (Sobin and Sackeim 1997), memory (Burt et al 1995; Cohen et al 1982; Golinkoff and Sweeney 1989), sustained attention (Cornblatt et al 1989), and executive functioning in domains including working memory and complex problem solving (Cassens et al 1990; Merriam et al 1999; Sweeney et al 1998). Several clinical and psychobiological correlates of these changes have been demonstrated. Memory deficits have been linked to dysregulation of the hypothalamic–pituitary–adrenal axis, an effect believed to result from adverse stress hormone effects on the hippocampus (Bemelmans et al 1996; Faustman et al 1990; Silberman et al 1985). Clinical correlates of cognitive deficits include various indices of episode severity including psychotic (Albus et al 1996; Gruzelier et al 1988; Nelson et al 1998), melancholic (Austin et al 1999; Cornell et al 1984), and endogenous (Rush et al 1983) features. Deficits also appear to be more robust in elderly patients (Deptula et al 1993; Harvey et al 1997; Rubinow et al 1984). Because of widely reported but generally modest correlations between symptom severity and neuropsychologic deficits in depressed patients, as well as studies showing improvement in function after treatment (Goldberg et al 1993), it has traditionally been accepted that cognitive deficits in mood disorders are related to the acute state of illness; however, there is growing consensus now that some neuropsychologic deficits in depressed patients may persist after symptom remission (Trichard et al 1995).

In bipolar patients, deficits in executive functions, psychomotor skills, and memory have been reported (Coffman et al 1990; Morice 1990; van Gorp et al 1998).
In the relatively few studies that directly compared unipolar and bipolar patients, bipolar patients generally performed more poorly (Savard et al 1980; Wolfe et al 1987), though this has not always been the case (Kessing 1998). As in nonbipolar depression, some cognitive deficits associated with bipolar disorder appear to persist into remission (Clark et al 1999; Savard et al 1980).

Powell and Miklowitz (1994) and Veiel (1997) have proposed that cognitive deficits in mood disorders primarily reflect frontal lobe dysfunction. A recently developed computerized test battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB), was designed with a significant focus on neuropsychologic functions subserved by frontostriatal circuitry (Fray et al 1997). This test battery has procedural advantages such as the separation of mnemonic and strategic components of working memory, as well as relatively strong data linking specific performance deficits to focal brain abnormalities in animal and human lesion studies. Whereas the CANTAB battery emphasizes assessment of frontostriatal functions using tests of spatial working memory, complex problem solving, and attentional set shifting, it also includes tests sensitive to temporal lobe (Pattern Recognition and Delayed Match to Sample tests) and parietal lobe (Spatial Span test) function.

When the CANTAB battery was used previously in studies of depression, selected tests rather than the entire test battery were administered. Deficits have been demonstrated in delayed recognition memory, problem solving, spatial recognition memory, and attentional set shifting. These effects have been most robust in elderly patients (Beats et al 1996; Elliott et al 1997).

Impairments in Pattern Recognition Memory, Spatial Recognition Memory, Delayed Matching to Sample, and problem solving have been reported in acutely ill manic patients (Murphy et al 1999). Murphy and colleagues noted that these deficits were more severe than those that they reported on previously in a study of unipolar depressed patients. Clark et al (1999) recently compared euthymic bipolar patients with healthy subjects using selected CANTAB tests, and reported disturbances in sustained attention and attentional set shifting, but no impairments in complex problem solving or spatial working memory.

The primary aim of our study was to directly compare the cognitive function of bipolar patients in mixed/manic or depressed phases of illness with nonbipolar depressed patients and healthy subjects. We utilized the complete main CANTAB battery, as well as its working memory battery, to broadly characterize neuropsychologic deficits associated with mood disorders in our sample of consecutively admitted inpatients.

