An MRI Study of Temporal Lobe Structures in Men with Bipolar Disorder or Schizophrenia

Lori L. Altshuler, George Bartzokis, Tom Grieder, John Curran, Tanya Jimenez, Kristin Leight, Jeffery Wilkins, Robert Gerner, and Jim Mintz

Background: Hippocampal atrophy has been described in postmortem and magnetic resonance imaging studies of schizophrenia. The specificity of this finding to schizophrenia remains to be determined. The neuropathology of bipolar disorder is understudied, and temporal lobe structures have only recently been evaluated.

Methods: Twenty-four bipolar, 20 schizophrenic, and 18 normal comparison subjects were evaluated using magnetic resonance brain imaging. Image data were acquired using a three-dimensional spoiled GRASS sequence, and brain images were reformatted in three planes. Temporal lobe structures including the amygdala, hippocampus, parahippocampus, and total temporal lobe were measured to obtain volumes for each structure in the three subject groups. Severity of symptoms in both patient groups was assessed at the time the magnetic resonance images were obtained.

Results: Hippocampal volumes were significantly smaller in the schizophrenic group than in both bipolar and normal comparison subjects. Further, amygdala volumes were significantly larger in the bipolar group than in both schizophrenic and normal comparison subjects.

Conclusions: The results suggest differences in affected limbic structures in patients with schizophrenia and bipolar disorder. These specific neuroanatomic abnormalities may shed light on the underlying pathophysiology and presentation of the two disorders. Biol Psychiatry 2000; 48:147–162 © 2000 Society of Biological Psychiatry