Methods and Materials

Subjects

Fifty-eight inpatients meeting DSM-IV (American Psychiatric Association 1994) criteria for nonbipolar major depression, 35 inpatients meeting criteria for bipolar disorder (21 in depressed phase and 14 in mixed or manic phase), and 51 healthy comparison subjects were studied. The Structured Clinical Interview for DSM-IV Disorders (First et al 1997) sections relevant to diagnosing mood and psychotic disorders were administered to all subjects to determine diagnoses. Patients were recruited from consecutive admissions to subspecialty inpatient units at the Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania. Healthy subjects were recruited from the community by newspaper advertisements so as to maintain group matching on age and IQ. These healthy individuals had never met criteria for a mood or psychotic disorder, and they reported no knowledge of affective disorders in first-degree relatives. No subject had a history of electroconvulsive therapy, significant systemic or neurologic disease, or recent substance abuse that might affect cognitive performance. Clinical ratings were obtained close to the time of testing using the Hamilton Rating Scale for Depression (17-item version; Hamilton 1960), the Bech–Rafaelsen Mania Scale (Bech et al 1979), the Brief Psychiatric Rating Scale (Overall and Gorham 1962), and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984), which assesses psychotic symptoms. Demographic and clinical characteristics of the subject groups are presented in Table 1.

Cognitive Testing

Tests from the CANTAB battery were presented on a high-resolution touch-screen monitor under computer control. Patients were tested as soon after admission as they were judged able to participate in the cognitive assessments, typically within 3 days (median time). The CANTAB tests have been described in detail previously (Lawrence and Sahakian 1996; Robbins et al 1994) and are described here briefly. The battery includes control tasks designed to assess psychomotor speed, the ability to follow instructions, and gross spatial perceptual skills, fundamental abilities that can influence performance on the cognitive tasks. The Big Circle/Little Circle task tests reaction time and the ability to follow and then reverse rule-based responses. Subjects are shown a pair of circles and instructed to touch the bigger circle for the remaining trials, and then are told to touch the bigger circle for the remaining trials. The Five Stage Reaction Time task assesses psychomotor speed. Subjects are told to hold down a press pad and release it and touch a yellow dot on the screen as soon as it appears.

Tests Sensitive to Frontostriatal Dysfunction

STOCKINGS OF CAMBRIDGE. This task, a modified version of the Tower of London task, requires subjects to rearrange colored balls in vertical columns to match a desired final arrangement in a specified minimum number of moves. Subjects are told to plan their sequence of moves before starting to move the balls shown on the monitor. The time to plan the sequence of
SPATIAL WORKING MEMORY TASK. In this self-ordered searching task, subjects are asked to search through boxes on the screen to discover which hides a token. Subjects are instructed that once a token is discovered on a trial that box will not hide a token on subsequent trials. Between-search errors (searching a box in which a token was found on a previous trial) and within-search errors (searching the same box twice in a trial) are tabulated. Subjects’ ability to adopt a consistent search strategy is also evaluated. Task difficulty is manipulated by increasing the number of boxes presented in a block of trials (i.e., hiding targets behind four, six, or eight boxes).

INTRADIMENSIONAL/EXTRADIMENSIONAL (ID/ED) ATTENTIONAL SET-SHIFTING TASK. This test was designed to examine component processes evaluated in aggregate by the Wisconsin Card Sorting Test (WCST). It assesses the ability to maintain attention to different examples within a stimulus dimension (ID stages) and the ability to shift attention to a previously irrelevant stimulus dimension (ED shifts as required in the WCST). The number of stages/categories completed and the number of errors before and during the ED set shift are recorded.

SPATIAL RECOGNITION MEMORY TASK. This task assesses the ability to remember the spatial location of visual stimuli. Five squares are presented in sequence at different locations on the screen, and then subjects are presented a pair of squares and asked to identify which is at a location where a square was previously presented.

Tests Sensitive to Temporal and Parietal Lobe Dysfunction

SIMULTANEOUS AND DELAYED MATCHING TO SAMPLE TASK. This task assesses subjects’ ability to recognize complex visual designs after different delay intervals (0, 4, and 12 sec). Subjects are shown a target at screen center, and after the delay interval four surrounding stimuli are presented. Subjects are told to identify the design identical to the one presented previously. In the Match to Sample simultaneous version of this test, subjects are instructed to select the one of one, two, four, or eight peripheral patterns that matches the pattern shown simultaneously at the center of the screen.

PATTERN RECOGNITION MEMORY TASK. This task assesses the ability to recognize abstract patterns. After a series of patterns is displayed, subjects are presented pairs of patterns, one shown previously and one being a novel pattern. They are asked to indicate the pattern they were shown previously.

PAIRED ASSOCIATE LEARNING TASK. This task requires subjects to learn the location of specific visual patterns. Designs are presented in boxes on the screen at varying locations. The designs are then presented sequentially in the center of the screen and subjects are instructed to indicate the box in which each design was initially presented.

SPATIAL SPAN TEST. This test of spatial short-term memory, similar to the Corsi block test, examines the ability to remember the order in which visual stimuli are presented. Nine white squares are presented on the monitor and the squares change color one by one. Subjects are to indicate the order in which the squares changed color. Subjects complete three trials

| Table 1. Demographic and Clinical Characteristics of Mixed or Manic Bipolar Patients, Depressed Bipolar Patients, Nonbipolar Depressed Patients, and Healthy Comparison Subjects |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Bipolar mixed/manic patients [n = 14, mean (SD)] | Bipolar depressed patients [n = 21, mean (SD)] | Nonbipolar depressed patients [n = 58, mean (SD)] | Healthy individuals [n = 51, mean (SD)] | F | p |
| Age 36.14 (11.01) | 31.90 (1.36) | 32.29 (9.10) | 36.31 (9.69) | 2.06 | .11 |
| Gender (M/F) 6/8 | 12/9 | 19/39 | 12/39 | $\chi^2 = 8.03$ | .05 |
| IQ 102.08 (16.63) | 100.60 (12.21) | 102.93 (10.38) | 103.81 (8.93) | 0.43 | .73 |
| BR Mania 16.00 (5.19) | 1.35 (2.60) | 0.07 (0.26) | — | 257.69 | .001 |
| HRSD 12.93 (9.09) | 17.30 (5.46) | 21.64 (4.30) | — | 15.64 | .001 |
| BPRS 32.93 (7.10) | 29.47 (4.09) | 30.02 (5.95) | — | 1.68 | .19 |
| SAPS 1.93 (2.76) | 0.32 (0.95) | 0.56 (2.18) | — | 2.84 | .06 |
| Medications (no. subjects) | | | | | |
| Antipsychotics 6 | 7 | 4 | 0 |
| Antidepressants 3 | 11 | 46 | 0 |
| Lithium 6 | 8 | 0 | 0 |
| Anticonvulsants 8 | 6 | 6 | 0 |
| Benzodiazepines 7 | 9 | 23 | 0 |

The number of patients receiving psychotropic medications is listed for each group. BR Mania, Bech–Rafaelsen Mania Scale; HRSD, Hamilton Rating Scale for Depression; BPRS, Brief Psychiatric Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms (sum of global ratings).

*Significantly different from nonbipolar depressed patients.

*Significantly different from depressed bipolar patients.
each of sequences in which progressively more squares change color (from two to nine squares). If subjects fail to correctly remember the order of color change in three trials with a given number of stimuli, then the test is terminated. The highest number of items remembered in sequence is recorded to assess performance.

**Statistical Analysis**

The primary statistical analyses were analyses of variance (ANOVAs) contrasting subject groups. Repeated-measures ANOVAs were conducted when tasks had difficulty manipulations (e.g., varying delay periods before memory was tested). The Huynh–Feldt correction was used in these analyses. The Tukey honestly significant difference post hoc test was used to clarify group effects. Because there were group differences in gender ratio, we treated gender as an independent factor in all ANOVAs. Gender effects are reported in Results when significant. Skewed distributions (response latency data and Paired Associate errors) were normalized (square root transformation) before statistical analysis. The CANTAB battery calculates average response latencies using the time to begin correct responses, and that convention was followed in our analyses. For the ID/ED Set Shift and the Paired Associate Learning tasks, we followed the CANTAB method of adjusting the number of errors such that if subjects failed to complete stages at a particular level of task difficulty, more difficult test levels were not administered, and performance at those levels was assumed to be random (50% correct). Exploratory correlational analyses were conducted to assess associations between test performance and both clinical symptom ratings and demographic characteristics.

**Results**

**Control Tasks**

There were no group differences in response latencies on the Big Circle/Little Circle test \( [F(3,134) = 3.97, \text{ns}] \), and there were no group differences in reaction time \( [F(3,134) = 2.62, \text{ns}] \) or movement time \( [F(3,134) = 0.36, \text{ns}] \) on the Five Stage Reaction Time test (Table 2). Thus, group differences on cognitive tests can be attributed primarily to differences in cognitive processing time rather than to slow motor speed.