Key Words: Amygdala, bipolar, limbic, hippocampus, schizophrenia, temporal lobe

Introduction


Volumetric MRI studies of temporal lobe structures in bipolar patients have been limited (Norris et al 1997; Table 1). The temporal lobe has been reported to be decreased in some studies (Altshuler et al 1991; Hauser et al 1989b; Schlaepfer et al 1994), but not all (Altshuler et al 1998; Johnstone et al 1989; Pearlson et al 1997; Swayze et al 1992), and has been reported to be enlarged in two studies in comparison to both schizophrenia and normal control groups (Harvey et al 1994; Pearlson et al 1997). In the few studies assessing hippocampal size, the findings have been similarly inconclusive. Hippocampal size has been demonstrated to be decreased in one study that measured this structure (Swayze et al 1992); however, in two other studies hippocampal size
<table>
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<tr>
<th>Study</th>
<th>Groups (N, mean age ± SD)</th>
<th>Imaging techniques and volume code (no. slices used in analysis)</th>
<th>Temporal lobe</th>
<th>Hippocampus (or parahippocampal gyrus if specified)</th>
<th>Basal ganglia structures (amygdala/caudate nucleus/globus pallidus/putamen)</th>
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</table>
| Hauser et al 1989b | 17 BP/UP (40 ± 12.8) 21 C (33.8 ± 6.2) | 0.5-T scanner Inversion recovery: TI = 600 msec, TR = 3,500 msec 12 1-cm coronal slices Volume code = 2 | ↓ TL/C bilaterally in BP vs. C | ns HC/TL | ns HC/C | 1. TL/C smaller in patients than in control subjects on both left (p < .02) and right (p < .03)  
2. Relationship of smaller TL/C ratio with longer duration of illness in right hemisphere only |
| Johnstone et al 1989 | 20 BP (35.2 ± 8.1 M/42.5 ± 8.2 F) 21 SCZ (35.6 ± 5.7 M/36.8 ± 7.1 F) 21 C (32.9 ± 5.6 M/39 ± 6.5 F) | 0.15-T scanner: TR = 544 msec, TE = 44 msec 6–10 8-mm coronal slices Volume code = 2 | ↓ left than right TL in SCZ vs. BP and C ↓ in SCZ vs. BP and C | ns left than right TL in SCZ vs. BP and C | ns left than right TL in SCZ vs. BP and C | 1. Trend for SCZ to have smaller temporal lobe than BP or control subjects (p < .08)  
2. Significant diagnosis × side interaction: left temporal lobe in SCZ smaller than right; in BP and control subjects, right temporal lobe smaller than left  
3. In male subjects, SCZ have enlarged temporal horn size compared with male subjects in other diagnostic groups; in female subjects, temporal horn size same in SCZ, BP, and control subjects |
| Alshuler et al 1991 | 10 BP I (39.8 ± 9) 10 C (37 ± 12) | 0.5-T scanner Inversion recovery: TI = 600 msec, TR = 3,500 msec 12 10-mm interval coronal slices Volume code = 1 | ↓ bilaterally in BP | ns across groups | ns across groups | 1. In BP males, significant negative correlation between duration of illness and right temporal lobe volume (r = .92, p < .028)  
2. Right–left asymmetry of temporal lobe greater in male BP than in female BP, greater in female SCZ than in male SCZ, and nearly equal between genders in normal control subjects  
3. Trend towards enlargement of caudate in SCZ vs. controls on left (p = .06) and right (p = .08) |
| Rossi et al 1991 | 16 BP (47 ± 11.98) 10 SCZ (28.6 ± 5.12) | 0.5-T scanner spin echo: TR = 2,400 msec, TE = 120 msec 15 coronal cuts, 5 mm thick, 2-mm interslice gap Volume code = 2 | ↓ bilaterally in SCZ vs. BP | ns across groups | ns across groups | 1. Both BP and SCZ had larger right temporal lobe volumes |
| Swayze et al 1992 | 48 BP (33.41 M/34.68 F) 54 SCZ (32.28 M/35.39 F) 47 C | 0.5-T scanner Inversion recovery: TI = 800 msec, TR = 1,600 msec 8 coronal cuts, 1-cm intervals Volume code = 2 | ns across groups | ↑ in BP on right vs. C ns, SCZ vs. C | ↑ putamen bilaterally in SCZ vs. C; ns, BP vs. C ↑ caudate bilaterally in SCZ vs. CS; ns, BP vs. C Amygdala: ns, BP vs. C or SCZ vs. C | 1. In all three groups, temporal lobe volume larger on right  
2. Right–left asymmetry of temporal lobe greater in male BP than in female BP, greater in female SCZ than in male SCZ, and nearly equal between genders in normal control subjects  
3. Trend towards enlargement of caudate in SCZ vs. controls on left (p = .06) and right (p = .08) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Controls</th>
<th>Study Details</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strakowski et al 1993</td>
<td>BP</td>
<td>C</td>
<td>1.5-T scanner Inversion recovery; TR = 800 msec, TE = 20 msec, TR = 2,000 msec</td>
<td>ns caudate (head and body)</td>
</tr>
<tr>
<td></td>
<td>15 BP</td>
<td>16 C</td>
<td>Volume code = 1</td>
<td>1. Significantly larger ratio of gray matter/white matter in BP</td>
</tr>
<tr>
<td></td>
<td>(28.4 ± 6.8)</td>
<td>(30.9 ± 7.3)</td>
<td></td>
<td>2. Structural volumes were divided by total cerebral volume to control for differences in brain size when making comparisons</td>
</tr>
<tr>
<td></td>
<td>16 C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aylward et al 1994</td>
<td>BP</td>
<td>C</td>
<td>1.5 T signa; TR = 2,500 msec, TE = 80 msec, one excitation T2; TR = 2,500 msec,</td>
<td>( \uparrow ) caudate in male BP</td>
</tr>
<tr>
<td></td>
<td>30 BP</td>
<td>30 C</td>
<td>TE = 80 msec, one excitation, axial sections 5-mm thick Volume code = 1</td>
<td>globus pallidus: ns</td>
</tr>
<tr>
<td></td>
<td>(39.3 ± 11.1)</td>
<td>(37.6 ± 9.0)</td>
<td></td>
<td>Putamen: ns</td>
</tr>
<tr>
<td></td>
<td>30 C</td>
<td></td>
<td></td>
<td>1. No significant main effect of diagnosis on caudate, putamen, globus pallidus, or total brain volume</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>2. Significant diagnosis ( \times ) gender interaction for caudate; male BP had significantly larger caudate volumes than male control subjects ( p &lt; .02 )</td>
</tr>
<tr>
<td>Harvey et al 1994</td>
<td>BP</td>
<td>C</td>
<td>0.5-T scanner Coronal Inversion recovery; TR = 4,420 msec, TI = 150 msec, TE</td>
<td>( \downarrow ) bilaterally in SCZ vs. BP</td>
</tr>
<tr>
<td></td>
<td>26 BP</td>
<td>34 C</td>
<td>= 40 msec, 20 contiguous 5-mm coronal slices Volume code = 1</td>
<td>1. Significant group difference for right and left Sylvian fissure and sulcal volumes, with SCZ greater than BP</td>
</tr>
<tr>
<td></td>
<td>(35.6)</td>
<td>(31.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schlaepfer et al 1994</td>
<td>BP</td>
<td>C</td>
<td>1.5-T scanner, simultaneous T2 and proton sequences: TR = 2,500 msec, TE = 20</td>
<td>STG analyzed as part of heteromodal association cortex</td>
</tr>
<tr>
<td></td>
<td>27 BP</td>
<td>60 C</td>
<td>80 msec, 5-mm-thick axial slices Volume code = 1</td>
<td>1. SCZ had less gray matter volume than control subjects in the “heteromodal association cortex” regions; dorsolateral prefrontal cortex; STG and inferior parietal lobe</td>
</tr>
<tr>
<td></td>
<td>(34.9 ± 8.6)</td>
<td>(31.6 ± 8.0)</td>
<td></td>
<td>2. Effect greater in female SCZ</td>
</tr>
<tr>
<td></td>
<td>46 SCZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dupont 1995</td>
<td>BP</td>
<td>C</td>
<td>1.5-T imager, full axial series: TE = 25, 70 msec, TR = 2,000 msec 5 mm thick</td>
<td>ns caudate</td>
</tr>
<tr>
<td></td>
<td>36 BP</td>
<td>26 C</td>
<td>2.5-mm gap Volume code = 1</td>
<td>1. SCZ had less gray matter volume than control subjects in the “heteromodal association cortex” regions; dorsolateral prefrontal cortex; STG and inferior parietal lobe</td>
</tr>
<tr>
<td></td>
<td>(36.6 ± 10.8)</td>
<td>(39.1 ± 9.4)</td>
<td></td>
<td>2. Effect greater in female SCZ</td>
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<tr>
<td></td>
<td>30 UP</td>
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<td></td>
<td>(38.6 ± 10.6)</td>
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</tr>
<tr>
<td>Pearlson et al 1997</td>
<td>BP</td>
<td>C</td>
<td>1.5-T scanner T1-weighted: TR = 800 msec, TE = 20 msec 3-mm thick contiguous</td>
<td>( \uparrow ) right anterior STG in BP vs. SCZ and C</td>
</tr>
<tr>
<td></td>
<td>27 BP</td>
<td>60 C</td>
<td>coronal slices Proton and T2-weighted slices: TR = 2,500 msec, TE = 30, 80</td>
<td>Hippocampus: ns</td>
</tr>
<tr>
<td></td>
<td>(34.9 ± 8.6)</td>
<td>(31.6 ± 8.0)</td>
<td>msec, axial contiguous 5-mm-thick slices Volume code = 2</td>
<td>( \downarrow ) amygdala on left in BP vs. SCZ and C</td>
</tr>
<tr>
<td></td>
<td>46 SCZ</td>
<td></td>
<td></td>
<td>Parahippocampal gyrus: ( \downarrow ) left anterior STG in SCZ vs C</td>
</tr>
<tr>
<td></td>
<td>(31.8 ± 7.8)</td>
<td></td>
<td></td>
<td>( \downarrow ) left posterior STG in SCZ vs C</td>
</tr>
<tr>
<td></td>
<td>60 C</td>
<td></td>
<td></td>
<td>Reversal of posterior STG asymmetry in SCZ (( \downarrow ) left, ( \uparrow ) right) vs. BP and C</td>
</tr>
<tr>
<td></td>
<td>(31.6 ± 8.0)</td>
<td></td>
<td></td>
<td>( \downarrow ) amygdala on right in SCZ vs. C</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (N, mean age ± SD)</th>
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<th>Hippocampus (or parahippocampal gyrus if specified)</th>
<th>Basal ganglia structures (amygdala/caudate nucleus/globus pallidus/putamen)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altshuler et al 1998</td>
<td>12 BP (50.8 ± 13.3), 14 SCZ (48.9 ± 7), 18 C (53.4 ± 11.1)</td>
<td>1.5-T scanner, steady-state sequence consecutive 4-mm coronal slices</td>
<td>ns across groups</td>
<td>↓ in SCZ vs. BP and C</td>
<td>↑ amygdala bilaterally in BP vs. SCZ or C</td>
<td>ns across groups, amygdala volume in left temporal lobe largest in BP I and smallest in BP II (but no different from control subjects)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volume code = 1</td>
<td></td>
<td>ns, BP vs. C</td>
<td>ns in SCZ vs C</td>
<td>ns across groups, amygdala volume in left temporal lobe largest in BP I and smallest in BP II (but no different from control subjects)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>ns across groups, amygdala volume in left temporal lobe largest in BP I and smallest in BP II (but no different from control subjects)</td>
</tr>
<tr>
<td>P.H. Hauser et al 1998</td>
<td>25 BP I (27.6 ± 7.5), 22 BP II (23.7 ± 4.3), 19 C (24.0 ± 4.5)</td>
<td>0.5-T scanner: TR = 533 msec, TE = 20 msec 5-mm interval slices</td>
<td>ns</td>
<td></td>
<td></td>
<td>ns across groups, amygdala volume in left temporal lobe largest in BP I and smallest in BP II (but no different from control subjects)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inversion recovery sequence: TI = 600 msec, TR = 3,250 msec coronal sections</td>
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<td></td>
<td>ns across groups, amygdala volume in left temporal lobe largest in BP I and smallest in BP II (but no different from control subjects)</td>
</tr>
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<td></td>
<td></td>
<td>Volume code = 1</td>
<td></td>
<td></td>
<td></td>
<td>ns across groups, amygdala volume in left temporal lobe largest in BP I and smallest in BP II (but no different from control subjects)</td>
</tr>
<tr>
<td>Hirayasu et al 1998</td>
<td>17 SCZ (26.7 ± 7.5), 16 affective disorders (23.7 ± 4); 12 BP manic, 2 BP mixed, 2 UP depressed 18 C (24.0 ± 4.5)</td>
<td>1.5-T scanner; TR = 35 msec, TE = 5 msec 124 coronal slices 1.5-mm thick 2. TR = 3,000 msec, TE = 30 and 80 msec 24-cm field of view and interleaved acquisition with 3.0-mm slice thickness</td>
<td>ns</td>
<td>↓ gray matter volume in left posterior STG in SCZ vs. affective and C</td>
<td>↓ gray matter volume in left posterior amygdala-hippocampal complex in SCZ vs. C</td>
<td>ns across groups, brain structure asymmetry in SCZ and affective vs. control subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volume code = 1</td>
<td></td>
<td></td>
<td></td>
<td>ns across groups, brain structure asymmetry in SCZ and affective vs. control subjects</td>
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<td></td>
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<td></td>
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<td></td>
<td>ns across groups, brain structure asymmetry in SCZ and affective vs. control subjects</td>
</tr>
<tr>
<td>Strakowski et al 1999</td>
<td>24 BP I (27 ± 6), 22 C (28 ± 6)</td>
<td>1.5-T scanner; TR = 22 msec, TE = 7 msec 1-mm-thick coronal slices covering entire brain</td>
<td>ns</td>
<td></td>
<td></td>
<td>Differences in amygdala volumes (enlarged in BP) contributed the only large effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volume code = 1</td>
<td></td>
<td></td>
<td></td>
<td>Differences in amygdala volumes (enlarged in BP) contributed the only large effect</td>
</tr>
</tbody>
</table>

BP, bipolar patients; UP, unipolar depressed patients; SCZ, schizophrenic patients; TI, inversion time; TR, repetition time; TE, echo time; IR, inversion recovery; TL/C, temporal lobe to cerebrum ratio; C, control subjects; ns, nonsignificant with p > .05; STG, superior temporal gyrus; HC/TL, hippocampus to temporal lobe ratio; HCC, hippocampus to cerebrum ratio.

a: Volume code (number of slices used for volumetric analysis): 1, volumetric measurements using all slices from brain structures; 2, area measurements using one or more slices; 3, qualitative read by a neuroradiologist; 4, unclear number of slices or unclear methodology.

b: Statistical trend, ns at the .05 level.
was no different than that of normal control subjects (Altshuler et al 1998; Hauser et al 1989).

The above studies of bipolar disorder have varied in methodology, including the affective state of the patient at the time the MRI was obtained; the slice thickness of the MRI, which in some cases may have been too large to accurately measure small structures (or separately measure the hippocampus and amygdala); and control of head position, which can substantially increase measurement variance across and within subjects (Bartzokis et al 1998). In a small MRI study of euthymic bipolar subjects, using 1.5-mm MRI sections and controlling for head position in three planes, we recently reported hippocampal and amygdala differences in schizophrenic and bipolar subjects, respectively, compared with a normal comparison group (Altshuler et al 1998). Specifically, we found 1) the hippocampus to be significantly smaller in the schizophrenic cohort (N = 14) compared with both the bipolar (N = 12) and the normal comparison (N = 18) groups and 2) the amygdala to be significantly enlarged in the bipolar cohort compared with both the schizophrenic and the normal comparison groups (Altshuler et al 1998). We report below on an expanded sample of bipolar, schizophrenic, and normal comparison subjects, and give an expanded level of detail on the MRI methodology.