<table>
<thead>
<tr>
<th>Test</th>
<th>Bipolar mixed/manic patients [mean (SD)]</th>
<th>Bipolar depressed patients [mean (SD)]</th>
<th>Nonbipolar depressed patients [mean (SD)]</th>
<th>Healthy individuals [mean (SD)]</th>
<th>( F )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big Circle/Little Circle</td>
<td>881 (162)</td>
<td>809 (152)</td>
<td>820 (176)</td>
<td>758 (129)</td>
<td>1.89</td>
<td>.13</td>
</tr>
<tr>
<td>Five Stage Reaction Time</td>
<td>404 (104)</td>
<td>385 (117)</td>
<td>380 (91)</td>
<td>354 (67)</td>
<td>1.07</td>
<td>.37</td>
</tr>
<tr>
<td>Movement time (msec)</td>
<td>595 (130)</td>
<td>570 (124)</td>
<td>620 (170)</td>
<td>602 (132)</td>
<td>0.36</td>
<td>.78</td>
</tr>
<tr>
<td>Stockings of Cambridge</td>
<td>6.79 (1.76)</td>
<td>7.19 (1.63)</td>
<td>7.67 (1.83)</td>
<td>8.16 (1.88)</td>
<td>3.44</td>
<td>.02</td>
</tr>
<tr>
<td>Spatial Working Memory</td>
<td>38.21 (3.40)(^a,b)</td>
<td>36.10 (4.41)</td>
<td>34.50 (4.88)</td>
<td>33.20 (4.99)</td>
<td>5.58</td>
<td>.001</td>
</tr>
<tr>
<td>ID/ED Shift</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stages completed</td>
<td>7.86 (1.66)</td>
<td>8.43 (1.72)</td>
<td>8.23 (1.85)</td>
<td>9.00 (5.7)</td>
<td>1.45</td>
<td>.23</td>
</tr>
<tr>
<td>Pre-ED errors</td>
<td>12.86 (10.65)</td>
<td>9.24 (5.84)</td>
<td>8.46 (5.80)</td>
<td>7.44 (6.09)</td>
<td>2.10</td>
<td>.10</td>
</tr>
<tr>
<td>EDS errors, adjusted</td>
<td>8.79 (11.68)</td>
<td>5.38 (7.19)</td>
<td>6.82 (8.32)</td>
<td>4.40 (6.13)</td>
<td>1.35</td>
<td>.26</td>
</tr>
<tr>
<td>Spatial/Pattern Recognition Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial percent correct</td>
<td>68.9 (16.5)(^a,b)</td>
<td>77.4 (15.4)</td>
<td>81.0 (12.1)</td>
<td>82.3 (11.0)</td>
<td>5.69</td>
<td>.001</td>
</tr>
<tr>
<td>Pattern percent correct</td>
<td>81.0 (14.0)(^a,b)</td>
<td>88.7 (8.9)</td>
<td>89.4 (10.4)</td>
<td>90.6 (7.9)</td>
<td>3.38</td>
<td>.02</td>
</tr>
<tr>
<td>Delayed Match to Sample</td>
<td>3.675 (1.277)(^a,b)</td>
<td>3.340 (1.046)</td>
<td>2.969 (854)</td>
<td>2.834 (561)</td>
<td>3.82</td>
<td>.02</td>
</tr>
<tr>
<td>Latency, all delays (msec)</td>
<td>3,542 (758)</td>
<td>3,460 (742)</td>
<td>3,562 (1,083)</td>
<td>3,549 (808)</td>
<td>0.18</td>
<td>.91</td>
</tr>
<tr>
<td>Match to Sample</td>
<td>95.2 (3.5)</td>
<td>95.0 (5.5)</td>
<td>94.5 (5.5)(^a)</td>
<td>97.2 (2.6)</td>
<td>3.15</td>
<td>.03</td>
</tr>
<tr>
<td>Paired Associate Learning</td>
<td>2,442 (1,461)(^b,c)</td>
<td>1,400 (803)</td>
<td>1,338 (859)(^a)</td>
<td>1,656 (546)</td>
<td>7.00</td>
<td>.001</td>
</tr>
<tr>
<td>Total errors, adjusted</td>
<td>26.00 (32.33)</td>
<td>21.67 (40.39)</td>
<td>14.37 (21.54)</td>
<td>9.58 (14.33)</td>
<td>2.36</td>
<td>.08</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>5.36 (1.01)(^a)</td>
<td>5.67 (1.43)</td>
<td>6.26 (1.60)</td>
<td>6.58 (1.26)</td>
<td>4.67</td>
<td>.004</td>
</tr>
</tbody>
</table>

\(^a\)Significantly different from healthy individuals.