Methods and Materials

Subjects

Patients between the ages of 18 and 65 years were recruited from the outpatient mental health clinic (MHC) at the West Los Angeles Veterans Affairs (VA) Medical Center. All subjects were male. Those who met DSM-III-R criteria for bipolar disorder or schizophrenia using the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al 1994) were recruited. Subjects were excluded from this study if they had a comorbid medical problem known to impact brain size, such as hypertension or diabetes (this excluded approximately 30% of patients otherwise eligible). An effort was made to recruit patients with no comorbid lifetime DSM-III-R disorder. Given that 80% of the 2000 patients in the outpatient MHC carry a diagnosis of schizophrenia, we were able to obtain a schizophrenic cohort without a history of a comorbid Axis I disorder. For the bipolar population this was more difficult, given that only 10% of the clinic population carries this diagnosis, and given the high rate of lifetime prevalence of substance abuse disorders in this cohort (Regier et al 1990). Bipolar patients with a history of substance abuse disorders other than alcohol were excluded from participation; however, bipolar patients with a history of alcohol dependence determined by the SCID (DSM III-R) were not excluded if they had been sober (by self-report and confirmation from a significant other) for at least 9 months. A serum γ-glutamyl transferase was obtained as well, and only patients with normal values were allowed to participate in the study. A normal comparison sample was recruited from newspaper advertisements and flyers placed in several hospitals. Those subjects who had no lifetime Axis I diagnosis on a SCID interview were included in the study.

All patients signed an informed consent form to participate in the study. As depression and mania have been associated with hypercortisolemia, and as elevated cortisol levels have been associated with altered brain size (Bentson et al 1978), bipolar patients were scanned only when euthymic. Bipolar patients were followed prospectively to ensure they were euthymic at the time of MRI. Euthymia was operationalized as 3 consecutive months of a Hamilton Depression scale (HAM-D; Hamilton 1960) score of less than 7 and a Young Mania Rating Scale (YMRS; Young et al 1978) score of less than 6 before undergoing an MRI. Outpatients who met DSM-III-R criteria for schizophrenia were also observed prospectively for 3 months with the Brief Psychiatric Rating Scale (BPRS; Overall 1988). When they were “stable” (operationalized as a less than 10% change in scores monthly over 3 months), they were appropriate for the MRI component. Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984a) and Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984b) scores were obtained on the schizophrenic subjects at the time of MRI to assess current level of psychopathology. Urine toxicology screens for metabolites of cocaine, amphetamine, methamphetamine, cannabinoi, opioids, and phencyclidine were obtained for all subjects before MRI. If the urine toxicology screen was positive, subjects were excluded from further study.

Twenty-four bipolar patients, 20 schizophrenic patients, and 18 normal comparison subjects were appropriate for MRI study; none had positive urine toxicology screens at the time of MRI. The demographic and illness characteristics of the groups are shown in Table 2. For the bipolar group, clinical interviews with patients, VA records, interviews with family members, and in many cases review of patients’ life charts (Squillace et al 1984) were used to determine the duration of illness (23.6 ± 16.4 years), prior number of manic episodes (5.3 ± 4.8), prior number of depressive episodes (8.0 ± 7.5), and prior history of alcohol dependence. Nine of the 24 bipolar subjects (38%) had a history of comorbid alcohol dependence, with sobriety for at least 9 months (6.7 ± 5.9 years).

Patients were on a range of medications at the time of the scan, including antipsychotics (six bipolar, 19 schizophrenic), lithium (17 bipolar), anticonvulsants (eight bipolar), antidepressants (seven bipolar, two schizophrenic), benzodiazepines (three bipolar, two schizophrenic), and anticholinergic agents (14 schizophrenic). All bipolar and schizophrenic patients had a history of exposure to antipsychotics, but accurate quantification of prior exposure was not possible due to poor record documentation and patient difficulty in recalling prior duration of exposure.

MRI

After signing an informed consent, all subjects were scanned using a 1.5-T General Electric (GE; Milwaukee) scanner. The image data were acquired using a three-dimensional (3D) spoiled GRASS sequence and displayed as contiguous 1.4-mm coronal slices spanning the entire brain (TR = 25, TE = 5, flip angle = 35, matrix = 256 × 192). Spoiled GRASS is a gradient echo
Table 2. Demographic and Illness Characteristics of Bipolar, Schizophrenic, and Normal Comparison Groups

<table>
<thead>
<tr>
<th></th>
<th>Bipolar (N = 24)</th>
<th>Schizophrenic (N = 20)</th>
<th>Control subjects (N = 18)</th>
<th>F</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean ± SD</td>
<td>50.2 ± 12.7</td>
<td>49.6 ± 7.8</td>
<td>53.4 ± 11.1</td>
<td>0.61</td>
<td>2.59</td>
<td>.5</td>
</tr>
<tr>
<td>Range</td>
<td>22–69</td>
<td>34–66</td>
<td>33–68</td>
<td></td>
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</tr>
<tr>
<td>Education (years)</td>
<td>15.5 ± 2.5</td>
<td>12.8 ± 1.9</td>
<td>15.2 ± 1.9</td>
<td></td>
<td>10.66</td>
<td>2.59</td>
</tr>
<tr>
<td>Race (N [%])</td>
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<td></td>
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</tr>
<tr>
<td>White</td>
<td>22 (92)</td>
<td>11 (55)</td>
<td>13 (72)</td>
<td>χ² = 10.9</td>
<td>6</td>
<td>.09</td>
</tr>
<tr>
<td>African American</td>
<td>1 (4)</td>
<td>7 (35)</td>
<td>3 (17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
<td>2 (10)</td>
<td>2 (11)</td>
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<tr>
<td>Marital status (N [%])</td>
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<tr>
<td>Married</td>
<td>6 (21)</td>
<td>1 (5)</td>
<td>2 (11)</td>
<td>χ² = 18.6</td>
<td>6</td>
<td>.005</td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>15 (62)</td>
<td>5 (25)</td>
<td>11 (61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3 (17)</td>
<td>14 (70)</td>
<td>5 (28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>23.6 ± 11.4</td>
<td>23.9 ± 6.7</td>
<td>—</td>
<td>0.01</td>
<td>1.42</td>
<td>.91</td>
</tr>
<tr>
<td>Age of onset illness (years)</td>
<td>26.6 ± 10.4</td>
<td>26.5 ± 5.4</td>
<td>—</td>
<td>0.06</td>
<td>1.42</td>
<td>.81</td>
</tr>
<tr>
<td>GAF</td>
<td>73.1 ± 13.3</td>
<td>55.3 ± 14.5</td>
<td>—</td>
<td>18.01</td>
<td>1.42</td>
<td>.0001</td>
</tr>
<tr>
<td>BPRS at time of MRI</td>
<td>31.7 ± 4.5</td>
<td>42.0 ± 14.0</td>
<td>—</td>
<td>11.5</td>
<td>1.41</td>
<td>.0016</td>
</tr>
<tr>
<td>SANS (Total) at time of MRI</td>
<td>—</td>
<td>7.7 ± 5.1</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS (Total) at time of MRI</td>
<td>—</td>
<td>4.6 ± 4.0</td>
<td>—</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HAM-D at time of MRI</td>
<td>5.5 ± 0.6</td>
<td>—</td>
<td>—</td>
<td></td>
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</tr>
<tr>
<td>YMR at time of MRI</td>
<td>1.9 ± 3.3</td>
<td>—</td>
<td>—</td>
<td></td>
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</tr>
</tbody>
</table>

GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale; MRI, magnetic resonance imaging; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; HAM-D, Hamilton Depression scale; YMR, Young Mania Rating Scale.
Figure 1. (A) Slice in which all four colliculi are visualized, used to delineate the posterior boundary of the temporal lobe and the posterior boundary of the hippocampus. Medially, the boundary between the temporal lobe and the cerebrum was determined by drawing a perpendicular line from the most inferior aspect of the Sylvian fissure across the narrowest portion of the temporal lobe. (B) The hippocampus was defined and measured from the first slice in which the alveus was well visualized to the first slice where all four colliculi could be well visualized. The anterior hippocampus shown here included the hippocampal formation and the dentate gyrus. The alveus represented its superior border, the hippocampal fissure its inferior border, and the lateral ventricle its lateral border. The structure outlined superior to the hippocampus is the posterior portion of the amygdala. (C) The amygdala was measured in its entirety. The most anterior portion of the amygdala shown here was defined as the region where the amygdala gray matter was 2.5 times as thick as the surrounding temporal lobe cortex.
correlated with amygdala volumes (unequal variances in the hemispheres. Age was negatively hemisphere entered separately as repeated measures. An unstruc-

ysis of covariance (SAS Proc MIXED), with the data from each

the statistical model was repeated-measures mixed-model anal-

were done by

follow-up pairwise comparisons

were evaluated

Diagnostic differences among the three groups (bipolar, schizo-

phrenic, and normal) in mean volumes of the amygdala, hip-

pocampus, parahippocampus, and temporal lobe were evaluated separately for each structure. Follow-up pairwise comparisons 

were done by t test when the diagnostic effect was significant. The statistical model was repeated-measures mixed-model analysis of covariance (SAS Proc MIXED), with the data from each hemisphere entered separately as repeated measures. An unstructured covariance matrix was specified to permit estimation of unequal variances in the hemispheres. Age was negatively correlated with amygdala volumes ($r = -.51, p = .01$) and hippocampal volumes ($r = -.45, p = .03$). Thus, age was used as a covariate in the analyses. Further, a dichotomous indicator of presence or absence of alcohol comorbidity was included as a covariate in all models. Including this history of comorbidity as an indicator provided a statistical test of whether alcohol made a significant difference in the bipolar group. The indicator provides a statistical rationale for pooling the group to increase power and to provide greater generalizability of the findings to the bipolar population. To evaluate the regional specificity of the differences and control for brain size, the temporal lobe volume was used as a covariate in the analyses of the hippocampus, parahippocam-

pus, and amygdala. Height in inches was used to control for the brain size in the analysis of the temporal lobe itself. Preliminary analyses included the main effect and interaction effects of hemisphere with diagnoses as fixed factors. With the single exception of the main effect of hemisphere in the hippocampus, those terms were all nonsignificant, and they were thus dropped from the final models reported below (statistical details of the full models are available on request). Significance tests were done at the two-tailed .05 level without experimentwise adjustment. Illness characteristics were assessed in relation to brain volumes using partial correlations (Spearman rank), with age and height partialed in the analyses of the temporal lobe, and age and temporal lobe partialed in analyses of the hippocampus, parahippocampus, and amygdala.

### Results

**MRI Volumes**

Table 3 summarizes the statistical analyses and presents the unadjusted group means (total volumes summed across hemispheres), standard deviation, and statistics for the diagnostic main effect and pairwise contrasts. The overall test of diagnostic differences (adjusting for age and total size) was significant in three regions (Table 3). The amygdala volume was significantly larger in the bipolar group than in either the schizophrenic ($p = .0003$) or the normal control ($p = .022$) groups. The bipolar–schizophrenic difference was also significant in the temporal lobe ($p = .007$). Schizophrenic and normal comparison subjects did not differ significantly in either amygdala ($p = .52$) or temporal lobe ($p = .12$) volumes. Schizophrenic subjects had significantly smaller hippocampal volumes than both the bipolar ($p = .004$) and the normal

<table>
<thead>
<tr>
<th>B</th>
<th>S</th>
<th>N</th>
<th>Diagnosis main effect (F)</th>
<th>B–S</th>
<th>B–N</th>
<th>S–N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>3.825.9 ± 695</td>
<td>3.213.2 ± 617</td>
<td>3.375.0 ± 639</td>
<td>5.29 ($p &lt; .008$)</td>
<td>$t = 3.06$</td>
<td>$t = 2.36$</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>4.577.7 ± 782</td>
<td>3.813.4 ± 606</td>
<td>4.320.3 ± 640</td>
<td>4.93 ($p &lt; .004$)</td>
<td>$t = 3.01$</td>
<td>$t = 0.55$</td>
</tr>
<tr>
<td>Parahippocampus</td>
<td>2.902.0 ± 565</td>
<td>2.625.6 ± 374</td>
<td>2.949.0 ± 466</td>
<td>1.68 ($p &lt; .004$)</td>
<td>$t = 0.89$</td>
<td>$t = 1.03$</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>146,425.4 ± 15,466</td>
<td>133,904.5 ± 13,440</td>
<td>139,523.0 ± 15,481</td>
<td>4.0 ($p &lt; .007$)</td>
<td>$t = 2.82$</td>
<td>$t = 0.99$</td>
</tr>
</tbody>
</table>

B, bipolar; S, schizophrenic; N, normal.

The internal landmarks for the temporal lobe, hippocampus, and amygdala were established a priori (Bartzokis et al 1993, 1998). Ten cases were measured twice and compared with the variance between groups of a sample of over 60 MR images read by the same rater. One rater (TJ, trained by LLA) measured all of the regions. Intrarater reliability was excellent (Bartzokis et al 1998). The intraclass correlation coefficients were .98, left temporal lobe; .95, right temporal lobe; .94, left amygdala; .95, right amygdala; .95, left hippocampus; and .98, right hippocampus.