\(^b\)Significantly different from nonbipolar depressed patients.

\(^c\)Significantly different from bipolar depressed patients.
Tests Sensitive to Frontostriatal Dysfunction

STOCKINGS OF CAMBRIDGE. A diagnostic group by gender by task difficulty repeated-measures ANOVA was performed using the number of moves greater than the minimum needed to solve problems to characterize test performance. There was a significant group effect \( F(3,135) = 3.74, p < .05 \) and group by task difficulty interaction \( F(5.7,258.3) = 2.41, p < .05 \). Post hoc group comparisons indicated that the mixed/manic bipolar patients made significantly more excess moves to solve problems than healthy individuals \((p < .05)\). The significant interaction term indicated that group differences became more pronounced as task difficulty increased (Figure 1). In analyses of initial thinking/planning time, there were no group differences \( F(3,135) = 1.10, \text{ns} \) nor was there a significant task difficulty by group interaction \( F(7.0,314.7) = 2.20, p < .05 \). This interaction resulted from progressively longer reaction times in male subjects, with increasing task difficulty in healthy individuals and nonbipolar depressed patients, whereas in mixed/manic bipolar patients female subjects had progressively longer reaction times as task difficulty increased.

SPATIAL WORKING MEMORY. A diagnostic group by gender by task difficulty (number of boxes to be remembered over sequential trials) repeated-measures ANOVA was performed on the number of between search errors. There was a significant group effect \( F(3,135) = 5.76, p < .01 \) and group by task difficulty interaction \( F(3.04,203.3) = 3.26, p < .01 \). Post hoc group comparisons indicated that mixed/manic bipolar patients performed significantly more poorly than healthy individuals \((p < .001)\) and nonbipolar depressed patients \((p < .05)\).
The significant interaction term indicated that group differences became more pronounced as task difficulty increased (Figure 2). Significant group differences were also observed on the strategy score, which reflects the consistency of planning responses over trials \[ F(3,135) = 5.58, p < .01 \]. Mixed/manic bipolar patients were less consistent in their search strategies than were nonbipolar depressed patients \( p < .05 \) and healthy subjects \( p < .01 \). Neither the group effect \[ F(3,135) = 0.97, \text{ ns} \] nor the group by task difficulty interaction \[ F(4.26,191.7) = 0.40, \text{ ns} \] was significant for within search errors.

**ID/ED ATTENTIONAL SET SHIFT.** There were no group differences in the overall number of stages completed \[ F(3,133) = 1.45, \text{ ns} \] or in the number of errors made before the ED shift condition \[ F(3,133) = 2.10, \text{ ns} \]. There were also no significant differences between groups in the number of errors made in the ED set shift condition \[ F(3,133) = 1.35, \text{ ns} \].

**SPATIAL RECOGNITION MEMORY.** There were significant group differences in spatial recognition accuracy across groups \[ F(3,135) = 5.69, p < .01 \]. Bipolar patients in the mixed/manic phase of illness performed significantly more poorly than both nonbipolar depressed patients \( p < .01 \) and healthy subjects \( p < .01 \). A group by gender interaction indicated that male subjects in both bipolar groups made more errors than female subjects \[ F(3,135) = 4.18, p < .01 \], whereas minimal gender differences were present in the other subject groups.

Figure 2. Between-search errors on the Spatial Working Memory test over varying levels of task difficulty by mixed/manic and depressed bipolar patients, nonbipolar depressed patients, and healthy comparison subjects. Hatch marks represent standard errors of measurement. “Significantly different from healthy individuals.” “Significantly different from nonbipolar depressed patients.”
Tests Sensitive to Temporal and Parietal Lobe Dysfunction