### Statistical Analyses

Diagnostic differences among the three groups (bipolar, schizophrenic, and normal) in mean volumes of the amygdala, hippocampus, parahippocampus, and temporal lobe were evaluated separately for each structure. Follow-up pairwise comparisons were done by t test when the diagnostic effect was significant. The statistical model was repeated-measures mixed-model analysis of covariance (SAS Proc MIXED), with the data from each hemisphere entered separately as repeated measures. An unstructured covariance matrix was specified to permit estimation of unequal variances in the hemispheres. Age was negatively correlated with amygdala volumes ($r = -.51, p = .01$) and hippocampal volumes ($r = -.45, p = .03$). Thus, age was used as a covariate in the analyses. Further, a dichotomous indicator of presence or absence of alcohol comorbidity was included as a covariate in all models. Including this history of comorbidity as an indicator provided a statistical test of whether alcohol made a significant difference in the bipolar group. The indicator provides a statistical rationale for pooling the group to increase power and to provide greater generalizability of the findings to the bipolar population. To evaluate the regional specificity of the differences and control for brain size, the temporal lobe volume was used as a covariate in the analyses of the hippocampus, parahippocampus, and amygdala. Height in inches was used to control for the brain size in the analysis of the temporal lobe itself. Preliminary analyses included the main effect and interaction effects of hemisphere with diagnoses as fixed factors. With the single exception of the main effect of hemisphere in the hippocampus, those terms were all nonsignificant, and they were thus dropped from the final models reported below (statistical details of the full models are available on request). Significance tests were done at the two-tailed .05 level without experimentwise adjustment. Illness characteristics were assessed in relation to brain volumes using partial correlations (Spearman rank), with age and height partialed in the analyses of the temporal lobe, and age and temporal lobe partialed in analyses of the hippocampus, parahippocampus, and amygdala.

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Table 3 summarizes the statistical analyses and presents the unadjusted group means (total volumes summed across hemispheres), standard deviation, and statistics for the diagnostic main effect and pairwise contrasts. The overall test of diagnostic differences (adjusting for age and total size) was significant in three regions (Table 3). The amygdala volume was significantly larger in the bipolar group than in either the schizophrenic ($p = .0003$) or the normal control ($p = .022$) groups. The bipolar–schizophrenic difference was also significant in the temporal lobe ($p = .007$). Schizophrenic and normal comparison subjects did not differ significantly in either amygdala ($p = .52$) or temporal lobe ($p = .12$) volumes. Schizophrenic subjects had significantly smaller hippocampal volumes than both the bipolar ($p = .004$) and the normal
comparison \((p = .02)\) groups. Bipolar and control subjects did not differ significantly in hippocampal volumes \((p = .59)\). As schizophrenic subjects had significantly less education than members of the other two groups, number of years of education was next included in the model. This did not change the results: The main effect of diagnosis in relation to hippocampal volumes remained significant \([F(2,56) = 6.08, p = .004]\), and the pairwise contrasts still indicated significant differences between schizophrenia patients and both the bipolar \([t(56) = 3.45, p = .001]\) and normal \([t(56) = 2.33, p = .024]\) groups. The amygdala volumes separated the bipolar group from the others, whereas the hippocampus separated the schizophrenia group from the others. Thus, combining the two produced maximal discrimination (Figure 2). No diagnostic main effect was found in the parahippocampus \((p = .20)\).

Volumetric Correlations of Course of Illness

For the schizophrenic subjects, illness characteristics were assessed in relation to hippocampal volumes. No significant correlations emerged for total hippocampal volumes and current illness severity as measured by the BPRS \((r = .04, p = .8)\), SANS Total \((r = .14, p = .6)\), SAPS Total \((r = .07, p = .8)\), or Global Assessment of Functioning (GAF; \(r = -.12, p = .6\)) scores. Hippocampal volumetric data also failed to correlate significantly with specific demographic and illness parameters, including age \((p = .58)\), education \((p = .15)\), duration of illness \((p = .98)\), and age of onset of illness \((p = .68)\).

For the bipolar subjects, the association between three course of illness variables (number of manic episodes, number of depressive episodes, and duration of illness) and brain volumes was assessed. Preliminary analyses based on the general linear mixed model (as above) indicated no main or interaction effects of hemisphere, but significant interaction effects of alcohol comorbidity (e.g., there was a significant interaction of comorbidity with the number of manic episodes \([F = 13.95, p = .002]\)). For these reasons, data from the two hemispheres were summed, and analyses were performed separately in the two subject groups. Age and height were partialed in these analyses, and the illness variables were log transformed due to extreme nonnormality. Temporal lobe, hippocampal, and amygdala volumes were not significantly correlated with the GAF, BPRS, HAM-D, YMR, or other demographic parameters \((p > .2\) in all cases). No significant correlations were seen between temporal lobe or hippocampal volumes and any of the course of illness variables in either the pure or the comorbid bipolar group; however, amygdala volumes were significantly positively correlated with specific demographic and illness parameters, including age \((p = .58)\), education \((p = .15)\), duration of illness \((p = .98)\), and age of onset of illness \((p = .68)\).
correlated with number of manic episodes (log) in the bipolar group without a history of alcohol comorbidity \((r = .76, p = .01)\). No significant correlation was observed in the comorbid alcohol group.

**Discussion**

Our results, with refined MRI methodology including 1.5-mm slice thicknesses and control of head position in three planes, suggest a neuroanatomic specificity for limbic abnormalities in patients with schizophrenia and bipolar disorder. Hippocampal volumes were significantly reduced in schizophrenic subjects compared with both patients with bipolar disorder and normal comparison subjects; the latter two groups did not differ significantly from each other. The overall temporal lobe size and amygdala did not differ in schizophrenic patients compared with control subjects, suggesting a disproportionate volumetric change within the hippocampus. As the temporal lobe volumes of the schizophrenic cohort in our sample were significantly smaller than those from the bipolar disorder group and weakly tended to be smaller than those from the control group, we covaried for this internal structure. The results of reduced hippocampal size remained significant and specific to the schizophrenic cohort, even when covarying for an overall smaller temporal lobe. Enlarged amygdalae were found only in subjects with bipolar disorder, suggesting a relationship between this brain structure and the illness.