**DELAYED MATCH TO SAMPLE.** A diagnostic group by gender by task difficulty (delay duration) repeated-measures ANOVA was performed using the percentage of trials performed correctly to assess task performance. There was a significant group effect \( F(3,135) = 10.88, p < .001 \) and group by task difficulty interaction \( F(9.0,405.0) = 4.28, p < .001 \). Post hoc group comparisons indicated that nonbipolar depressed patients \( (p < .05) \), depressed bipolar patients \( (p < .01) \), and mixed/manic bipolar patients \( (p < .01) \) all performed more poorly than healthy subjects, and that the mixed/manic phase patients performed more poorly than nonbipolar depressed patients \( (p < .01) \). Group differences became more pronounced as task difficulty increased (Figure 3). A significant group by gender interaction \( F(3,136) = 4.67, p < .01 \) indicated that, in healthy subjects and nonbipolar depressed patients, male subjects performed better than female subjects, whereas male subjects performed more poorly than female subjects in both bipolar groups.

Figure 3. Percent correct trials on the Delayed Match to Sample test over varying delay intervals achieved by mixed/manic and depressed bipolar patients, nonbipolar depressed patients, and healthy comparison subjects. Hatch marks represent standard errors of measurement. *Significantly different from healthy individuals. **Significantly different from nonbipolar depressed patients.

On the Match to Sample task, groups differed in the percentage of trials performed correctly \( F(3,134) = 3.15, p < .05 \). Post hoc tests revealed that the only significant pairwise group difference was between the nonbipolar depressed patients and healthy subjects \( (p < .01) \); however, these differences were very modest in size, with depressed patients performing 94.5% of trials correctly, as compared with 97.2% accuracy in healthy subjects. Also, the reaction times of the depressed patients were relatively fast, suggesting a speed/accuracy tradeoff rather than significant visual perceptual disturbances.

**PATTERN RECOGNITION MEMORY.** There were significant group differences in the accuracy of encoding and recognizing visual designs \( F(3,135) = 3.38, p < .05 \), such that mixed/manic bipolar patients were less accurate than nonbipolar depressed patients \( (p < .05) \) and healthy subjects \( (p < .01) \).

**PAIRED ASSOCIATE LEARNING.** On the spatial Paired Associate Learning test there was a significant
group difference in the number of errors made \[F(3,134) = 2.77, p < .05\], with mixed/manic patients performing more poorly than healthy subjects \((p < .05)\). There was also a significant group by gender interaction \[F(3,134) = 3.13, p < .05\] due to male subjects in both bipolar groups performing more poorly than female subjects.

**SPATIAL SPAN.** Significant group differences in span length were observed \([F(3,135) = 4.67, p < .01]\). Mixed/manic bipolar patients had significantly shorter spatial spans than healthy subjects \((p < .05)\).

**Clinical and Demographic Status and Cognitive Functioning**

For mixed/manic bipolar patients, Bech–Rafaelsen mania ratings were not significantly correlated with any CANTAB measures. Task performance of depressed bipolar patients was not correlated with ratings of depression (Hamilton depression ratings) or mania severity. In contrast, the severity of depression in nonbipolar depressed patients was correlated with several aspects of cognitive performance, including the total number of errors on the Paired Associate Learning task \((r = .40, p < .01)\), percent correct on the Spatial Recognition Memory task \((r = -.29, p < .05)\), problems solved in the minimum number of moves required on the Stockings of Cambridge task \((r = -.41, p < .01)\), movement time on the Reaction Time test \((r = .41, p < .01)\), and response latency on the Match to Sample test \((r = .28, p < .05)\).

Severity of psychosis (sum of SAPS global ratings) was correlated with response latency on several tasks, including the Match to Sample test in both the mixed/manic bipolar group \((r = .60, p < .05)\) and the depressed bipolar group \((r = -.47, p < .05)\), and the Big Circle/Little Circle task \((r = .35, p < .01)\) and the Delayed Match to Sample task in the simultaneous condition \((r = .29, p < .05)\) for nonbipolar depressed patients. Also, in the nonbipolar depressed patients, psychosis ratings were related to the number of errors on the ID/ED Shift task \((r = .42, p < .01)\), number of errors on the Paired Associate Learning task \((r = .70, p < .001)\), percent correct on the Spatial Recognition Memory task \((r = -.37, p < .01)\), span length on the Spatial Span task \((r = -.40, p < .01)\), between-trial errors on the Spatial Working Memory task \((r = .34, p < .01)\), and the number of problems solved in the minimum number of moves required on the Stockings of Cambridge task \((r = -.33, p < .05)\).

There was no pattern of significant correlations between test performance and treatment with different classes of psychotropic medication. Those treated with lithium did not perform more poorly on any test in either bipolar group. The observation that bipolar depressed patients receiving anticonvulsants made more errors on the Paired Associate Learning task \([t(19) = 2.43, p < .05]\) was the only association between anticonvulant therapy and test performance in any patient group.

Age was associated with test performance, especially in the nonbipolar depressed patients. Excluding measures of response latency, which were associated with age as expected across groups, cognitive parameters associated with age in the healthy subjects included only Spatial Recognition Memory errors \((r = -.33, p < .05)\) and Spatial Working Memory strategy score \((r = .28, p < .05)\). In contrast, in the nonbipolar depressed patients, age was associated with errors on Paired Associate Learning \((r = .44, p < .001)\), Spatial Span length \((r = -.59, p < .001)\), Spatial Working Memory strategy score \((r = .44, p < .001)\), within-search errors \((r = .29, p < .05)\) and between-search errors \((r = .35, p < .01)\) on the Spatial Working Memory task, and Stockings of Cambridge problems solved in the minimum number of moves \((r = -.36, p < .01)\). In bipolar depressed patients, age was correlated with errors on the Paired Associate Learning task \((r = .46, p < .05)\), Spatial Span length \((r = -.48, p < .05)\), and the number of problems solved in the minimum number of moves on the Stockings of Cambridge task \((r = -.43, p < .05)\). There were no significant correlations between age and test performance in the mixed/manic bipolar patients.

**Discussion**

Results of our study indicate a pattern of widespread neurocognitive disturbances in patients with bipolar disorder during mixed/manic phases of illness in domains subserved by multiple cortical association areas. These deficits were seen in executive functions, episodic memory, and spatial span performance, which suggest dysfunctions in frontostriatal systems, mesial temporal lobe systems, and the posterior parietal cortex, respectively. The pattern of deficits in the manic/mixed bipolar patients stands in contrast to the more limited and generally less severe deficits demonstrated by both bipolar and nonbipolar depressed patients. Deficits in both groups of depressed patients were confined to episodic memory functions, suggesting a relatively restricted abnormality in mesial temporal lobe memory systems during episodes of depression.

Findings from this study provide important new evidence indicating that neuropsychologic deficits are significantly more pronounced during mixed/manic phases than during the depressed phase of bipolar illness, and influence a wide array of neocortical functions. In addition, our data indicate that in bipolar patients, regardless of whether
they were in a mixed/manic or a depressed phase of illness, neuropsychologic deficits were greater in male patients on tests including Spatial Recognition Memory, Delayed Match to Sample, and Paired Associate Learning. Thus, gender-related factors appear to modulate the severity of neuropsychologic deficits in bipolar disorder, a pattern we did not detect in nonbipolar depression.

The wide array of neurobehavioral deficits observed in the mixed/manic bipolar patients, in addition to the deficits on the Delayed Match to Sample test that were present in both groups of depressed patients, included performance on tests of spatial and pattern recognition memory, spatial span of attention, spatial working memory (both in retrieval and the consistent use of efficient response strategies), complex problem solving, and paired associate learning. Their performance in the areas of spatial recognition memory, delayed matching to sample, pattern recognition memory, and response accuracy and use of efficient strategies on the spatial working memory test was impaired relative both to healthy subjects and to nonbipolar depressed patients. The one test of executive functions on which bipolar patients did not demonstrate impairments was on the ED attentional set-shifting task, indicating an absence of significant inflexibility or perseveration in problem-solving efforts.