We did not replicate our earliest findings of reduced temporal lobe volumes in bipolar patients compared with normal control subjects (Altshuler et al 1991). This may be due to the refined method used in the current study of controlling for head position in three planes, which reduces partial volume effects and variability across subjects. Using this refined method, we replicated the results of others, demonstrating small temporal lobes and hippocampi in subjects with schizophrenia.

Hippocampal abnormalities in the brains of patients with schizophrenia have previously been demonstrated in most postmortem studies (Arnold et al 1991; Bogerts et al 1984, 1985; Brown et al 1986; Falkai and Bogerts 1986; Jakob and Beckman 1986; Jeste and Lohr 1989; Kovelman and Scheibel 1984), but not all (Altshuler et al 1990; Christison et al 1989; Heckers et al 1991a). Magnetic resonance imaging studies have similarly found abnormalities in the hippocampus (volume reduction). A recent meta-analysis (Nelson et al 1998) of 18 MRI studies of the hippocampus in schizophrenic and control subjects demonstrated that schizophrenia is associated with bilateral volumetric reduction of the hippocampus, a conclusion consistent with our findings. Further, in our study another paralimbic region, the parahippocampus, was smaller, although not significantly, in the schizophrenic cohort. Differences in hippocampal volume between schizophrenic patients and control subjects have ranged from 10% to 20% (Bogerts et al 1990, 1993; Buchanan et al 1993). Our study is consistent with this, finding a volumetric reduction of 12% when compared with the normal comparison group.

A selective structural hippocampal abnormality may be in part responsible for some of the neuropsychologic abnormalities in schizophrenia, including deficits in verbal memory, “working memory,” attention, and abstract reasoning (Buchanan et al 1993; Gilbertson and van Kammen 1997; Goldberg et al 1994; Gur et al 1998; Karaken et al 1995; Nauta 1971; Pribram 1986; Saykin et al 1991, 1994; Shenton et al 1992; Weinberger et al 1992). Morphological abnormalities in the mesiotemporal lobe may result in impairment of frontal lobe function, as the frontal lobes and hippocampal formation comprise an integrated functional system (Gilbertson and van Kammen 1997; Karaken et al 1995; Nauta 1971; Pribram 1986; Weinberger 1993; Weinberger et al 1992). Decreased volumes in the hippocampi of schizophrenic subjects have been associated with impairment of frontal lobe function, as demonstrated by lower scores on measures of executive function (Bilder et al 1995). Thus, impaired verbal memory and working memory often seen in patients with schizophrenia may be related to impaired hippocampal and hippocampal–prefrontal cortical circuits (Weinberger et al 1992).

We did not find significant correlations between cross-sectional BPRS, SANS, or SAPS scores and cross-sectional volumetric measurements of the hippocampus or temporal lobe. Correlations between the size of temporal and frontal lobe structures and clinical symptoms have been reported in other cross-sectional studies (Barta et al 1990; Buchanan et al 1993; Gur et al 1998; Shenton et al 1992; Turetsky et al 1995). Further studies are warranted to evaluate the correlations between hippocampal size and clinical symptomatology.

Hippocampal abnormalities (and associated cognitive impairment) have been found in other neuropsychiatric illnesses, including Alzheimer’s disease (Kesslak et al 1991; Killiany et al 1993; Pearlson et al 1992; Seab et al 1988) and posttraumatic stress disorder (Bremner et al 1995). Thus, this structural abnormality may not be specific to schizophrenia; however, in the few studies that have looked for hippocampal abnormalities in bipolar subjects as compared with normal control subjects, most have failed to find them (Altshuler et al 1998; Hauser et al 1989a). Our study also does not support the presence of hippocampal abnormalities, at least at the morphometric level, in patients with bipolar illness.

The enlarged amygdala findings in the bipolar subjects were unexpected in our prior report (Altshuler et al 1998).
and remain intriguing. We had originally used this other limbic region as a “control region” in the temporal lobe; however, this structural abnormality (enlargement) appears specific to the bipolar population. The areas of significance between and within groups (enlarged amygdala volume in the bipolar cohort, and a positive correlation between amygdala size and the number of manic episodes) reinforce each other and point in the direction of amygdala involvement in bipolar disorder. Very few investigators have measured amygdala size in bipolar subjects. Swayne and colleagues, using one slice and making an area measurement, observed no differences in amygdala size between bipolar patients and volunteers (Swayne et al 1992). More recently, Pearlson and colleagues reported a reduction in size in the left amygdala in bipolar subjects compared with both schizophrenic and control subjects (Pearlson et al 1997); however, this study sampled only two slices rather than the total amygdala volume. It is possible that these inconsistencies in results reflect methodological differences, including head position and number of slices obtained. Another group, using our anatomic landmarks and volumetric analysis methods, found enlarged amygdalae in a bipolar sample compared with a normal comparison group (Strakowski et al 1999).

The amygdala is considered a basal ganglia structure. Other basal ganglia structures have been reported to be enlarged in bipolar patients. Aylward and colleagues reported enlargement of the caudate nucleus in patients with bipolar disorder (Aylward et al 1994), although other investigators who have assessed the caudate in bipolar subjects have found no differences in caudate size between bipolar patients and comparison subjects (Dupont et al 1995; Strakowski et al 1993). As the basal ganglia have been reported to enlarge with exposure to antipsychotic treatment (Breier et al 1992; Chakos et al 1994, 1995; Elkashef et al 1994; Frazier et al 1996; Heckers et al 1991b; Hokama et al 1995; Jernigan et al 1991; Keshavan et al 1994; Swayne et al 1992) and many bipolar I patients have been exposed to antipsychotics, it is possible that our finding represents a drug rather than an illness effect; however, the enlargement of a basal ganglia structure in association with antipsychotic exposure has been reported only in the striatum, not the amygdala. The schizophrenic subjects in the current study—all of whom, no doubt, had substantial antipsychotic exposure—did not exhibit amygdala enlargement. In fact, in the very few studies of psychiatric populations where amygdala size has been evaluated, including patients with Alzheimer’s disease (Cuenod et al 1993) or schizophrenia (Bogerts et al 1984, 1985), the amygdala has been found to be atrophied.