Our findings of diverse cognitive impairments in bipolar patients are consistent with those reported by Murphy and colleagues (1999) with the selected CANTAB tests they administered. Murphy et al (1999) reported impairments in Delayed Match to Sample, on the Stockings of Cambridge, and in both Spatial and Pattern Recognition Memory during the manic phase of illness. The fact that we observed these and other deficits in patients during the mixed/manic phase but not in patients during the depressed phase of bipolar illness suggests that pronounced neuropsychologic deficits of the mixed/manic group may be related primarily to their state of illness at the time of testing rather than to persistent stable neurocognitive deficits. Consistent with the view that a significant component of the neuropsychologic deficits shown by mixed/manic patients is related to their acute state of illness, a recent study of euthymic bipolar patients performing CANTAB tests found no impairments on the Stockings of Cambridge and Spatial Working Memory tests (Clark et al 1999); however, Clark and colleagues did report an impairment in attentional set-shifting in the ID/ED task in their euthymic bipolar patients, a finding that is inconsistent with our own findings because we observed no deficits on this test in our acutely ill sample. The ability of acutely ill mixed/manic and depressed bipolar patients to perform the attentional set-shifting task at a level not significantly worse than healthy subjects in our study suggests that deficits in this domain are not commonly associated with bipolar disorder; however, longitudinal studies of bipolar patients are needed to fully clarify the discrepancy in findings on this particular test.

Previous studies of cognitive deficits in unipolar depression using the CANTAB battery have demonstrated impairments in psychomotor speed, memory, and executive functions, but findings across studies have been somewhat inconsistent. Robust patterns of deficits in multiple domains of function were reported in elderly depressed patients (Beats et al 1996) and in depressed patients recruited within the age range of 40 to 70 years (Elliott et al 1996). In contrast, findings from a large sample of young adult depressed patients (Purcell et al 1997) and from our study indicate few cognitive deficits in younger adult patients with nonbipolar depression.

It is noteworthy that our sample of young to midlife nonbipolar depressed patients only demonstrated deficits on the Delayed Match to Sample task, indicating a selective episodic memory disturbance. This finding is consistent with those of previous neuropsychologic studies suggesting a relatively selective disturbance of episodic memory function during episodes of depression (Austin et al 1999; Calev and Erwin 1985; Golinkoff and Sweeney 1989). An adverse stress steroid effect on the hippocampus may mediate this selective effect in depressed patients. Our results indicate that a similar specific neurocognitive impairment affecting episodic memory is associated with the depressed phase of bipolar illness, suggesting that the effects of depression on memory function, and by inference on mesial temporal lobe function, are similar in unipolar and bipolar disorders.

Deficits in executive functioning were evident in bipolar patients in the mixed/manic state. The absence of such deficits in both nonbipolar and bipolar depressed patients was somewhat surprising because studies using other neuropsychologic and neuropsychologic procedures have demonstrated deficits in this domain (Freedman 1994; Rush et al 1983; Sweeney et al 1998). The reasons for this difference are not clear, but they most likely result from the fact that executive function deficits associated with depression are not common in younger adult patients, except perhaps in those with particularly severe episodes of illness.

Despite the minimal overall cognitive impairments in the nonbipolar depressed patients, we did observe that age, severity of overall depression, and ratings of psychotic features were all correlated with performance of several tests in these patients. This pattern of results suggest that although generalized neuropsychologic deficits are not typically prominent in young adults with nonbipolar depression, increasing age and more severe depression dur-
ing midlife may cause the pattern of more generalized neuropsychologic deficits that have been observed in elderly depressed patients. These data suggest an important interaction of aging and severity of illness effects on the neuropsychologic function in midlife nonbipolar depression. This could be due to synergistic adverse effects of depression severity and aging processes on brain function, or to cumulative effects of more frequent prior episodes of illness in older patients.

One important future research direction in this area is the application of functional neuroimaging methods to better clarify and localize the neural system disturbances underlying cognitive deficits in mood disorders. Most brain imaging studies of mood disorders have focused on anatomy, resting-state brain physiology, or receptor physiology (Agren et al 1993; Drevets et al 1992; Mayberg et al 1997), and few have used cognitive activation strategies. Investigating the interaction of biochemical, anatomic, and functional changes in cortical systems during episodes of mood disorder may be a particularly useful strategy for developing an integrated systems-level understanding of brain abnormalities in mood disorders. Another important line of work that needs to be pursued in this relatively understudied area is longitudinal investigations of the course and persistence of neuropsychologic deficits in mood disorders, especially following mixed/manic phases of bipolar disorder through acute episodes of illness and remission (Altshuler 1993). Such neuropsychologic studies will not only help to differentiate state- and trait-related deficits, but also to determine whether there is any accelerated cognitive decline over the age span associated with the occurrence of more frequent or severe episodes of illness, whether achieving prolonged states of remission is associated with a gradual recovery of cognitive abilities, and whether different treatments have differential benefits for cognitive functioning.

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