There is considerable evidence that the amygdala plays a role in assigning affective significance to experiential stimuli and in regulating emotional and social behavior (Aggleton 1992; Brothers et al 1990; Gloor et al 1982; Kling et al 1993; LeDoux 1993; Rolls 1992).

Activation of the amygdala has been demonstrated to increase dopamine in the nucleus accumbens and other motor centers, resulting in increased motor activity and increased goal-directed and fear behaviors (Aggleton 1992). Stimulation of the amygdala electrically (Halgren 1981) or chemically (Ketter et al 1996; Servan-Schreiber et al 1998) in humans can give rise to intense emotional feelings of fear, anxiety, or, in some cases, pleasure. Bilateral removal of the amygdala in monkeys produces a striking nonmanic behavioral presentation, including tameness, social withdrawal, lack of emotion, and defects in learned active avoidance tasking responsivity (Kling et al 1993; Weiskrantz 1956). Neurochemically, bilateral lesions of the temporal poles in monkeys have been associated with reduced dopamine metabolites, reduced 5-hydroxyindoleacetic acid, and increased norepinephrine in the amygdala (Kling et al 1993), suggesting partial deafferentation of excitatory projections to the amygdala. Behavioral consequences of this procedure include anorexia, hunched posture, loss of social rank, and social withdrawal. It is possible that stimulation or inhibition of the amygdala could lead to some of the behavioral manifestations of mania (including mood lability/intensity, goal-directed behaviors, lack of avoidance of aversive stimuli, and anxiety) or depression (decreased motivation, social withdrawal, and lethargy), respectively. The amygdala receives inputs from the temporal lobe association cortex, orbitofrontal cortex, and multiple subcortical regions, including the midline thalamic nuclei, hippocampus, hypothalamus, and substantia inominata. Its main outputs are to the hypothalamus and ventral striatum, including the nucleus accumbens and entorhinal cortex, as well as to the mediodorsal nucleus of the thalamus, hippocampus, and neocortex (Ben-Ari 1981; Heimer et al 1982; Nauta 1961; Price 1981). The amygdala has connectivity to the prefrontal cortex and other limbic-related forebrain structures that are involved in attention, motility, fear conditioning, and facial recognition (Gloor et al 1982; LeDoux 1993; Morris et al 1996; Rolls 1992). Its anatomic connections suggest the amygdala’s role in receiving highly processed information from the cortex and organizing the autonomic and behavioral responses associated with emotion.

Recent neuroimaging studies further support the role of the amygdala in the regulation of mood (Schneider et al 1997). A recent study using functional MRI in 12 normal subjects demonstrated a significant increase in signal intensity in the left amygdala in sad as well as happy mood induction. This is consistent with earlier human neuroimaging studies that demonstrated amygdala activation during the presentation of emotionally valenced stimuli (hap-
pler or sad/fearful faces; Breiter et al 1996; Morris et al 1996).

In patients with mood disorders, prefrontal and whole brain cortical metabolisms have been demonstrated to be altered in mania (increased) and in depression (decreased; Baxter et al 1989; Drevets et al 1997). No study, to our knowledge, has assessed amygdala function in mania, and only one study thus far has assessed amygdala function in patients with depression. Drevets and colleagues, using positron emission tomography to measure differences in regional cerebral blood flow, assessed amygdala and prefrontal cortical activation in 13 patients with unipolar depression who were depressed at the time of the scan, 10 subjects with unipolar depression who were euthymic, and 33 normal control subjects. Compared with the control group, only the depressed group had increased activity in the left prefrontal cortex, whereas both the depressed and the remitted groups demonstrated increased activity in the left amygdala (Drevets et al 1992). These limited studies suggest the possibility that some brain abnormalities (e.g., prefrontal hyper- or hypometabolism in states of mania or depression) may represent the physiologic manifestation of some of the clinical symptoms of the disorder, whereas others (e.g., amygdala overactivation) may represent an abnormal neurophysiologic process that exists or persists when mood is stable, but renders one more vulnerable to developing a mood episode/disorder (Drevets et al 1992).

Increased size of the amygdala could be due to any of a number of factors, including increased neuron size (e.g., increased arborization), increased number of neurons (e.g., decreased pruning), increased glial cell size or number, increased vascular density (to support sustained increased metabolic demand), increased connective tissue (e.g., scarring), and increased intercellular fluid (e.g., edema). The etiology of structural enlargement of the amygdala in bipolar patients is uncertain. It is possible that with repeated episodes of mania the amygdala is stimulated and hypertrophies. This notion would be consistent with our finding of a significant positive association between the number of manic episodes and the volume of the amygdala, at least in the group without alcohol comorbidity (alcohol, a known toxin to brain cells, may cause amygdala cell loss and counteract/confound any relationship of episode number to brain region size); however, to our knowledge again, no animal or human studies exist that could shed light on whether stimulation or kindling of the amygdala results in hypertrophy. Further, the number of subjects is small, and whether this association would persist with a larger sample remains to be determined. Alternatively, it is possible that enlarged amygdalae are present in persons with bipolar illness before the first episode, and that this represents a trait marker that contributes to developing mania (e.g., increased neuron number due to decreased pruning). Studies of patients with first episodes may shed light on this. Further, postmortem studies of patients with bipolar illness may reveal what particular regions in the amygdala (e.g., specific nuclei or white matter) are altered, which may further elucidate the functional neuroanatomy of bipolar illness.

Several limitations exist with the current study. First, all the patient and control subjects were male and the patients were all veterans receiving their care in the VA setting. The generalizability of this finding to women and to a nonveteran patient population is not clear. Second, the amount of prior antipsychotic exposure is not well documented, and thus could not be fully evaluated as a prior potential confound. Third, it is possible that the medications used to treat bipolar illness—such as lithium or anticonvulsants—can cause hypertrophy in specific brain regions; however, to our knowledge no studies (animal or human) have been done to assess this. Future studies involving both genders and a broader mix of veteran and nonveteran bipolar patients may shed further light on the generalizability of the current findings to persons with bipolar disorder. Such studies are ongoing in our laboratory.

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